

# Research on the Fetus

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

This Appendix contains the entire text of papers and reports that were prepared for the Commission, and certain other materials that were reviewed by the Commission during its deliberations.



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# NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH

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### **CONTENTS**

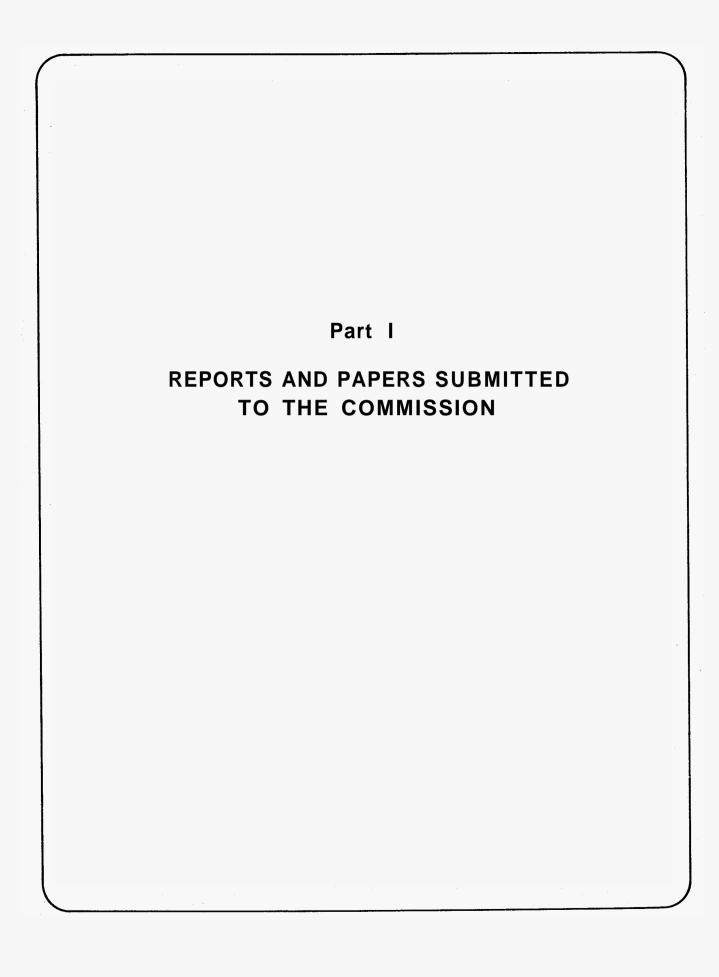
### I. Reports and Papers Submitted to the Commission

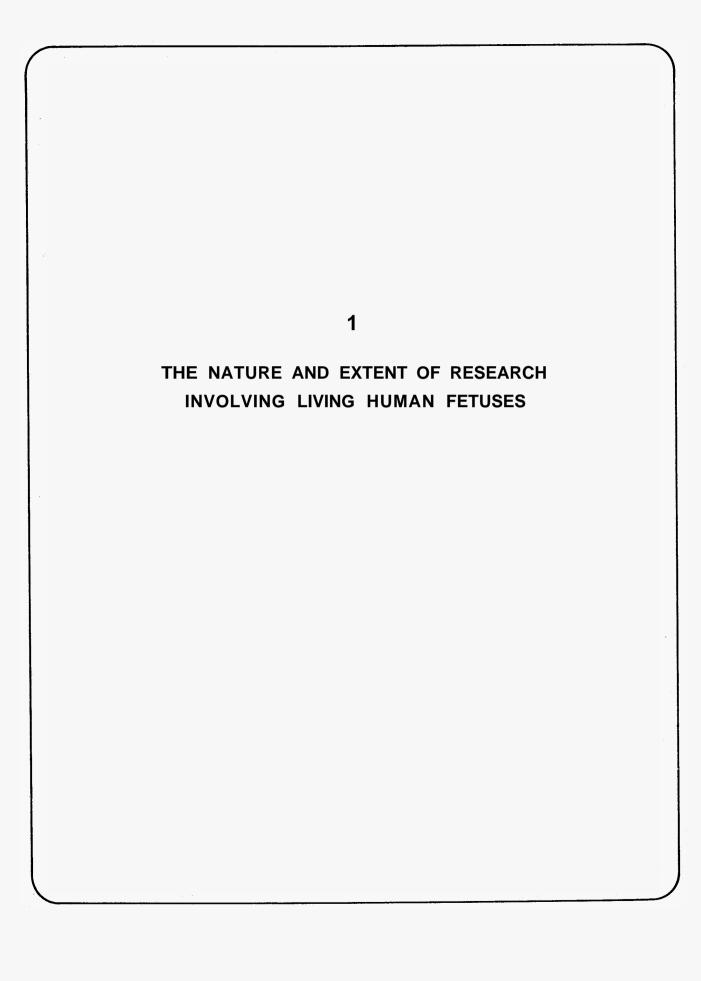
1.	The Nature and Extent of Research Involving Living Human Fetuses
2.	Fetal Research and the Value of Life
3.	Fetal Research: An Ethical Appraisal
4.	Balancing Obligations to the Living Human Fetus with the Needs for Experimentation
5.	Experimentation on the Fetus: Policy Proposals
6.	Moral Issues in Fetal Research
7.	Experimentation on Fetuses Which Are Judged to be Nonviable Seymour Siegel, D.H.L.
8.	Ethical and Public Policy Issues in Fetal Research LeRoy Walters, Ph.D.
9.	Ethical Issues Involved in Experimentation on the Nonviable Human Fetus
10.	Fetal Experimentation: Moral Issues and Institutional Controls
11.	Determining Death and Viability in Fetuses and Abortuses Leon R. Kass, M.D., Ph.D.
12.	Report on Viability and Nonviability of the Fetus
13.	The Law Relating to Experimentation with the Fetus
14.	A Report on Legal Issues Involved in Research on the Fetus John P. Wilson, LL.B.
15.	An Assessment of the Role of Research Involving Living Human Fetuses in Advances in Medical Science and Technology
	Critique of the Battelle Report
	Response to the Cooke Critique
16.	The Stability of the Decision to Seek Induced Abortion

### **CONTENTS** (Continued)

### II. Supplemental Resource Information

- 17. The Nuremberg Code of Ethics in Medical Research
- 18. Declaration of Helsinki
- 19. The Use of Fetuses and Fetal Material for Research, Report of the Advisory Group, Chaired by Sir John Peel, London, 1972
- 20. Protection of Human Subjects: Policies and Procedures, Federal Register, November 16, 1973, DHEW
- 21. Protection of Human Subjects: Proposed Policy, Federal Register, August 23, 1974, DHEW





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LeRoy Waiters, Ph.D. Kennedy Center for Bioethics Georgetown University Fetal death: the state in which the fetus shows none of the signs of life and is incapable of being made to function as a self-sustaining whole.

Fetal tissue: a part or organ of the fetus.

### Organization of Report

This report organizes the literature review in four broad areas:

- Normal and abnormal growth and development of the implanted fetus in utero
- 2. Diagnosis of fetal disease or abnormality
- 3. Fetal therapy and pharmacology
- 4. Research with the previable fetus outside the uterus.

It should be recognized that certain areas have been excluded from this literature review. These are: (1) the fetus in utero before implantation or the fetus outside of the uterus of comparable age (up to 7-10 days); (2) the implantation process or research to interfere with implantation; (3) research using the clearly dead fetus; (4) research with the extrauterine viable fetus which we define as being synonymous with the premature infant. With regard to the fourth item, we recognize the impossibility of operationally defining viability in a strict sense, and have reviewed research with fetuses up to 28 weeks gestational age that have signs of life outside of the uterus. Research with fetuses in utero is reviewed through parturition.

### LITERATURE REVIEW

### Area One: Growth and Development In Utero

The primary purpose and rationale of anatomic and physiologic investigations of the human fetus is the obtaining of information concerning normal developmental processes in order to understand the aberrant and ultimately to meet the clinical aim of providing broad medical services to the fetus. At the present time, although considerable basic information exists, much more is required to be able to understand and treat the abnormal. Developmental information has been obtained through evaluation of each developing system at various stages in gestation. Not infrequently, studies of the abnormal situation have catalyzed the investigations directly.

Over 600 publications were identified dealing with investigations of fetal development and physiology. Close to half of these have defined anatomic parameters and the others have sought physiologic or metabolic information.

A. Anatomic Studies. Extrauterine dead fetuses and preserved fetal materials have been the most widely utilized systems for anatomic studies. These have involved virtually all major tissues and organs, fetal membranes, and the placenta. Techniques utilized include cytological, cytochemical, histological and histochemical analyses of tissues at the light microscope and electron microscope levels. X-ray diffraction and membrane studies utilizing optical, thermal, nuclear magnetic resonance and spin-labelling techniques have recently been employed. Detailed anatomic information regarding both normal and abnormal growth and development of the fetus is available in several recent compilations.<sup>2-7</sup>

The anatomic definition of the human fetus at various stages of development has, of course, required human material. Similar studies have been done with other animal species and comparative information is available. The human studies have used aborted fetuses from both spontaneous and induced abortions. For some purposes, such as electron microscopic study of the brain, tissue must be obtained very quickly after death. In those instances, induced abortions (often hysterotomy abortions) are providing the fetuses.

B. Physiologic and Metabolic Studies. Living fetuses, live fetal materials and preserved fetal material have been studied utilizing numerous experimental approaches and sampling techniques which include: amniocentesis, amnioscopy, angiography, maternal blood-fetal lymphocyte isolation, sonography, amniography, fetography and fetoscopy. These techniques were often coupled with tissue culture and biochemical assays. Just as with anatomic studies, the majority of investigations examining metabolism have used tissues excised from dead aborted fetuses after similar studies with animal tissues. Some investigators have begun the experimentation before or during induced abortion, often recovering chemicals afterwards from umbilical cord blood or from tissues of the abortus.9 Similar studies have been done during caesarian section at term when a chemical is given to the mother a few hours before operation and metabolic products are measured in fetal umbilical cord blood at the time of delivery. 10 Scalp blood has also been used to measure a blood constituent before and during labor with vaginal deliveries.11 These studies are low risk, nonbeneficial studies for the fetus participating and have the aim of establishing normal fetal function so that future fetuses in distress can be recognized and helped.

Other studies establishing normal data in the midtrimester human pregnancy have measured fetal blood volume by injecting a chemical into an umbilical cord vessel at the time of elective hysterotomy abortion, 12 and have measured amniotic fluid volume by injecting into the amniotic fluid just before abortion. 13 Amniotic fluid volume in later pregnancy has been measured at the time of amniocentesis for Rh disease management or in normal term pregnancies when consent is given solely for that purpose. Animal data exist for these parameters and the studies are being done to establish normal data for the human as the basis for improved fetal medicine. Many chemicals have been measured in amniotic fluid, obtained for another indication, to establish normal data also.

Isolated organ culture using a tissue or organ from an aborted fetus has given physiologic and developmental information about human organs after similar studies in animals. Fetal muscle tissue is being examined in hopes of finding

leads to muscular dystrophy problems.<sup>14</sup> Fetal hearts, removed just after death Of a fetus following hysterotomy abortion, have been studied to establish physiologic response data. <sup>15,16</sup>

C. <u>Fetal Behavior</u>. Some aspects of central nervous system development have been studied via brain anatomy and brain metabolism in tissue from a recently deceased fetus. Another approach has been to study behavioral phenomena of the fetus in utero. Ultrasound has been used to document breathing and gasping in animal and human fetuses (as early as 13 weeks); breathing patterns change when a fetus is in jeopardy. Breathing has also been documented by injecting radiolabelled blood cells and radio-opaque dyes into the amniotic cavity before the birth of deformed fetuses which were expected to die soon after birth; the injected materials could be located in the lungs. 18

Many studies have been done to document fetal hearing. A sound stimulus is given through the maternal abdomen and a response noted by change in fetal heart rate<sup>19</sup> or fetal electroencephalogram recorded from the fetal scalp or, earlier in pregnancy, from the surface of the mother's abdomen.<sup>20</sup> The nature of intrauterine noise has also been studied by inserting a microphone inside the uterus before and during labor.<sup>21</sup>

Fetal movements have been recorded by deflections in an imposed electromagnetic field and found to correlate well with a mother's sensation of movements. Taste has been inferred from rates of swallowing amniotic fluid after saccharin or a radio-opaque dye was added to the amniotic fluid, and vision has been inferred from a change in fetal heart rate when light was shined transabdominally.

Using movie films, the reflexes of previable fetuses outside of the uterus have been documented along with the response of the fetus to touch.<sup>25</sup> These studies have shown a response to touch in a 7-week fetus, swallowing movements in a 12-week fetus, and crying expressions at 23 weeks; the fetuses were studied after hysterotomy while they were immersed in a salt solution.

D. Studies of the Pregnant Mother. Physiologic and pharmacologic studies during pregnancy are also done with the mother. Reports only occasionally mention effects in the fetus or say that effects were sought unless there was some reason to believe there might be some problem for the fetus. The effects of insulin and glucose infusions in the pregnant woman close to term have been studied to define the normal response in pregnancy and angiotensin II for blood pressure response in pregnancy. Any responses of the fetus are generally unknown in such studies.

Dietary changes during pregnancy have been the subject of a few studies. The effects of wartime starvation on the fetus have been studied in retrospect, 28 and the benefit of nutritional supplementation on pregnancy outcome in deprived populations has been cited. 29 Women undergoing elective midtrimester abortion have been starved for 87 hours before abortion in an attempt to learn the effects of caloric deprivation on pregnancy and to gain some information as to whether the fetus could adapt to fuels other than glucose. 30 Extensive nutritional

experimentation has been done in animal species where significant detrimental effects of nutritional deprivation have been demonstrated.

In general, attempts at defining growth and development in the human fetus have followed the obtaining of similar information in animals. Some experiments have been merely observational in nature while others have been invasive. Most of the research is seeking data to benefit the field of fetal medicine and fetuses as a class. Close to term, fetuses which will be born alive are involved; in midtrimester, fetuses that will be electively aborted are often involved. The risks are low for the fetus in most instances and the abortion process. usually is not prolonged.

### Area Two: Diagnosis of Fetal Disease or Abnormality

A. <u>Genetic Defects</u>. Over 800 papers have been published in the scientific literature since 1966 dealing with the detection of genetic defects in the human fetus. These articles exclude those dealing with blood group incompatibility and with lung maturation or fetal physiology.

The approaches used for the detection of genetic defects in the fetus have included: (a) amniocentesis and the study of amniotic fluid or amniotic fluid cells, (b) radiologic techniques including fluoroscopy, amniography, fetography, (c) ultrasound, (d) fetal cells identified within the maternal circulation, (e) fetal metabolites in maternal urine or, (f) most recently, direct endoscopic approaches including fetoscopy and/or fetal tissue or blood sampling under direct observation. Three comprehensive reviews on these subjects have recently been published. 31-33

This research has led to the current situation whereby virtually all cytogenetic aberrations of the human fetus can be detected by transabdominal amniocentesis, amniotic fluid cell culture and cytogenetic analysis. With recessive genetic disorders, of the more than 100 disorders in man in which the specific inborn metabolic error has been identified, approximately 60 of these can now be detected by amniotic fluid cell study in vitro. 34 It is apparent from many papers in the literature that inborn metabolic errors continue to be exponentially identified and in so doing investigators are being greatly aided by the use of somatic cell systems, particularly skin fibroblasts cultivated in vitro. Wherever an inborn error has been identified in the cultured skin fibroblast system it has been similarly studied in cultured amniotic fluid cells obtained from preabortion amniotic fluid samples from otherwise normal pregnancies. This has enabled the preliminary data to be derived from which the potential application to at-risk pregnancies has been developed. Of the 60 inborn errors which are potentially detectable by amniocentesis and amniotic fluid cell study, 23 of these disorders have been successfully identified in at-risk pregnancies to date.34

Fluoroscopy, amniography, and fetography have been utilized for the identification of structural defects in the fetus including meningomyelocele, obstructive lesions of the gastrointestinal tract, genito-urinary abnormalities, bony malformations involving the extremities, and anencephaly. 35-39 In addition, radiologic approaches have been applied to the detection of multiple pregnancies, and

have been uniformly employed as an adjunct procedure with intrauterine transfusion. Such procedures have permitted investigations to be made of fetal and placental circulatory dynamics through dye studies conducted immediately before or after fetal transfusion.

In addition to this form of therapy (intrauterine transfusion) other therapeutic attempts have been made as an adjunct to amniocentesis. In particular the intrauterine administration of hydrocortisone following third trimester intrauterine diagnosis of adrenogenital syndrome has suggested the possibility of treating this disease in utero from early in gestation.  $^{40,41}$  In two instances an intrauterine diagnosis of galactosemia has led to selective dietary therapy in the pregnant female through the remainder of pregnancy. On another occasion diagnosis of vitamin  $\rm B_{12}$ -responsive methylmalonic acidemia early in gestation led to therapy of the fetus for the last nine weeks of pregnancy by administering huge amounts of vitamin  $\rm B_{12}$  to the mother.  $^{42}$  These few reports represent therapy after diagnosis. They have all come in the last five years concomitant with the application of fetal diagnostic attempts to identify genetic defects in early pregnancy.

With the exception of the relatively few inborn metabolic errors where therapy is an available alternative, the intrauterine studies which have been done by amniocentesis or other methods have primarily been used as an adjunct to genetic counseling in families at-risk for such disorders in their offspring. Where amniotic fluid studies were performed in pregnancies not at-risk for a genetic disorder, this was utilized as a method for ascertainment of normal levels of biochemical parameters in cultured amniotic fluid cells and for determination of culture methods for subsequent application to at-risk pregnancies. rationale in these studies has been to establish techniques for the prenatal detection of genetic defects and to apply such information to at-risk families as an improved form of genetic counseling. Prenatal genetic diagnosis enables families at-risk for genetic disease in their offspring to obtain additional information in a given pregnancy about that fetus. For the most part therapy is not available for such disorders but if the fetus is found to be affected the parents may elect to terminate the pregnancy by abortion as an alternative. Conversely, where the fetus is unaffected they can be reassured and thereby have unaffected children selectively. The goals of this work, in addition to obtaining improved diagnostic skills, are repeatedly stated by many authors to be a means of enabling at-risk families to reproduce without fear of often tragic genetic disorders in their offspring. 31-34

Such studies have provided important information about the onset and early pathology of genetic disease in the human fetus and to its detectability by such indirect means as those indicated. An important offshoot of these studies has been the acquisition of data related to the normal parameters of fetal biochemistry and development. The use of radiologic methods and particularly ultrasonic techniques have provided important normative data concerning fetal growth and development in utero.

The availability of a prenatal diagnostic method also has provided a basis for the consideration of control of certain genetic disorders where they tend to occur in particular high risk populations. Specifically the suggestion has been made that consideration of amniocentesis and fetal cytogenetic screening in

pregnancies occurring in women over 35 years of age could result in a substantial reduction in the incidence of Down's syndrome and other chromosomal aberrations, nearly all of which lead to multiple abnormalities (mental retardation most particularly). In addition, the availability of prenatal detection methods for certain inborn metabolic errors (where accurate carrier detection methods are also available) has provided a basis for screening specific populations in which particular recessive inborn metabolic disorders tend to occur, e.g., the Ashkenazi Jews for the Tay-Sachs gene. Carrier screening in the child-bearing age group can permit the identification of couples at-risk for the disease prior to the birth of affected offspring. Prenatal monitoring of all pregnancies in couples so identified to be at-risk could achieve the prevention of births of infants with disease (through selective abortion) and still enable such couples to have unaffected offspring.

Although a number of investigators have used animal models (sheep,monkeys) for amniocentesis and fetoscopy, each of these animal models offers major limitations as a true model for the human situation. Accordingly, amniocentesis, which was first developed in the 1930s as a technique for fetal monitoring for blood group incompatibility between fetus and mother, has been extended to the second trimester for genetic disease detection primarily through human experimentation.

A number of genetic and ethical concerns have been raised regarding the widespread application of prenatal diagnosis of genetic defects and selective abortion. Several important articles and texts have been written on this and related subjects.<sup>45-47</sup>

B. Rh Incompatibility Between Mother and Fetus. Articles were covered which reflect a global experience with the diagnosis and management of fetuses and pregnancies where Rh incompatibility is involved. Selected reviews are referenced. 48-50

The early introduction of amniocentesis in the 1930s as a means of monitoring pregnancies at-risk for this problem has developed widely throughout the world. Spectrophotometric determination on amniotic fluid supernatant has been developed as an important technique for evaluation of the sensitized or potentially sensitized pregnancy. In addition, the development of fluoroscopic and radiologic techniques as an adjunct to intrauterine fetal transfusion (carried out either by intraperitoneal or intracordal catheterization)<sup>51</sup> has been widely reported. In essentially every instance, these methods have been employed in pregnancies where clear evidence existed as to the dire prognosis for the fetus unless some intervening action was taken. Accordingly these procedures were carried out as potentially lifesaving procedures on a fetus who would otherwise be severely jeopardized by the hematologic incompatibility. In a number of instances additional experimental data was collected during the course of fetal transfusion (fetal angiography and pylography).

This area of therapeutic and clinical research has provided a basis for a more expanded understanding of the hematologic interrelationships between the fetus and mother and has provided a foundation for the development of techniques

for lifesaving procedures in certain specified situations. Moreover, the development and experience with amniocentesis for this purpose provided the basis for extending the procedure into earlier pregnancy for genetic disease monitoring using amniotic fluid cells.

Through investigations related to Rh incompatibility, the role of fetal/maternal hemorrhage in various stages of pregnancy (particularly in the period surrounding delivery) and its relationship to maternal sensitization became established. This led to the development and use of prophylactic anti-D immunoglobulin for the prevention of Rh isoimunization.

Throughout these investigative efforts, the judgement of the investigators was that the risk for the fetus was greater than those risks envisioned or known to be associated with the procedures. For example, the use of fluoroscopy and diagnostic radiologic procedures as an adjunct to intrauterine transfusion, although of some recognized risk to the fetus, was felt to be a much lower risk than the risk to the fetus from the primary disorder for which the procedures were conducted.

Studies in animal models have not been reported with specific regard to Rh incompatibility. However, the extensive immunobiological data related to immune tolerance and runt disease has been extensively studied in laboratory animals.

C. <u>Neural Tube Defects</u>. In three years approximately 100 medical-scientific publications have been published relating to the detection of neural tube defects in the human fetus.<sup>52-54</sup> The majority of these investigations have been conducted in Great Britain and the United States. The preponderant direction of these studies has been to develop techniques by which one could identify serious structural abnormalities of the neural axis (such as anencephaly and myelomeningocele) either through visualization techniques such as roentogenography (with or without radio-opaque substances introduced into the amniotic fluid), sonography, direct fetoscopy, or by several biochemical determinations which could relate to such abnormalities in the fetus.

Radiological procedures have primarily been applied to pregnancies in women who have previously borne infants with structural abnormalities in the neural axis. Using water soluble radio-opaque substances introduced into the amniotic fluid afteramniocentesis, this approach has been used to enhance the contrast within the uterine cavity in order to better visualize specific structures in the fetus. This technique, amniography, has been used also for the evaluation of fetal gastrointestinal lesions since the fetus, in swallowing amniotic fluid, allows the radiologist to view it's G.I. tract. With lipid soluble radio-opaque substances introduced into the fluid, the chemical tends to adhere to the vernix of the fetus and thereby outlines the outer perimeters of the fetus. This technique, called fetography, has been successfully applied to the detection of several structural abnormalities (phocomelia, meningomyelocele and anencephaly) in the second and third trimester fetus.

Relatively recently it has been shown that in a number of situations where neural tube closure is abnormal (leaving an open defect in the neural axis),

there is an elevation in the amniotic fluid alpha-fetoprotein level. Investigators in Great Britain, United States and Scandinavia have confirmed the finding of elevated amniotic alpha-fetoprotein level in early pregnancy (10 to 20 weeks) being associated with major structural aberrations of the neural tube. Elevations of alpha-fetoprotein also have been found with gastrointestinal obstructive disorders, with fetal death in utero, and with a few other serious fetal conditions. Related research has demonstrated that in many such conditions the level of alpha-fetoprotein in the serum of the pregnant woman may similarly be elevated. It has been suggested that screening the maternal serum alpha-fetoprotein level between 10-20 weeks of pregnancy may provide a potential screening method for identifying pregnancies with high risk for such structural aberrations in the fetus. Accordingly the identification in the mother of elevated serum levels would be followed by amniocentesis to assess the amniotic fluid alpha-fetoprotein level. This might then be helpful in reducing the frequency of births of children severely afflicted with such conditions (again implying selective abortion as an alternative).

The primary rationale for these investigations has been to develop a method for the accurate fetal diagnosis of serious structural aberrations in the development of the neural axis. In certain parts of the world such abnormalities are frequent (Wales, Ireland). Because the recurrance risk for such conditions in families already having an affected child is between 4-6 percent the availability of such techniques could be helpful in reproductive counseling of such families.

The interest in developmental biochemistry and fetal specific proteins has been of considerable relevance to understanding of certain maturational processes in the human organism. An important adjunct of these studies has been the handle which some fetal proteins have provided for the study and detection of certain kinds of cancer occurring in adulthood.

As such defects have only sporadically been identified in animal models there has not been extensive study of such problems in animal models. The ethical questions raised by such investigations relate to the applicability of any test as a screening method for the prevention (through abortion) of the birth of structurally abnormal fetuses.

D. <u>Lung Maturity</u>. Extensive studies have been reported in the literature regarding the study of fetal lung maturation. <sup>55-57</sup> In addition a number of papers dealing with possible techniques to enhance lung maturation have been reported. These studies primarily have considered the use of amniotic fluid obtained by amniocentesis as a means to evaluate the lipid profile of the fluid (particularly emphasizing sphingomyelin and lecithin determinations). Other studies designed to monitor fetal respiratory movements in utero with ultrasonic scanning techniques in the third trimester have also appeared. <sup>58,59</sup> The latter has been proposed as a potentially helpful means to evaluate fetal well-being and status in the latter stages of pregnancy. The identification of respiratory movements and particularly abnormal "gasping" movements in the fetus during labor or near term may prove to be a critical and life saving new method in perinatal medicine.

The primary rationale behind such studies has been the development of techniques to assess fetal maturation in pregnancies where intervention and premature delivery might be considered. Particularly in pregnancies in which isoimmune sensitization has occurred or in the diabetic woman, such information may have

critical importance. From these studies it has been established that with the maturation of the fetal lung and the dynamics of amniotic fluid (fetal swallowing and equilibration) increased concentrations of lecithin relative to sphingomyelin in the fluid is a reflection of maturation of the fetal pulmonary system. This has proven to be of considerable predictive value as to the likelihood of pulmonary complications in the neonate. Obviously this kind of information has had enormous impact on the management of certain high-risk pregnancies and has reduced a major complication of premature delivery, pulmonary insufficiency or respiratory distress syndrome. In addition this has given insight into the developmental systems involved in lung maturation. In recent studies the introduction of corticosteroids into the amniotic fluid has been reported to enhance this maturation process. This opens the possibility that when delivery is indicated in a given pregnancy, assessment of fetal lung maturation can first be made. Then if delivery must be carried out, some attempt can be made to enhance the pulmonary maturation of the fetus before delivery.

Relevant animal research in this area has been conducted. Studies in the rabbit and sheep have shown a maturational process with regard to the lung lipid profiles and an enhancement of this process with the use of corticosteroids introduced intra-amniotically. A major issue which has been raised about such investigations is that the use of agents such as corticosteroids may have a multiplicity of effects on the developing organism although only a single organ system is the target for such therapy.

E. Fetal Well-Being. In addition to many of the aforementioned studies, a secondary value in all of these investigations has been the development of a battery of information relating to determination of fetal well-being. Ultrasonic, radiologic, amniotic fluid and fetoscopic techniques conceivably do or will relate to such an assessment. Accordingly all the data derived from amniotic fluid and from radiologic studies of the fetus in utero are important in establishing data about the normal fetus at varying stages of pregnancy. This is particularly true of techniques utilized in near term fetuses for the assessment of fetal metabolic status through studies on fetal scalp blood samples. Fetal electroencephalography has been evaluated in term fetuses and may prove valuable as a means of evaluation of the status of the fetus at late stages of pregnancy. 44,65

All of these studies also relate to the development of normative data about the fetus and help to establish certain parameters by which to better evaluate the fetus either in early pregnancy or near term. Consistently, these studies have been carried out in an effort to enhance the pediatrician's or obstetrician's capability to identify the threatened fetus (either from inherent, intrauterine, or maternally related factors) so that appropriate avoidance methods or intervention might be carried out. 66,67

Such studies have provided considerable new information about the fetus in utero. The respiratory movements and the growth and development of the fetus as determined by ultrasound or radiographic techniques has provided important normative data against which selected pregnancies can be compared. Such data are extraordinarily helpful in assigning accurate gestational ages to fetuses. This is of enormous importance in many pregnancies where the possibility of elective delivery is a consideration (isoimmunization, diabetes mellitus).

In spite of the enormous data base that exists regarding fetal well-being in the sheep and other laboratory animals, little of this is directly applicable to the human situation. Anatomical peculiarities and physiologic differences have meant that these models do not provide sufficient data necessary to answer these questions in the human situation.

F. Effects of Amniocentesis. More than 100 papers in the 1969-1974 literature relate to the potential or actual hazards of amniocentesis. 68-70 The overwhelming majority of these papers deal with anecdotal experiences, or case reports or with sizeable series of pregnancies in which amniocentesis was utilized in the third trimester to monitor for isoimmunization and/or fetal maturation. Only a few papers are available dealing with complications of amniocentesis during the second trimester. A major study carried out by the National Institutes of Child Health and Human Development is currently being completed and within the next six months an extensive report of this collaborative study, assessing the risks of midtrimester amniocentesis, will be published. Although there potentially are a wide variety of immediate, short-term, or long-term effects of amniocentesis on the developing fetus, the reported experience to date concerning both second and third trimester amniocentesis is extremely encouraging. has been minimal evidence of complications or deleterious effect on those fetuses which have gone on to delivery. However these are primarily retrospective studies and their design and completeness might be improved. It is hoped that the prospective control study previously mentioned, and similar studies like it being carried out in Canada and Great Britain, will more accurately resolve these questions. In addition to following pregnancies through to term each of these studies involves an assessment of the offspring of those pregnancies through one or more years after birth. This should provide some data about the long-term hazards of amniocentesis. In the third trimester experience, the frequency of significant complications with amniocentesis is also small considering that hundreds of thousands of amniocenteses in later pregnancy have been conducted throughout the world.

The emphasis in conducting such studies has been to ascertain the definitive risk level associated with amniocentesis so that a more informed judgement could be made both by the medical people involved and by families where this procedure might be used on an elective basis. The potential value of amniocentesis and the information it can provide must be balanced against the overall risk of the procedure.

Such studies have provided additional basic information about the composition of amniotic fluid, fluid dynamics, and the possible effects of such procedures on certain complications such as fetal/maternal hemorrhage and isoimmunization.

Because of important biological, anatomical, and physiological differences, no animal species has proven ideal as a model for human amniocentesis studies. Difficulties in achieving pregnancy in certain animals in captivity, multiple pregnancies, distinct anatomical differences in the type, location, size and availability of the uterus and placenta, high spontaneous abortion rates in some species, and a lack of adequate postnatal developmental milestones in most animal species (in order to appreciate subtle long-term effects on psycho-behavioral function and intelligence) are some of the major limitations to such studies.

G. Diagnostic Ultrasound Applications and Hazards. Between 100-200 papers in the literature since 1968 are related to the use of diagnostic ultrasound in pregnancy. $^{71-73}$  As previously mentioned much of this work centers around the use of ultrasound in both early and late pregnancy as a noninvasive method for ascer-ment of fetal respiratory movements as well as fetal maturation. Recent investigations would indicate that the optimal method for evaluation of normal fetal development in utero is the use of sonography to determine fetal head size and growth. This is also the optimal means for determination of the gestational age of the fetus. More recent studies have demonstrated that with advanced equipment design (water coupled-grey scale sonography), enormous detail concerning both internal and external structure of the fetus can be ascertained in early pregnancy. In parts of Australia and Scotland, routine grey scale sonography or B-mode sonography is conducted in early and late pregnancy as a means for assessment of fetal maturation. Investigators in both countries have pioneered much of the recent physical and engineering advances in this area. Studies in these and other countries have demonstrated the enormous potential of ultrasonography as a critical noninvasive instrument €or the detection of structural abnormalities of the fetus (anencephaly, meningomyelocele, congenital heart disease, congenital renal disease) and as a vital instrument in the assessment of fetal well-being. Such techniques have enormous and obvious potential importance for improved obstetrical practice and for optimizing the management of pregnancy and the newborn.

Similar studies in animal models have been conducted by numerous investigators and have demonstrated the distinct capability to visualize external and internal structures of the fetus from very early stages of gestation through term.

The major concerns about ultrasonic diagnosis or diagnostic studies in pregnancy relate to the adequacy of studies concerning biological hazards of high frequency sound. It should be noted that diagnostic ultrasound utilizes relatively low frequency, short duration, sound pulses and with newer equipment the exposure may even be reduced further.

The potential hazards of ultrasonic exposure to the fetus have been considered by numerous investigators. The entire July 1972 edition of the British Journal of Radiology is devoted to this subject. Experiments in plants, bacteria, and animal models (with the level of intensity utilized for diagnostic ultrasound in human pregnancy) have not been associated with any clear or obvious deleterious effects. Preamniocentesis ultrasonic B-mode scanning for placental localization is now widely practiced throughout this country as a routine part of this diagnostic procedure. Professor Ian Donald's group in Glasgow, Scotland, has probably had the longest experience with ultrasound use in pregnancy. This group has recently evaluated a substantial number of Glasgow children who were exposed as fetuses to ultrasound as many as seven or eight years previously. No evidence of hearing deficit or developmental abnormality could be identified in this substantial series of school children.

While a number of questions may still remain unanswered as to the potential hazards of diagnostic ultrasound in pregnancy, no evidence exists at this point in either animal, plant, or human species indicating any clear evidence of hazard. On the other hand the demonstrated value of ultrasonic utilization in certain

pregnancies and the potential use of this technique in practically all pregnancies (particularly for gestational age determination and assessment of fetal well-being) are already obvious.

H. <u>Diagnostic X-Ray of the Fetus</u>. The diagnostic use of X-ray and related procedures in pregnancy has been widely reported. Pelvimetry and assessment of multiple pregnancy by radiologic technique is recognized and established obstetrical practice. In addition, radiologic techniques have been utilized in selected pregnancies where concern regarding bony or structural abnormality of the fetus was an issue. In addition, as previously mentioned, radiologic techniques have been extensively utilized as an adjunct to intrauterine transfusion. The associated use of radio-opaque materials for amniography or fetography have also been implemented in pregnancies where structural anomalies of the fetus were suspected or as an adjunct to intrauterine fetal transfusion.

Such techniques have been applied in full recognition of the biological hazards of X-radiation. In every instance it was regarded that the benefits to be gained by utilization of X-ray techniques outweighted the risks associated with the exposure of the fetus.

Extensive bacterial, plant, and animal investigations have been conducted regarding the hazards of X-ray exposure. The teratogenic, carcinogenic, mutagenic and cell replication effects of X-ray have been characterized in lower forms and have been consistently associated with doses of X-ray exposure considerably in excess of those utilized in the aforementioned procedures. However there are certainly considerations regarding the zero threshold for deleterious effects of X-ray with any experimental or procedural activity regarding the fetus and X-ray should be avoided whenever possible.

I. Fetal Cells in Maternal Circulation. Relatively little information is available on this approach to intrauterine fetal study as yet. It has been reported in several publications that throughout pregnancy a small amount of fetal blood is introduced into the maternal peripheral blood. 75 Investigators have recently demonstrated that lymphocytic cells in addition to red blood cells can be identified in maternal peripheral blood in small numbers. enabled identification of male fetuses from karyotypes prepared from peripheral blood samples obtained from the mother. One important limitation in this approach is that lymphocytes from the fetus apparently "colonize" in the mother and remain there for substantial periods of time. As long as two years after the birth of a male fetus, cytogenetic analyses of maternal peripheral blood have been reported to still show small numbers of male 46XY cells. This is a rather remarkable phenomenon and merits further investigation. Obviously such techniques are not applicable as yet to the study of the female fetus. it may be possible with further study that a technique to selectively isolate leukocytic, lymphocytic or erythrocytic cells could enable investigations to be carried out on selected fetal cells derived from the peripheral blood of the mother. Certain immunologic and cell size differences between fetal and maternal cells may prove helpful in such an isolation procedure. Further research is being conducted in this regard.

This approach would be most appealing. The concept that a peripheral blood sample obtained from a pregnant woman would provide the medical scientist with selected cells of fetal origin would have enormous potential for fetal diagnosis. Other considerations along these lines, involve the potential use of maternal urine samples to assess certain metabolic parameters in the fetus. The established use of estriol determinations in maternal urine as a measure of fetal well-being has been well substantiated by many investigators, and is an example of such an approach. Certain inborn metabolic errors might also prove detectable in the fetus with such approaches.<sup>76</sup>

J. <u>Fetoscopy</u>. Another new approach to diagnosis in fetal medicine is endoscopic viewing within the uterus and the biopsy of fetal tissues, especially of fetal blood. 77.78 This technique was developed with women undergoing midtrimester elective abortion and holds great promise for significantly widening the scope of fetal diagnosis of both genetic (e.g., hemoglobinopathies) and acquired disease (e.g., growth failure *in utero*); the technique should also allow the development of therapies which would have to be monitored by a skin or blood sample from the fetus. Clinical application is just starting. Three fetuses at risk for beta-thalassemia have been correctly diagnosed as free of the disease; fetoscopy was used in one of the pregnancies and direct placental aspiration of fetal blood in the other two.

Accurate diagnosis must be the basis for all medical considerations, whether it be treatment, correction, prevention, or intervention. Although much of the research to date has been directed primarily toward diagnosis, this must be the first step if effective treatment, cures, or prevention are to be ultimately achieved.

## Area Three: Fetal Therapy and Pharmacology Which Has Involved the Living Human Fetus

A. Developmental Pharmacology. A precise, quantitative determination of how many studies have been carried out in the area of developmental pharmacology is virtually impossible to achieve. One of the major reasons for this is the difficulty encountered in clearly distinguishing prima facie studies directed toward assessment of drug action in the human fetus from those which may become research studies by secondary intent, a posteriori so to speak, e.g., where a pharmacologic agent has been utilized to manage a specific therapeutic situation in a pregnant woman resulting in some pharmacologic effect upon the fetus or neonate.

From the current literature search, approximately 400 publications dealing with fetal pharmacologic research were identified, and about 70 of these fit the criteria of human fetal research which we have adopted. These data indicate that a rather broad spectrum of pharmacologic agents has been studied in the human fetus. The relative frequency of publications in specific areas of developmental pharmacology has been summarized in Table 1. This information is quite intriguing,

since it clearly suggests that a majority of investigations in this area are merely appendages to clinically acceptable therapeutic procedures performed during the prepartum (early and late) or parapartum phases of pregnancy. In this regard the overwhelming majority of studies were carried out close to parturition or during the parapartum period.

Table 1. Pharmacologic Investigations Involving the Living Human Fetus\*
(Frequency Distribution of Studies Published from 1969-1974)

Item <u>Number</u>	Drug Investigated	Number of Studies	Percent of Total
1	Anesthetics and Analgesics	24	33
	<ul> <li>a. Obstetrical anesthesia</li> </ul>	(13)	(18)
	<ul><li>b. Local anesthetic; placental transfer, fetal effects</li></ul>	(11)	(15)
2	Cardiovascular Agents ( ß-adrenergic agonists; atropine, prostaglandin)	9	13
3	Oxytocic Agents (Effect on fetal acid base balance; uterine perfusion)	9	13
4	Hormones (Oral contraceptives, insulin, thyroi	8 d)	11
5	Anti-infective Agents (Antibiotics, quinine, chloroquine)	6	9
6	Anticonvulsants		7
7	Antineoplastic Agents	3	4
8	Drugs of Abuse (Addicting agents, morphine, alcohol)	3	4
9	Diuretics	2	3
10	Psychopharmacologic Agents	1	1
	TOTAL	70	98%

<sup>\*</sup>This table illustrates the broad spectrum of drugs and problems investigated. It is not intended to be all inclusive and some studies performed during the period 1969-1974are omitted.

With the exception of a very few published investigations, research involving the assessment of drug action in the human fetus has utilized techniques which are generally noninvasive and/or low risk in nature. The procedures which have been employed are categorized below:

### (1) Invasive or Potentially Harmful Procedures:

- a. Amniotic fluid sampling.
- b. Scalp vein sampling at the time of parturition.
- c. Fetal blood sampling obtained by fetoscopic techniques (this procedure has not been utilized for any fetal pharmacologic studies as yet; however it presents a major tool for the future).
- d. Prepartum fetal blood transfusions containing drugs.
- e. Drugs administered to the mother for therapeutic reasons or for the purpose of studying placental passage and fetal distribution patterns. (While such investigations generally are carried out in individuals terminating pregnancy by abortion, some studies have been performed in which placental transfer was determined in normal pregnancies at the time of parturition.)

### (2) Noninvasive and Minimal Risk Procedures:

- a. Fetal electrocardiogram.
- b. Ultrasonic detection of fetal structures and movements.
- c. Analyses of umbilical cord blood (studies have been carried out in Sweden during which radioisotopes were injected into the fetus while it remained in situ and connected to the placenta for relatively prolonged periods of time. Blood specimens were obtained from the umbilical vessels and fetal steroid biosynthesizing capability estimated).

### (3) Isolated Tissue Studies:

- a. Tissues are generally biopsied after fetal death (cessation of spontaneous respiration and heart beat) and utilized to study drug metabolism in vitro.
- B. Major Objectives and Rationale for Research in Developmental Pharma-cology Involving the Living Human Fetus. The human living fetus has seldom, if ever, been used for the exclusive purpose of determining what specific pharmacodynamic actions a drug may exert upon the fetus or its physiologic maintenance systems. The rationale for research studies and protocols in developmental pharmacology evolve from several major information deficits regarding

drug action on human development. In general, the need for specific types of data has provided the stimulus for discrete investigations in the human; as such, objectives, and perhaps rationale, vary in a temporal sense, according to the stage of gestation under scrutiny:

### (1) Drugs Administered Prepartum:

a. Agents Used Early in Pregnancy: Virtually no preconceived research in the living human fetus has been carried out with agents falling into this category, and retrospective studies are the general rule. If compounds administered prenatally are observed to produce untoward effects on fetal development or neonatal survival, then a stimulus for studies in the human is provided; if not there is seldom further inquiry. Studies of this sort always occur after the fact or are a posteriori in nature.

Examples are quite common and drugs currently being discussed are the (1) oral contraceptives and the potential influence that they exert on twin births and the production of congenital defects (heart and limb); (2) drugs of abuse such as morphine and methadone which may produce addiction and withdrawal symptoms in the neonate. It is surprising that virtually no pharmacodynamic studies on the latter question were initiated until 1965 considering that the symptom complex was clinically observed and well documented in 1930.

Another aspect of this overall problem is related to the utilization of over-the-counter medications by pregnant women. It is virtually impossible to establish any meaningful data regarding the potential hazards of such compounds and there appears to be no regulatory requirement necessitating that the potential hazards of such drugs be assessed in pregnant women prior to their utilization. 79,80

b. Agents Used in a Medically Accepted Manner for the Treatment of Maternal Illnesses: The unanticipated effects of compounds employed in the management of intercurrent maternal illnesses during pregnancy provides a major impetus for many investigative studies. Many illustrations of this phenomenon exist and some of the more significant examples are cited below:

Classification	Specific Agent	Reference
Anti-infectives	Antibiotics, Antimalarials	81-85
Hormones	Thyroid, estrogens, progestins, oral contraceptives	85-90
Antineoplastic Immunosuppressive	Ethambutol, cytosine arabinoside 6-MP	91-93
Anticonvulsants	Diphenylhydantoin, phenobarbital	94-96
Drugs of abuse	Morphine, alcohol	97-98
Local anesthetics	Mepivacaine	99-100

### (2) Drugs Administered Parapartum:

- a. Agents Used to Facilitate Delivery: The compounds in this general category (analgesic agents and anesthetics) are probably the only major classification of drugs which have been extensively investigated in the human maternal/placental/fetal unit, at least by primary intent. An important force in this respect appears to be the societal pressures placed upon clinical obstetrics to produce a safe, relatively painless birth by use of drugs which exert minimal influences upon fetal and neonatal viability and development. In consequence thereof, numerous new anesthetic procedures and agents have been extensively investigated in the living human fetus, primarily at the time of parturition (see Table 1).
- C. Nature and Relevance of Information Obtained from Pharmacologic Investigations in the Living Human Fetus. Despite the difficulties encountered in designing studies for the assessment of drug effects in pregnant women and on the fetus, a surprisingly broad range of problems in developmental pharmacology has been investigated. Among the most significant of these are the following:

### (1) Placental Transfer and Fetal Disposition of Drugs:

- a. Data describing which drugs cross the placenta, their relative rates of passage, the amount of drug reaching the fetal circulation after maternal administration, and the influence of modifications in molecular structure upon these parameters has been obtained. The disposition of maternally administered drugs in the fetus has been studied indirectly by analyzing tissues obtained shortly after fetal death.
- b. The relevance and application of these data to the treatment of fetal disease can be identified in many areas:
  - 1. Knowledge regarding placental drug transfer is crucial for the proper selection of antibiotics in the treatment of intrauterine infections of pregnancy.
  - 2. Studies relating molecular configuration, physical chemical properties and placental transfer may allow the development of drugs for use specifically in pregnant women (i.e., agents whose pharmacodynamic effects will be exerted in the maternal organism for treatment of maternal illness with no effects on the fetus). Contrariwise, if the problem involved the maternal/placental/fetal unit, it may be possible to modify drugs so that they are able to enter the fetal circulation and exert appropriate effects therein.
  - 3. The development of fetal drug therapy (e.g., digoxin administration with intrauterine blood transfusions) requires data describing the most efficient way to administer drugs to the fetus. It may be possible to administer drugs to the mother and achieve therapeutically effective blood

levels in the fetus without the potential hazards of intrauterine fetal drug administration. In a similar manner, certain drugs can be instilled into the amniotic fluid compartment to achieve therapeutically effective concentrations in the fetus.

4. Understanding the nature of fetal distribution is important since it determines how much drug will reach a given fetal organ and potentially modify normal physiologic functioning. Fetal blood circulation exerts a major effect on fetal drug metabolism by selectively shunting drugs through the liver (via the ductus venosus) thereby preventing biotransformation by this organ during the initial circulation of the drug.

### (2) Drug Disposition in the Maternal/Placental/Fetal Unit:

- a. The fetal metabolism of drugs has been studied through virtually the entire phylogenetic range of mammals. It is startling to note that the human fetus differs remarkably from the subhuman in that appreciable metabolism of drugs and other xenobiotic agents can be detected within the first trimester of pregnancy. Numerous studies on the metabolism of drugs by fetal tissues (e.g., liver, placenta and kidney) excised from dead fetuses have been carried out in order to confirm these particular characteristics of the human. There is still minimal data describing drug metabolism in the maternal/placental/fetal unit under in vivo conditions, so that at the present time it is difficult to state the physiologic importance of these observations.
- b. The studies on drug metabolism by isolated tissues have particular relevance in that these data suggest the fetal liver has the capacity to form specific toxic products which are known to be noxious to biological tissues. The important question which arises is whether these metabolic by-products are responsible for causing the teratologic effects produced by many drugs. Investigations of drug metabolism in the fetus are also important for the information they provide regarding enzyme induction at different stages in development, with particular emphasis on the role it may play relative to enhancing neonatal survival. Thus, the action of inducing agents (e.g., phenobarbital) or the effects of environmental pollutants (e.g., DDT) upon enzyme systems suggests that some important physiologic processes can be stimulated by exposure of the fetus in utero to specific drugs (e.g., phenobarbital and increased conjugation of bilirubin). The response of the fetus to certain drugs of abuse, such as the addicting analgesics, is important to understand since addiction and withdrawal symptoms have been described in the fetus in ever increasing numbers.

- (3) <u>Drug Effects on Specific Physiologic Processes Unique to the Maternal/</u>
  Placental/Fetal Unit:
  - a. Agents Acting on the Cardiovascular System: The response of the umbilical and placental circulations to a variety of vasoactive drugs has been studied in detail. Many of these agents have been used to inhibit uterine motility, particularly during premature labor, and as such are also able to exert marked effects upon vascular smooth muscle. Data regarding placental blood flow and alterations in oxygen diffusion are crucial if these agents are to be used as standard therapeutic procedures at the time of parturition.

Not only can vasoactive agents modify diffusion and transfer of substrates across the placenta, but if these compounds are able to enter the fetal circulation in effective concentrations, they may significantly alter drug distribution within the fetus itself, perhaps in a manner which may be deleterious to survival. Thus it is important to distinguish the effects of such agents upon the distribution of fetal cardiac output since local alterations in blood flow may exacerbate fetal distress or decrease neonatal survival.

b. Agents Acting on the Endocrine System: The fetus and placenta act in a synergistic manner with regard to endocrine function during gestation. The products produced by this integrated unit are essential for fetal survival, and it is extremely important to identify how these processes may be influenced by drugs. Not only must interrelationships between fetus and placenta be considered, but maternal and fetal interrelationships relative to organs like the thyroid gland and the production of thyroid hormones, the kidney and the production of renin and the adrenal gland and the production of adrenocortical hormones must be considered in response to maternal hormonal changes and any drug therapy the mother may be receiving.

In this regard it is worth noting that treatment of maternal hyperthyroidism with goitrogenic agents may lead to neonatal goiter; administration of insulin to the mother may so lower maternal blood glucose levels as to initiate responses to this hypoglycemic stress on the part of the fetal pancreas and fetal sympathetic nervous system. Also, changes in placental perfusion with alterations in fetal blood volume may cause secretion of renin from the fetal kidney in order to maintain homeostasis. Any pharmacologic agents which modify or alter the processes described above can significantly influence fetal well-being.

D. Alternative Methods for Predicting the Effects of Drugs on the Human Living Fetus. A substantial amount of information regarding the pharmacology of the maternal/placental/fetal unit has been derived from studies on experimental animals, particularly subhuman primates (baboons, monkeys), ovine species (sheep, goat) and rodents (rats, guinea pigs). Quite obviously the selection of an animal species for any given study is dependent upon the problem to be investigated, and this will vary for each particular system under study.

It is extremely difficult to predict whether observations made in a particular animal species will have relevance with regard to the human maternal/placental/fetal unit. Several examples are cited below:

- (1) The fetal distribution of drugs may differ between species. Thus, the tissue localization pattern of diphenylhydantoin in the mouse, rat and human is similar; whereas, that of digoxin differs markedly in the rat in comparison with that observed in the sheep or human where it is virtually the same.
- (2) The matabolism of drugs by the human fetal liver is different from that which occurs in fetal tissue obtained from other mammalian species. In particular it has been shown that many oxidative activities are barely detectable in tissues obtained from fetal or newborn animals, whereas human fetal liver is able to metabolize appropriate drug substrates to a significant extent. Indeed, observations in subhuman species have been misleading with respect to identifying events occurring in the human fetus.
- (3) The study of placental function in the human is obviously best undertaken in that species; wherever this is not feasible some subhuman primates may be acceptable. Ironically, a large amount of our information on placental function is derived from observations carried out in the sheep and its fetus, which may have very significantly different drug transport characteristics when compared with the human. It is always questionable whether general principles enunciated in such experimental models have validity for the human. For this reason it is imperative that extensive investigations be carried out in order to identify those subhuman models which are most appropriate for predicting a given pharmacologic effect in the human, if models can be found.
- E. <u>Live Virus Vaccines</u>. A few viruses are known to cause disease in the human fetus. One of these is rubella (German measles) for which an attenuated live vaccine was recently developed. Studies were designed to learn whether the vaccine virus would invade the fetus after negative answer to that question in monkeys. Women who requested abortion were asked to accept vaccination and to postpone abortion for 3-4weeks. In one study two previously immune women declined abortion after the vaccination. These studies have shown that the vaccine virus can infect the fetus. A similar study has been done with attenuated mumps virus; abortion was 7-10 days after vaccination and virus was recovered from the placenta but not the fetus. These studies have emphasized the dangers of attenuated virus vaccines for pregnant women.
- F. Therapeutic Abortion. Efforts to develop new methods or agents to terminate pregnancy have been oriented toward maternal safety. We have found no evidence that these studies concern themselves with fetal considerations. The recent development of the prostaglandins as midtrimester abortifacients has produced a method which is less destructive to the fetus than the previously used saline injections. This was fortuitous, however; maternal safety was the major impetus.

### Area Four: Research With the Previable Fetus Outside the Uterus

An immediate problem that arises in analyzing extrauterine research on previable infants concerns the definitions of living and dead fetuses. Distinctions must be drawn between organism death, organ death, tissue death, and cellular death. The vast majority of reported research on the extrauterine previable fetus involves fetuses which are clearly dead as organisms, be the criteria cardiac, respiratory, or brain death. There are many therapeutic and research uses for tissues from dead fetuses. After death of the whole fetus, many tissues continue to live for a considerable period of time. They are used for tissue and cell culture, for transplantation into defective living persons, and for studies of metabolic and cellular function. Tissue cultures from human fetuses have become indispensible for the growth of certain human viruses and the development of viral vaccines. The dead fetus is also used in completing studies that have commenced while the fetus was still alive in utero. Thus, pharmacologic studies investigating placental transfer of a drug or distribution of a drug in fetal tissues require recovery of the fetus after it has been delivered. Similar requirements have been present to learn whether a virus has infected a fetus before delivery.

Research on fetuses outside of the uterus that have signs of life may be classified according to the degree of intervention with the fetus. For example:

- (1) <u>Chart Research</u>. This would be the least hazardous research on previable, living infants, consisting of retrospective analysis of data already recorded for other purposes, such as anthropometric data, malformations noted while still alive presence and duration of signs of life.
- (2) Observation Research. Prospective studies may involve only looking or measuring. This would include pure inspection, without altering the infant's environment for the purposes of study. Slightly more intervention would include mild manipulation, such as occurs to collect anthropometric data. Monitoring with instruments such as EEG, X-rays, radioisotope scans, would involve further manipulation.
- (3) Collection of Body Fluids and Tissue. These would range from simple samples such as urine, hair, fingernails, to blood samples obtained by fingerstick or venepuncture, to secretions from nasopharynx, trachea or stomach, to cerebro-spinal fluid. Tissue collection might include biopsies, such as skin or brain, or removal of whole organs.

Research on the previable fetus is often done with protocols which are also being applied to a viable fetus or premature infant. At the time of the research it is not known whether the fetus has the potential to achieve independent life. Thus, many of the therapeutic modalities and research efforts of modern neonatology that have been applied to the premature infant have also been applied to larger previable fetuses. With these fetuses, there is no clear distinction

between fetal research and neonatal research. The research is meant to be either beneficial to the subject or is a minimal intervention that would not limit the opportunity for the subject to achieve viability.

Research with living previable fetuses outside of the uterus has not been extensively reported in the medical literature. The studies listed below represent all those found in reviewing the more than 3,000 citations in the literature research.

- (1) Studies in other species and in adult humans had indicated that the brain could utilize other substrates than glucose for fuel. Also, ketone bodies appear in the mother's blood stream and in amniotic fluid during starvation. To learn whether the human fetal brain could metabolize ketone bodies, brain metabolism was isolated in 8 human fetuses (12-17weeks' gestation) after hysterotomy abortion by perfusing the isolated head (the head was separated from the rest of the body). The study demonstrated that, similar to other species, brain metabolism could be supported by ketone bodies during fetal life suggesting avenues of therapy in some fetal disease states. 104
- (2) Endocrine functions of the placenta and fetus combine to support the maintenance of a pregnancy and the growth and maturation of the fetus. To study the fetal endocrine system, arginine (an amino acid) was injected into a blood vessel in the neck of 8 human fetuses (450-600 grams) while the umbilical cord and placenta were still attached to the uterus. Blood samples were taken from the umbilical cord to yield information about fetal endocrine regulation.<sup>105</sup>
- (3) Another technique for studying the ability of the midtrimester fetus to carry out endocrine reactions used 4 fetuses (16-20 weeks' gestation) immediately after hysterotomy abortion. The fetuses were perfused through their umbilical veins while being housed in a perfusion tank. Fetal tissues were examined at the end of the study. The study showed that the fetus alone, independent of the placenta, could snythesize estriol, an important compound in assessing fetal and placental health in later pregnancy.<sup>106</sup>
- (4) Amino acid levels are low in malnourished children and adults. To learn if this were true in newborns that had been malnourished in utero, blood samples from a peripheral vein were taken to measure amino acid concentrations. This study was done in infants, most of whom were older than 28 weeks' gestation so that only a few were likely previable. 107
- (5) Another study that represents neonatal research more than research on the previable fetus used the umbilical vein to measure total body water (bromide space) in low birth-weightnewborns. This study also suggested that changes in prenatal malnutrition were similar to those in postnatal malnutrition.<sup>108</sup>

- (6) Some studies which use umbilical cord blood are completely noninvasive for the newborn (previable fetus or viable premature infant). One such study measured hemoglobin in cord blood to learn if there was a correlation with maturity.<sup>109</sup>

  A few studies with the previable fetus have made attempts to support life in novel ways that might eventually allow similar fetuses to achieve viability or might be methods for treating premature infants with otherwise fatal respiratory distress syndrome. These studies are part of attempts to develop an artificial placenta. The life of the previable fetus was pro-
- (7) After studies with newborn and fetal mice, cutaneous respiration (breathing through the skin) was studied in 15 fetuses (9-24weeks' gestation) from induced abortions. The fetuses were immersed in a salt solution with oxygen at high pressure. The fetuses were judged to be alive by a pulsating cord or visible heart beat; if necessary the chest was opened to observe the heart. Four fetuses were supported for 22 hours in this attempt at developing a fetal incubator.<sup>110</sup>

longed (death was delayed) in some instances.

- (8) Seven previable fetuses (200-375 grams) from spontaneous or induced abortions were immersed in a perfusion tank and perfused with oxygenated blood through their umbilical vessels. The fetuses survived and moved for 5-12 hours.
- (9) After considerable work with rabbits, a similar experiment was done with perfused, oxygenated blood with 8 fetuses (300-980 grams) after hysterotomy abortion. If perfusion was stopped early, the fetus could live only about 20 minutes; continuous perfusion enabled maximum survival of 5.1 hours.<sup>112</sup>
- (10) Following opening of the uterus for hysterotomy abortion, a segment of umbilical cord was exteriorized and blood samples were obtained from it for 10-15 minutes. Studies were attempted in 38 cases, at 14-23weeks' gestational age. The study provided a model for obtaining data from the human midtrimester fetus without additional hazard to the mother.<sup>113</sup>
- (11) Labeled noradrenaline was injected into either the umbilical vein or jugular vein of the fetus while the placental circulation was kept intact for 15 minutes. Metabolites were assayed in various fetal tissues following completion of the abortion. The study demonstrated activity of the fetal sympathetic nervous system early in gestation. In a similar study, radiolabeled testosterone and testosterone sulphate were injected into a 15 week and a 16 week fetus during hysterotomy abortion. The products of conception were removed 15 minutes later, and metabolites analyzed in tissues of the dead fetus to study fetal hormone synthesis and metabolism.

- (12) In a study to develop methodology for research in fetal physiology, intact fetoplacental units at 15-19 weeks' gestation were transported to the laboratory, immersed in artificial amniotic fluid, and perfused via an umbilical catheter. 116
- (13) Ten fetuses of 20-24 weeks' gestation had carotid artery cannulations following hysterotomy abortion to study the relationships between growth hormone, plasma glucose, and stress in the fetus or premature infant.<sup>117</sup>
- (14) Six fetuses (16-20 weeks' gestation) were perfused via the umbilical vein immediately following hysterotomy abortion. Studies following injection of labeled progesterone showed that the fetus could utilize progesterone for male steroid hormone manufacture. 118

The above experiments with previable fetuses were all extending previous animal work to the human situation. The experiments vary widely in invasiveness for the fetus. When the fetus was clearly previable, the research was not beneficial for that subject but was seeking information that could be of benefit to other fetuses.

# SUMMARY OF LITERATURE REVIEW

Our literature review has revealed extensive research in fetal medicine from all parts of the world during the past ten years. Several thousand reports have been published in that period. A large percentage of this effort has been directed at identifying the threatened fetus in utero, especially in later pregnancy and during labor, and devising methods to successfully manage fetal problems. There have been major changes in obstetric practice which involve monitoring of the fetus and concomitantly a significant decrease in perinatal mortality. In recent years there has been increasing attention to the fetus earlier in gestation with major efforts being made to evaluate maturity (expecially lung maturity) and readiness for extrauterine life and to diagnose fetal abnormalities and disease. Diagnostic capabilities, most notably through the use of amniocentesis and ultrasonography, have progressed rapidly. Therapeutic possibilities are just beginning to be developed. One major consequence of increasingly sophisticated fetal diagnosis has been decision making in midpregnancy resulting in selective abortion of fetuses with various abnormalities.

For the most part, knowledge that has resulted in improved diagnosis and therapy for the fetus has been developed in continuing human pregnancies where there has been beneficial intent toward the fetus. There have also been observations in parallel on normal pregnancies. When diagnostic or therapeutic interventions have been made, such as amniocentesis or fetal transfusion, opportunities have been recognized for obtaining unrelated data at minimal risk to

that fetus or mother. These are attempts to benefit a larger class of fetuses. When attention has been given to the midtrimester fetus, investigations have often involved the fetus or fetal materials (e.g., amniotic fluid) in the setting of induced abortion.

Investigation of normal human development has generally used observational, noninvasive methods in the past; much of the work has been anatomic definition. The expanding interest in the human fetus at present has brought an effort to gather physiologic, biochemical and pharmacologic data. This has resulted in increased use of living fetuses close to delivery either at term or at the time of abortion. Many times these studies are nonbeneficial for the fetal subject involved and instead seek data to aid future fetuses. With occasional exception, these studies have not put the fetus at increased risk nor prolonged the delivery or abortion process. There is often the necessity to complete the experiment after delivery by obtaining fluid or tissue samples from the placenta, newborn or abortus. The most active areas of experimentation have been in endocrine studies of the placenta and fetus and in drug metabolism and disposal.

Animal experimentation has usually preceded human experimentation. In some areas this has been extensive and in others only exploratory. Many investigators emphasize the need to establish the appropriateness of an animal model to the questions being asked and note major differences in the animal and human pregnancy in some areas. There has been increasing recognition of the need for primates and increasing use of them in fetal research. A problem has also been voiced about the huge costs of primate research and the impact on the world population of these animals should they be extensively utilized.

Fetal tissues are being used more and more in other medical areas including virology, cancer research and transplantation therapy. The needs of these disciplines require tissues from recently dead fetuses and haven't strictly involved research with live fetuses. The definition of death has been an important issue, however, and fetuses from induced abortions have been extensively used.

There is very little research at present with living, previable fetuses outside of the uterus. Some metabolic and pharmacologic studies have been done and a few of these have involved prolonging the life of the fetus. There have also been a few studies aimed at incubating the fetus outside of the uterus. Since results have been discouraging and technology seems still to be primitive, almost no experimentation is currently being done.

Interest in behavioral and psychologic development of the fetus has increased recently with recognition that sensory perception and other integrated nervous system function can be studied during fetal life. Experiments have utilized non-invasive monitoring techniques such as sonography, electrocardiography or electroencephalography with either naturally occurring or experimentally applied stimuli. Data are being developed in normal pregnancies and in pregnancies being studied for other reasons.

Until very recently there has been almost no mention of legal or ethical considerations when reporting fetal research in the medical literature. In the last few years most reports have stated the legal sanctions for induced abortion if aborted fetuses have been used and in the past year or two there are often statements about informed consent. Except in articles discussing ethical issues there has rarely been any ethical analysis of the experimental procedure.

#### CURRENT RESEARCH DIRECTIONS

We attempted to assess current activity in fetal research in two ways. First, we requested by mail a brief summary of any ongoing or imminent fetal research projects from each Department of Obstetrics and Department of Pediatrics in medical schools in the United States and Canada. Our second approach was to survey grant applications to the National Institutes of Health for the period 1971-1974.

Forty replies were received describing fetal research projects currently in progress or planned.<sup>119</sup> Twelve letters noted that fetal research at their institution had been halted because of an uncertain legal status at both national and local levels. In most instances, discontinued research had not been proscribed by federal law (Public Law 93-348). In addition to the 40 replies that described research, 26 other letters stated that no research was in progress and made no comment about any future plans.

In the four year period of NIH grant review, 48 applications were made for research with live fetuses, 41 were approved by Study Section, and 36 were funded. There were also 4 contracts involving the living fetus in the years 1973-74. Over 100 additional grant applications dealt with research with the dead fetus or with fetal tissues.

Current and proposed research with living fetuses mirrored the kinds of experiments cited in the literature review except there were very few proposals addressing the previable fetus outside the uterus. Many studies would obtain amniotic fluid for analysis of various constituents and for use of cells in tissue culture. Diagnostic questions were being addressed along with attempts to find greater expression of the fetal genome in the cells. Monitoring studies involved electrocardiography, ultrasound including transmitter-receivers at the cervix to follow labor, scalp blood sampling, and use of computers. Studies of placental transfer of drugs with recovery in aborted fetuses and of drug metabolism in fetal tissues were proposed. Tissues for transplantation and for organ culture were desired.

Fetoscopy, fetal blood sampling, and diagnosis of hemoglobin disorders were proposed and the effect of fetoscopy on uterine blood flow and contractility were to be examined. Steroid and other hormone metabolism would be examined in body fluids of mothers, in placentas, in anencephalic fetuses, and in tissues of aborted fetuses. Determination of effect on the fetal heart rate of mild steady state exercise, mild hypoxia, and anxiety in the mother was proposed.

Malnourished women would receive a food supplement and be contrasted with a control group as to effects on the fetus. Women with sickle hemoglobinopathies would be transfused and careful fetal monitoring carried out to try to improve reproductive performance.

The direction of fetal research continues to want to expand diagnostic capabilities, define normal metabolic parameters for pregnancy and the fetus and fetal tissues, and monitor fetuses for problems that can be identified and treated.

# ETHICAL CONSIDERATIONS IN FETAL RESEARCH

1. <u>Introduction</u>. We regard the human fetus as part of the human community and as such believe that the fetus should legitimately benefit from the main goals of the medical profession, i.e., the optimizing of human potential for a full and healthy life, the prevention of disease and deformity, the return of the diseased human being to a healthy state, and the minimizing of suffering. The recognition of the legitimacy of the fetus as a patient requires of the medical profession attempts to learn how to fulfill these goals. This requires that the human fetus participate in research whose aim is the accomplishment of those purposes. As with any other class of research subjects, it is paramount that safeguards be secured which insure that adequate experimental work has been performed in other systems where applicable, that risks to the research subjects be acceptably low, that the information sought by the research be deemed significant by the biomedical community, and that legal and ethical norms of our society be central to the design and execution of experimentation.

It is evident that large numbers of fetuses do not enjoy an optimum intrauterine life and start extrauterine life with diminished potential. Many fetuses succumb during intrauterine life or are born diseased and require extensive therapy which, by that late date, may be ameliorative only. Estimates suggest that 25 percent of fetuses die in utero and another 2 percent die at the time of birth or in the first week of life. About 3 percent of all live born infants have a serious disorder diagnosable at the time of birth apart from problems of prematurity. Fetal disease and disorders provide a massive medical problem and one which must be addressed by an ethical profession. Abandonment of the fetal patient is clearly unethical and abhorent to the profession. Prevention or correction of disease during fetal or neonatal life, prevention of death at that period in life, and providing an environment conducive to optimum development are benefits for that human individual which extend over the entire lifetime, a potential of seventy or more years. The child and infant for many decades did not benefit proportionately with adults from advances made in medical science. Energies and monies expended for the control of medical problems during childhood have historically been much lower than those expended for the problems of the adult population. The fetus is even more vulnerable in this regard. child, the infant, and the fetus are not capable of sounding their own advocacy and must depend upon other members of the human community. The concept that the fetus is a therapeutic orphan has substantial validity when one considers the proportion of the biomedical research effort extended for the fetus and contrasts that with efforts made at controlling diseases of the adult population. that the diseases of adulthood and aging continue to receive wide popular support from a political constituency that views these diseases as more immediate threats than it views diseases of the fetus. This situation continues even though evidence is accumulating that fetal research, including the understanding of growth processes and of fetal diseases, may play a key role in solving problems of adultonset diseases. But even considering the fetus alone, we believe that progress in curtailing and preventing diseases of fetal onset should have high priority and will result in great benefit both to the individuals and to the collective society. We further believe that fetuses and neonates, as classes of human beings, have the same right to benefit from medical progress as do other groups in our community.

- The Viable Infant. Any viable live-born infant should receive the best possible medical care including experimental therapies performed under appropriate safequards. This is a first responsibility of the medical profession and of the community. To stay on the safe side of this duty, any possibly viable live-born subject should be included in this class. At the present time this might include all subjects over twenty weeks' gestational age or over 500 grams. Viability is primarily a statement about technology, not about the fetus. Thus a statement about viability is a relative statement and must be reassessed periodically. We believe that this reassessment should be made at annual or biannual intervals. In this view, viability cannot be equated with personhood, but can only be the basis for practical line drawing at a particular moment and place. The most important reason for drawing such a line as it applies to human experimentation is the desire to avoid an injury to a fetus that will survive. To avoid this possibility, a definition of viability should be drawn below the lower limit of possible viability at a given time. We believe that the viable infant, even though born very early in gestation, is conceptually no different than the full-term newborn infant and that considerations of research with these human subjects requires the same regulations as applied for the protection of infants and children.
- 3. The Deceased Fetus. We consider that the fetus which is clearly dead after delivery should be viewed as any other dead human being. Legal regulations and ethical constraints on the handling of the deceased human being should be applicable to the dead fetus. These should permit removal of still living tissues or organs for biomedical research and therapy functions. Examples would include the carrying out of planned experimentation to learn about fetal metabolism, physiology, or disease; beneficial therapy for other human beings like transplantation of fetal organs, and the teaching of health professionals who must be the guarantors of continued care and progress in fetal medicine for the future. For some studies, such as examination of brain ultrastructure and metabolism, the transplantation of some tissues, or possibly the recovery of very fastidious viruses, access to tissues would be required very soon after death.

This means that the definition of death becomes important and we suggest that this definition focus on the whole organism. We further believe that the use of the dead human fetus for any of the above cited purposes must be contingent upon consent of the person who retains legal responsibility for the deceased fetus. In almost all circumstances this would be the mother or both parents. We do not believe that the deceased fetus should be viewed differently if from a spontaneous abortion rather than an induced abortion and we know of no evidence to suggest that use of tissues from deceased fetuses increases requests for abortion.

4. <u>Informed Consent and the Mother</u>. Problems of informed consent are central to the current societal debate about all kinds of human experimentation and we do not propose to comment extensively on problems dealing with the consenting adult. When a mother is a coparticipant in fetal research, such as when an abortion is contemplated, her clinical needs must continue to have primary consideration. Thus the timing and method of abortion should not be altered in a way that would place the mother at significantly increased risk for the purpose of experimental design. We do believe however, that the pregnant woman, who has received adequate information, should retain the option and be free to participate in approved research; at times this could include an alternate method of clinical care.

Considerable controversy exists about the relationship of an investigator who does fetal research and a mother who may elect or has elected abortion. It is obvious that investigators cannot be influencing women to decide whether to have an abortion. After a decision to abort a pregnancy has been made, the investigator should have a close relationship to the mother if the investigation will start either before or during the abortion procedure. The mother needs to know the investigator and she must feel that the investigator will be continually cognizant of and responsive to her interests. The participation of another person as intermediary may at times be desirable but at other times unnecessary.

Informed Consent and the Fetus. We believe that the human fetus is a legitimate participant in the human community. The human being is a social species. A social contract is entered into by the members of the species for their own protection and for the benefits of collective action to enable a more satisfactory life for all members of the community. This social contract has definite limits in our society and does not include the acceptance of undue risk or any mandate to self sacrifice. It does include a mandate for cooperative behavior for the benefit of other members of the community and this includes, most importantly, the preservation of basic human individual rights. It seems evident in observing adult members of our community that actions are often taken for the purpose of benefiting other members of the community. Thus we see consenting adults freely participating in medical research which has no immediate benefit to that person. This is done by healthy individuals and also by individuals who recognize that their death is imminent. The important consideration in participation by these individuals is that they have the ability to consent to their own participation. Consent by the fetus is an impossibility. Nonetheless we believe that it is reasonable to view the fetal members of the human community in this regard similarly as adult members. We believe that asking fetal participation for the purpose of advancing medical benefits for the class

of human fetuses under stated circumstances is acceptable and ethical. These circumstances are that the information being sought is important to biomedical advance, that the information cannot be obtained except by the participation of human fetuses, and that the risks involved are acceptably low. We believe that a scientific and ethical review process and an advocate for the individual human fetus should both agree that any proposed research is acceptable. To eliminate the participation of human fetuses from experimentation because they are unable to consent, denies fetuses as a class the right to benefit from medical progress and directly contradicts the presumption that the human fetus is a legitimate participant in the human community.

In our human community all individuals participate in human experimentation without their consent at all times. There are planned and unplanned manipulations of the environment including the addition of large numbers of pollutants, and the application of many types of social and psychologic pressures. Usually, analysis of the effects of such manipulations is retrospective. Nonetheless, we recognize how important planned observation and control of many of these parameters are to prevent harm to those living today. This is just as true for the fetus and for the many fetuses yet to be conceived. Planned experimentation and controlled prospective observation give a much increased likelihood of preventing harm than the often unplanned way of acting. Again, fetuses as a class should legitimately benefit from this type of planned experimentation via the mechanism of proxy consent by an informed advocate.

Relationship to Societal Ethics. Research must be guided by the ethical norms of our society. Over centuries there has been advance in the human's view of his or her fellows; actions which would be regressive in this regard should not proceed. Thus activity which would be viewed as dehumanizing or debasing to our concept of the human individual should be proscribed. We further recognize that in a pluralistic democracy that there must legitimately exist different views of the human individual and the nature of humanness or personhood. We feel that no person should participate or have pressures placed upon him or her to participate in research which violates that person's ethical concepts. We further believe that the view of one segment of our population should not dictate the activities of other large segments of the population as long as fundamental human rights are preserved. We suggest that any given experimentation should receive rigorous review for both scientific and ethical content and that this review be carried out by review boards which are informed about the scientific and ethical issues and which are representative of the community. We believe that primary review should occur locally and that there be options for coordination and analysis of its reviews process at a national level. Scientific and Scientific assessment must consider ethical assessments are equally important. experimental design, the nature of the information desired, risk-benefit analysis, and the use of appropriate alternate means to gain information where applicable. A review board must be assured that this kind of scientific assessment by appropriate competent persons has been carried out. Ethical analysis must be just as rigorous and must heed the community in which experimentation is being done. see a twofold reason for not allowing experimentation which is deemed dehumanizing by a large segment of the community. First, activities of this type may, by a process of slow spread of ideas, undermine the view of the human individual within the scientific and medical communities. We know of no evidence to suggest that such a phenomenon occurs but we agree that a reversal of improved or increased concern for other human beings must be guarded against. Another phenomenon is more easily documented when experiments are carried out that are unacceptable to a community. There results a reaction against the scientific and medical fields such that support of experimentation to enable medical progress is withdrawn. Thus, in this pragmatic sense, experimentation which is offensive on ethical grounds has the effect of decreasing all human experimentation, thereby violating a central ethic of the medical profession to continually seek better methods of prevention and therapy.

The Fetus In Utero. The fetus in utero or in process of being aborted provides a more difficult ethical analysis than does the dead fetus or the living viable infant. There is a presumption of viability at any stage in gestation for the living fetus as long as it remains inside the uterus. Thus experimentation involving that fetus must have acceptably low risk of any harmful effect on viability or on the potential for meaningful, healthy life. If the process of abortion has begun, the life of the fetus will soon end. There is debate about whether different standards apply in that situation and we disagree in our own analysis. One view holds that no risks can be imposed that would not be acceptable for the fetus which was continuing life. Another view will accept an increase in risks if the information is important and alternate ways of obtaining the information are not practical, if the methods of the experiment are acceptable in themselves (i.e., would be used in other classes of human subjects), and if the process of dying for the fetus were not altered in an unacceptable way. event, expected benefits from the experimentation still must be clear and must require the use of the human fetus to gain the desired information. Ethical considerations as to sensory perception by the fetus also must be addressed. know of no evidence to suggest or support a contention that the fetus at midgestation or earlier, when abortions are performed, is aware of pain or has a psychologic fear of death. We would prefer seeking such information rather than assuming or ascribing these anthropomorphic parameters of later life to this early stage of human development when the central nervous system is relatively primitive. We do not believe that the fetus which will die by elective abortion or is in the process of dying should be automatically excluded from experimenta-Imminent death does not automatically exclude participation of children or adults from medical research. Assessment of an individual research protocol must still look at the nature of the information sought, the necessity of using this group of human subjects, and an analysis of whether there was any increase in suffering entailed by the dying subject. Experimentation in anticipation of abortion or in process of abortion should not be categorically prohibited but again should be assessed in terms of risk to the fetus as well as risk to the mother. With regard to experimentation which starts before abortion starts, we note that there are many procedures of minimal risk that can be applied to the intact pregnancy which could yield important information by examination of an aborted fetus at a somewhat later time. These procedures are noninvasive or minimally invasive such as the use of sound waves to obtain fetal measurements for correlation with the abortus or administration of a drug or chemical in trace amounts, perhaps tagged with a nonradioactive isotope like carbon 13. be important that risk to the fetus were very small, so that if the fetus should survive to viability, there would be little likelihood that it would have been Careful assessment of the individual research protocol should be the paramount activity rather than categorical prohibition.

- 8. The Living Previable Fetus. Experimentation with the living previable subject outside of the uterus falls into two classes. In the first there are efforts to replace the many functions of the maternal placenta with artificial alternatives. If this research is meant to be beneficial to a class of fetuses which cannot survive outside of the uterus at the present time, appropriate work must have been done in other species, and careful risk analysis should precede application of the new technologies to the human fetus. The other class of research with the previable fetus is research which is not beneficial to that particular subject although it would be expected to be beneficial to other fetuses. In this instance it appears paramount to avoid the possibility of the fetus surviving with an injury derived from a nonbeneficial experiment. If one views the fetus as being nonviable as a consequence of the inadequacy of technology rather than a statement about the lack of personhood in the fetus, then the previable fetus can be seen as comparable to an adult with a disease or physiologic derangement which renders that person unable to continue life because a technological solution to the problem does not exist. The impending death of the adult would not deprive that person of certain protections as a possible experimental subject nor would it exclude the individual as a possible subject. The patient would presumably consent, or an advocate would consent, only to those procedures which sought important information, unobtainable in any other way, with minimal risk. These same guidelines should be applied to the previable fetus outside of the uterus.
- 9. Parental Rights. In considering the ethics of fetal research, the rights and expectations of currently living adults must also be recognized. Today there is a major concern about restricting the human population of the world and of conserving natural resources. With attempts to restrict the quantity of human beings born there is a natural wish to maximize the potential that each human being has at the time of birth. Thus, the quality of each child is a major and legitimate concern of each individual parent. Parents have historically been given the right of advocacy for their children and this continues to be the most likely group to best protect the interests of the child, born or unborn. We believe that parents should be allowed to participate in medical research for the benefit of their own offspring and of future offspring and to have their children, both born and unborn, participate when the risks are acceptably small and the information sought deemed important. Fetal research has been of great benefit to many families desiring to have normal children and can be of continued great benefit in providing normal children to future families. The government through its tax structure and its involvement in the economy already excercises considerable pressure upon the reproductive decisions of individuals in this country. It should even more be the government's role to continue to support research which will give options for reproductive decisions that have a better and better likelihood of resulting in normal children.
- 10. Induced Abortion and Consent. The consent process by which fetuses participate in research has aroused most controversy when considering research involving a subject before, during, or after elective abortion. In other circumstances it would seem that the mother or parents are the most likely to protect the interests of their fetus. In the setting of elective abortion, the mother has rejected the possibility of life for her fetus and many persons have questioned whether she any longer can represent the interests of the fetus. It

is possible, however, that the mother may continue to be the best advocate even in the setting of elective abortion. It is our experience that the mother continues to consider the welfare of her fetus during abortion and afterward. At least it would seem that should she have objection to participation of her fetus in an experimental protocol, that the fetus would not participate. Another source of advocacy for the fetus does exist. This is the review process that assesses the acceptability of the research. When the research is deemed acceptable for a class of fetuses, then the problem of consent for an individual fetus must be faced. A variety of procedures for selecting an advocate in addition to the mother could be proposed.

11. Regulation of Fetal Research. There is concern about the difficulty of substantive policy achieving an acceptable degree of ethical "rightness" when it results from a process which is so layered over with political, personal, religious and other conflicting pressures.

The previous method of protecting the rights of human subjects in this society has been through procedural safeguards rather than policy on discrete issues of substance. While such procedural safeguards have had a short history, and were preceded in this country by a long era of episodes which would now be considered unethical experimentation, our review of fetal research suggests that the system has worked well and that the number of ethically questionable studies is a miniscule part of the whole. Even in those few instances, the projects have been discontinued in this country.

If this analysis is accurate, there would be considerable advantage to a policy which required a vigorous review process, coupled with mechanism and resources for exposure and broad discussion of controversial issues. Such a policy would be more flexible and adaptable to the rapid changes in this field, and would reduce the dangers of a policy resulting from political pressures rather than reasoned ethical consideration of all relevant data.

For these reasons, it is the recommendation of this study group that the final policy recommended by the Commission be one which includes an ample exposition of the many legal, ethical, and medical issues but which mandates only a vigorous review process rather than specific restrictions.

# CONSEQUENCES OF RESTRICTING RESEARCH

The impact on biomedical advance of restricting fetal research is very difficult to predict and, by nature, must be speculative. Our literature review suggests that almost all advances utilizing extrauterine fetal subjects have been based on research using clearly dead fetuses, or research with therapeutic intent for the fetal subject. Advances which depended upon intrauterine fetal subjects in most instances were made with minimally invasive techniques and low risk to the fetus. Many of these advances could not have been made, however, had there been a categorical ban in given areas of fetal research. The following suggests some of the costs that would ensue should fetal research of various types be banned in the future.

1. <u>Dead Fetus</u>. The deceased fetus after delivery has been and can remain a very important contributor of living tissues or organs for both research and therapy. This requires use of a fetus which is only recently dead. Tissue cultures have been used in the growing of human viruses and the development of vaccines to protect against these viruses. Restriction of this source of material would significantly impede progress in understanding the biology of viral infection and in developing preventive therapy. Certain human viruses can be cultured only with the use of human tissues and for some of them only with the use of human fetal tissues. This may be true of several neuropathic viruses. Another problem in developing vaccines is the presence of animal viruses in the tissues from nonhuman species. The potential harm of these viruses to human beings is not known but currently there is significant concern about possible effects on both investigators and on producers and recipients of viral vaccines when the vaccine viruses are grown in nonhuman tissues.

Understanding the regulation of growth and its relationship to the neoplastic, cancerous process and to the aging process may depend upon the use of human fetal tissues in culture. This may especially be true in investigating the hypothesized link of human viruses with human cancer. Currently there is considerable investigation of the relationship between antigens in placental and embryonic-fetal tissues and those in neoplastic tissues; this work depends on tissues from dead fetuses.

A promising avenue of treating individuals who have a genetic defect in one of their body organs is the transplantation of fetal tissues to that individual. Fetal tissues often incite less of an immune response and are less likely to react against the recipient than are child or adult tissues. Fetal thymus, liver and bone marrow have been used for this purpose successfully and consideration has been given to the use of other fetal endocrine glands. Should tissues or organs not be available from the recently deceased fetus, this avenue of therapeutic approach to diseased persons would be unavailable. Animal tissues would probably be unacceptable because of major immunologic problems.

Tissues and organs from the deceased fetus will be important in defining the developmental biochemistry and metabolism of the fetus in order to understand disease states. In turn this knowledge will form the basis of projected therapies aimed at overcoming the effects of genetic disease in the fetus and of overcoming or preventing the effects of malnutrition on the fetus. For most purposes where still living fetal tissues from a deceased fetus can be used for tissue culture, transplantation, or biochemical studies, tissues from an induced abortion would be more satisfactory than those from a spontaneous abortion. Tissues from a spontaneous abortion are often of only marginal viability and planning for the tissues usually cannot be done.

2. <u>Fetus In Utero</u>. In order to diagnose and treat diseases of the fetus and in order to understand the fetal environment so as to maintain it in an optimal condition, the human fetus, alive within the uterus, must participate in the research, at least at the final stages. To categorically deny research with the living fetus in utero simultaneously denies the fetus the benefit of research that will allow birth in a healthy condition and denies parents the possibility of selecting normal intact children rather than diseased children. With the presumption that the living fetus at any stage during gestation has the potential for viability, important considerations in deciding about a given

research protocol are not whether the fetus at a given age is previable or viable but rather the importance of the information sought, the necessity to seek it in the proposed manner, and the risk to which the fetus is placed. Research which is nonbeneficial for the fetus in question may lead to benefits for the large class of fetuses which can then be defined as either normal or abnormal. This is just as true during fetal life as it is for children or adults. Description of the normal situation and the range of normal variability must precede the definition of abnormal and therefore the ability to diagnose the abnormal state. Likewise the ability to diagnose the abnormal precedes attempts at preventive or curative therapy. Thus a ban on nonbeneficial research would preclude knowing how to define the normal versus the abnormal fetus and further how to prevent or treat abnormalities. This would close the door to further advances in diagnosing many more diseases during fetal life that have genetic or environmental origins. Some of these diseases may not be correctable or treatable in any significant sense and thus failure to develop ways to diagnose them will negate giving prospective parents an option of having normal rather than diseased offspring. For other diseases there is already real hope of developing in utero therapies. 42 Major disease problems of the fetus which are a consequence of maternal and placental abnormalities and which result in malnourished and poorly grown fetuses or death of the fetus in utero likewise would be more difficult to solve should nonbeneficial research be proscribed with the fetus in utero.

Understanding development of the fetal nervous system and behavior of the fetus will require studying the human fetus in utero after initial information is learned in animals. Swallowing, breathing, response to sound, and response to touch are known to develop well before full term gestation. Studies in monkeys suggest that the fetus is quickly affected, perhaps in a negative way via asphyxia, when acute anxiety occurs in the mother. To further this knowledge, which would then serve as the basis of diagnosis and treatment of the fetus and lead to management of pregnancies in an optimal way for fetal development, will depend on nonbeneficial research with some fetuses in utero.

Research on fetuses whose lives are about to be ended by elective abortion involves a special class of potential research subjects. In these subjects it is possible to carry out research procedures that will give information about the fetus at that stage of gestation which is largely unavailable if the fetus continues in utero. The current development of instrumentation to view the fetus and sample the fetal blood stream or otherwise obtain a tiny sample of fetal tissue has made use of fetal subjects about to be aborted or in the process of abortion. After animal experimentation had indicated the feasibility of such approaches but not at all the possible problems to be anticipated in the human situation, it was necessary to utilize human pregnancies to test out the ideas and the instrumentation. The techniques give major hopes of diagnosing a wide range of fetal disease, of monitoring the progress or adequacy of treating a diseased fetus, and of defining normal and abnormal while the fetus is living, before death occurs in the process of abortion. Although this technique is now entering the stage of clinical trial, its further development and development of similar technologies can be done most safely if fetuses who are being aborted are the first to participate in the new research. A ban on this kind of research forces the development of new technology in fetuses where the intent is to maintain viability and carry the fetus to the end of gestation. Should

there be unrecognized or unknown risks associated with the procedure, they will be discovered from this group of fetuses rather than from a group of fetuses who will not live to grow into children and adults.

Placing a ban on research which started before an abortion process started would also prohibit the gaining of significant information about the fetus in its normal environment. Techniques which are noninvasive or which are invasive with very low, if any, risk exist at the present time and are being developed further. These include amniocentesis, the use of sound waves, the use of nonradioactive isotopes such as carbon 13 or tracer amounts of radioactive isotopes, and the monitoring of fetal movements or electrical activity from outside of the uterus. Such techniques could be used in anticipation of abortion without any significant risk to the fetus. If abortion were never carried out, the fetus would not have suffered any problem and the only loss would be the research data. The important consideration in this type of research is the risk to which the fetus is to be placed by the research being planned.

The field of fetal pharmacology is one of the most crucial areas requiring research with the living fetus in utero and with the fetus that will be or is being aborted. Recent reviews in the United Kingdom and the United States document that during pregnancy women take, on average, six pharmacologic agents. 30 In addition, dietary manipulations are often carried out during pregnancy. effects of this enormous amount of drug therapy, some physician-prescribed and some self-prescribed, on a developing fetus are almost entirely unknown. In a very real sense the human fetus is incubated in a sea of drugs. We know very little about the effect of these drugs on the human fetus or the distribution within the human fetus. Drugs may distribute differently in lean (e.g., malnourished) fetuses than in obese (e.g., diabetic) fetuses due to the respective lipid solubilities of each drug. Drugs may concentrate in different tissues depending upon the time and gestation at which studies are carried out and upon the nature of the fetal circulation at that point in gestation. Consequently, different pharmacodynamic effects may be manifest at discrete points in gestation making it essential to study tissues obtained over a broad time spectrum. Unanticipated accumulation of drugs within its environment may have significant teratogenic effects on a given fetal organ. Thus, for intelligent information about drug effects in the fetus, one requires detailed information about the pharmacokinetics of drug transfer across the placenta and into various parts of the fetus, and one requires detailed information on the disposition of the drug both anatomically and metabolically within the fetus. The use of fetoscopy to obtain a small blood sample immediately before abortion would enable investigators to study the transfer of the drug from the maternal circulation to the fetal circulation. The use of aborted fetuses would enable the determination of where drugs go within the fetus and what happens to them in different parts of the fetus. When in utero treatment of a fetus is being tried, sampling of amniotic fluid or fetal tissue may be necessary to know if the therapy is of any use. term, the study of the transfer of pharmacologic agents to the fetus and the concentration of drugs reached in the fetal circulation can be done by giving agents just before the induction of labor or during labor and then measuring concentrations of drugs in the newborn infant. Continued development of fetal monitoring to make labor as safe as possible for the fetus will also require investigation of the fetus at this final stage of pregnancy.

Important areas of obstetric research with primary relationship to the mother also require involvement of the fetus in the research. An active area of research has been the development of effective analgesics and anesthetics to be used during labor which are also safe for the fetus and neonate. Studies related to improving methods of inducing abortion, such as the development of new chemical compounds to enhance the safety of abortion, would be inhibited if there was a ban on research which involved the living fetus in utero. Research seeking ways of inhibiting premature labor simultaneously involves the living fetus. This research is necessary if obstetricians are to enable the fetus to remain inside the uterus, where it can most safely grow, rather than being born prematurely to the many dangers of extrauterine life.

For many of the studies mentioned above, the aborted fetus from a spontaneous abortion does not provide an adequate research model. For some purposes, e.g., a drug transfer study, the research must start at some interval before abortion starts. The abortion process itself is very unpredictable; the time at which the fetus dies is not known and in a spontaneous abortion may have predated the onset of the abortion by days or even weeks. Ofttimes the fetus after spontaneous abortion, because of a long period of in utero death, provides limited information about biochemical or metabolic activity or the distribution of chemicals within various fetal tissues.

3. The Previable Fetus Outside the Uterus. One major area of research with the extrauterine previable fetus in the future will probably be aimed at supporting life of the fetus in ways significantly different than those used today until the fetus is large enough to be sustained in a more conventional premature nursery. These research attempts will be toward the development of placental functions whereby gas exchange and delivery of nutrients are carried out artificially outside of the uterus. Extensive development and success in other animal species would necessarily precede attempts in the human. Initial human studies will likely be done in seriously ill viable premature infants. At some stage, if these advances are to be made, there will be application of the methods to what, at the time, would be termed a previable fetus. A ban on this type of research might preclude the opportunity of life for this group of human patients in the future.

A second major class of experimentation with the previable fetus outside the uterus is research which would establish metabolic, physiologic, or psychologic parameters at that stage of human life. For example, the study of brain electrical activity at a certain fetal age could be carried out outside of the uterus, or a study of sense organ maturity with the purpose of knowing whether light or sound energy had the potential of harming a sense organ at the same stage in utero might be learned from the extrauterine fetus before death. The safety of new diagnostic or therapeutic techniques that are to be applied to the fetus in utero in some instances could be answered in part by investigations in the previable fetus outside of the uterus. These studies would not be beneficial to the given fetal subject, but could be to many other fetuses.

There would seem to be little difference in the information obtainable from a previable fetus which was the product of a spontaneous abortion versus the fetus that was a product of an induced abortion if the investigator was adequately

prepared when either type of fetus became available. In practice, the planned nature of induced abortion would make the intelligent gathering of information much more possible.

The requirement of using the human fetus in gathering knowledge applicable to the human fetal situation varies considerably depending upon the questions being asked. Certain animal models are very satisfactory for developing some types of intrauterine monitoring and intrauterine instrumentation. For other problems the human pregnancy is the only practical model and always becomes so when one wishes to transfer information obtained in animal species to the human situation. Thus learning whether it was possible to draw blood from the fetal blood stream progressed from the theoretical as assessed in animal species to the practical when attempted in the human pregnancy just before abortion. some areas of metabolism and physiologic function, there are quite satisfactory animal models. In other areas the schedule of biochemical and physiologic maturation is entirely different in the human species and only the human species can be used to acquire the desired knowledge. The same thing is true for the transfer of drugs from the mother to the fetus and for the disposition and metabolism of those drugs within fetal tissues. Each research question must be addressed individually in this regard to know whether appropriate animal research could be done in seeking to answer a problem of human fetal medicine. This reinforces the conclusion of this study group that categorical bans on areas of research are short-sighted and that; instead a process of rigorous review of individual research projects is much to be preferred.

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- 120. Short descriptions of the applications are on file with the Commission staff.

# The Nature and Extent of Research Involving Living Human Fetuses

#### INTRODUCTION

The literature review is based on a National Library of Medicine (NLM) MEDLARS search for published material reporting human fetal research. The search matrix was designed by Ms. Charlotte Kenton at the NLM. We are indebted to her and to other NLM personnel for their expertise and complete cooperation in generating literature materials. The NLM search covered the indexing years 1969-1974 plus a supplement for January 1975. The search was an all language search but the review utilized only published material in English and other West European languages, in Russian, or where English abstracts of East European and Asiatic languages were available. We did not identify, via titles and indexing terms, a significant literature in languages that were not surveyed. Supplementation of the NLM search used major reviews for research prior to 1970, Biological Abstracts (BIOSIS), and Chemical Abstract Services (ACS).

A selected bibliography, primarily for the use of the Commissioners, which emphasizes review articles or signal articles that highlight methodologies, is made a part of this report. The extensive bibliography generated by the MEDLARS search is available to the Commission through its staff.

# Definitions

We have accepted as working definitions those advanced by the Advisory Group to the Department of Health and Social Security, Scottish Home and Health Department, under the chairmanship of Sir John Peel, in their report "The Use of Fetuses and Fetal Material for Research," Her Majesty's Stationery Office, London, 1972.

### These are:

Fetus: the human embryo from conception to delivery, without distinction of an embryonic and fetal period.

Previable fetus: a fetus, with some signs of life, which has not yet reached the stage at which it is able, and is incapable of being made able, to function as a self-sustaining whole independently of any connection with the mother; the term is used for the human organism at this stage in development whether inside or outside of the uterus (contradicting the classic definition that an organism outside of the uterus would no longer be a fetus).

2 FETAL RESEARCH AND THE VALUE OF LIFE Sissela Bok, Ph.D.

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# Fetal Research and the Value of Life

# I. INTRODUCTION

As our ability to predict the effects of social policies on human lives increases, the dilemmas of weighing these effects humanely and justly grow more intense. Fetal research throws these dilemmas into sharp relief, since it raises hopes for the alleviation of much suffering but also fears of abuses and brutalization. 1,6,7,8,26,27

Fetal research affects human lives in three controversial ways:

- The processes of fetal research can use some fetuses aborted or about to be aborted - for the benefit of others.
- The results of diagnostic fetal research can at times influence parental choices for and against abortion.
- 3. The results of fetal research could save hundreds of thousands of babies from early death or severe disease.

All these effects on lives must be seen, in turn, against the background of environmental, social, and individual factors which already harm the fetus. Environmental radiation, working conditions, or maternal taking of drugs, for example, affect fetuses, yet the nature and incidence of these effects are not yet thoroughly known.

At present there is profound disagreement as to how these different harms and benefits should be weighed. Ethical views play a major role in this disagreement, and must be analyzed in order to set national policy for fetal research.

The intense opposition to much fetal research stems from two lines of argument, both connected with positions on abortion.

The first argument holds that a fetus is a person, and should have the same rights with respect to experimentation as any other person. Research without consent by or benefit for the fetuses subjected to the research, therefore, is seen as an assault upon their humanity.

The second argument is designed to speak to those who do not share the premise of early fetal personhood. It stresses, not the inherent wrong in fetal research, but rather the fearful consequences flowing from a social policy permitting such research. It holds that fetal research risks the development of

attitudes in researchers, hospital personnel, and society in general which are insufficiently sensitive to human rights and interests. In this way, if we allow fetal research to continue, there will be no way of stopping at research early in fetal life; eventually, society may come to permit practices of using infants, children, those condemned to die, and all who are defenseless. (Already, according to this argument, in utero research, in anticipation of abortion, constitutes a threat to fetuses who might have lived unharmed, had their mothers been permitted to change their minds about their abortions. This last concern, though important, can be met by well drawn and practicable regulations, which I shall suggest on pages 2-7 to 2-10 of this paper.)

These two main objections might appear to threaten all fetal research not therapeutic for the subjects themselves; they will be the principal subjects of this paper. I hope to show that the first argument is inapplicable to fetal research, and that safeguards can be provided so that the second argument fails to apply to such research. Most importantly, this paper is intended to stress the fact that the safeguards we consider for fetal research should be extended to those numerous experiments and therapeutic ventures on pregnant mothers not now considered fetal research but placing fetuses at risk.

# II. DEFINITIONS

- 1. The Living Fetus--the living product of conception--will be discussed in this paper as follows:
  - a. In utero from the time of ascertainable presence up to the beginning of abortion or labor.\*
  - b. During process of abortion or labor.
  - c. After abortion but prior to viability.

Experiments using solely dead fetuses or fetal materials will not be considered here; presumably regulations governing autopsy will be applicable in such cases. Nor will experiments on clearly viable fetuses after birth be considered here; such experiments should be regulated no differently than all others where infants and young children are at risk.

2. Experimentation. All intervention in a study which can have an effect on the fetus will be considered here, whether it be intervention involving the maternal-fetal unit, the fetus alone, or the mother alone, so long as she is pregnant.

<sup>\*</sup>To preserve simplicity, "fetus" will stand for both "fetus" and "embryo" and any other appropriate terms.

3. <u>Viability of the Fetus</u>. In the present study, the following definition will be used, suggested in the August 23, 1974, DHEW Proposed Policy:<sup>12</sup>

The ability of the fetus, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.

The purpose of the present article, however, is to avoid having to draw a line at viability because of the difficulties of ascertaining viability and the chances of error.<sup>2</sup> Rather, I shall suggest a time earlier in fetal development beyond which experiments should at present be ruled out—a time when viability is not yet in question.

# III. DIMENSIONS

In order to arrive at useful distinctions among the different kinds of research, the chart entitled Dimensions of Fetal Research on the following page will list the factors which may determine the judgment on the propriety of any particular research protocol. These factors can be divided into two categories: Those whose application is relatively straightforward and those where line-drawing problems can arise most easily. This distinction is essential for my conclusion, which is that a different kind of safeguard must be established for the two types of factors. For the distinctions easily made, requirements can be stated and ascertained by Human Studies Committees, and abuses spotted. For the dimensions where there are line-drawing problems, on the other hand, it will be necessary to err far on the "safe" side, so that no dangerous spread takes place, and so that individuals do not unwittingly commit acts for which they can be found liable.

# IV. SHOULD THERE BE ANY RESEARCH ON FETUSES NOT FOR THEIR OWN BENEFIT?

# 1. The Argument for Rejecting All Such Experiments

The main categorical objections to all such experiments come from those who hold that fetuses are human beings entitled to life and to consent. Their argument takes this form:

- Premise 1 The fetus is demonstrably a human being.
- Premise 2 Experiments should be performed on human beings only with their consent or with that of others having a concern for their safety.
- Premise 3 Mothers who intend to have an abortion clearly have no concern for the safety of their fetuses, and are thus incompetent to give consent to research involving these fetuses.

<u>Conclusion</u> - Therefore, experiments should be performed on fetuses, when they themselves cannot be benefitted, only if they can give consent.

<u>Practical</u> - Since fetuses clearly cannot give consent, no such <u>Consequences</u> research should be done where they are subjects.

This argument is too sweeping in its conclusion. It relies uncritically on the vague notion of "humanity"; when closely examined, it cannot support the conclusion or its consequence of excluding fetal research.

# 2. The Premise of Fetal Humanity

"The temptation to introduce premature ultimates - Beauty in Aesthetics, the Mind and its faculties in Psychology, Life in Physiology, are representative examples - is especially great for believers in Abstract Entities. The objection to such ultimates is that they bring an investigation to a dead end too suddenly."

-I.A. Richards15

In discussions about the fetus, the premature ultimate is "humanity." Does the fetus possess humanity? When in the life of a cell or of fetal life does humanity begin? What rights go with such possession? 4,9,10,11,17,19,20

These and similar questions have arisen beginning with the earliest speculations about human origins and characteristics. But they cannot help us come to grips with the problems of abortion and fetal research; instead they short-circuit all discussions in these domains and lend themselves to superficial interpretations precisely because of their obscurity.

For the various views as to when humanity begins do not depend upon factual information. Rather they are representative of different world views, often of a religious nature, involving deeply held commitments with consequences for action and policy.

The Supreme Court opinions on abortion have already declared that the fetus has no legal personhood, thus no right to give consent. For many, this permission to abort without fetal consent suffices to permit experimentation without such consent as well, wherever an abortion is planned or has taken place.

I should like to present an analysis which could support the Supreme Court view insofar as early abortions are concerned, while finding strong reasons to be much more cautious with respect to later pregnancies. In order to do so, it is necessary to ask what are the reasons underlying the protection of human life, and then to see whether these reasons are present in early pregnancy.

A failure to scrutinize these reasons lies at the root, not only of the confusion about abortion and fetal research, but of the persistent vagueness and consequent abuse of the notion of "respect for life." The result is that everyone, including those who authorize or perform killings of civilians and bombardments of hospitals, can and do profess their belief in life's sacredness. I shall try, therefore, to list instead the reasons which underlie the elemental sense of the sacredness of life, reasons concerning the meaning which a threat of harm can have to the victim, to the agent, to those who care about the victim, and to the community at risk from the spread of such harm:

- a. For the victim, harm and/or killing:
  - If anticipated, causes intense anguish, fear, and a sense of loss of all that can be experienced and valued in life,
  - (2) Can cause great suffering,
  - (3) Can unjustly deprive those who have begun to experience life of their continued experience thereof.
- b. For the agent, killing and harming others can be brutalizing and criminalizing. It is not only destructive to the agent, therefore, but a threat to others.
- c. For the family of the victim and others who care there can be deep grief and loss. They may be tied to the victim by affection or economic dependence; they may have given of themselves in the relationship so that its severance causes deep suffering.
- d. All of society, as a result, has a stake in the protection of life. Permitting killing and harm sets patterns for victims, agents, and others, that are threatening and ultimately harmful to all.

These are principles that underlie the protection of life. They are shared by those who reflect upon the possibility of being harmed or dying at the hands of others. If these principles are applied in the absence of the confusing terminology of "humanity," they rule out the institutionalized killing perpetrated in bombings of hospitals and villages, as well as in witch-hunts and racial persecution. The victims of these acts fear death and the suffering of dying; their survivors grieve; and the societies engaging in such acts are brutalized and degraded. Similarly, these principles would rule out experimentation on infants, children and adults without the strictest safeguards for consent and safety.\*

<sup>\*</sup>Ramsey<sup>13</sup> resorts to an analogy between research without consent upon the fetus and upon those condemned to death, or dying, or unconscious. It is clear, however, that the analogy is very weak, precisely because the principles which I have listed would rule out research on these individuals without lawful consent.

Turning once again to abortion and fetal research, how do these principles apply to the risk to life in the first weeks of gestational age? Consider the very earliest cell formations a few days after conception. Clearly the reasons for protecting life fail to apply here.

This group of cells cannot feel the anguish or pain connected with death, nor can it fear death. Its experiencing of life has not yet begun; it is not yet conscious of the interruption of life nor of the loss of anything it has come to value in life. Nor is it tied by bonds of affection to others. If the abortion is desired by both parents, no grief will be caused such as that which accompanies the death of a child. Almost no human care and emotion and resources have been invested in it. Nor is such an early abortion and consequent research brutalizing for the person voluntarily performing it, or a threat to society. Because there is no semblance of human form, no conscious life or capability to live independently, no knowledge of death, no sense of pain, words such as "harm" or "deprive" cannot be meaningfully used in the context of early abortion and fetal research.

The reasons to preserve life, therefore, are absent in the early stages of gestational age;\* as a result, the argument opposing all fetal research because of the humanity of fetuses fails. The word "humanity" has been used as a "premature ultimate" in the words of Richards. Moreover, it has different meanings, in terms of the reasons to protect life, in early unwanted pregnancies as distinguished from other contexts.

Because this premise of early fetal humanity fails to apply, the second premise of the argument set forth on page 2-3 concerning fetal consent is invalid as well, as is the conclusion and its practical consequences of ruling out all fetal research of the kind discussed.

# 3. Consent

# A. Fetal Consent

For the reasons stated, then, fetal consent is not required. It ought not, therefore, to be an issue in the discussion; and it is unnecessary to group fetuses with prisoners, children, and the institutionalized, whose competence to consent or freedom to do so is in question, and where there is special need for protection.\*\* Whatever "consent committees" or other protective mechanisms are worked out to provide protection of such a nature should not be required also in the case of early fetal research.

<sup>\*</sup>As for research early in pregnancy on fetuses which are not to be aborted, every effort must be made to see that they arrive unharmed to the point where all the reasons to preserve life will operate fully. Even from the earliest moments of a wanted pregnancy, however, the third reason operates—attachment to the child to be born, and grief and worry at the thought that it might be harmed.

<sup>\*\*</sup>See DHEW Proposed Policy, August 23, 1974.12

## B. Maternal Consent

For the same reason, the need for proxy or third-party consent by the mother is also basically unnecessary as far as the fetus is concerned. Nevertheless, I believe that a conflicting force enters in here, rendering the request for consent from the mother mandatory. If the mother acknowledges that the fetus may have a right to live, though not a right to live attached to her, then she may well be pained at the thought of dissection or autopsy or other experimentation on the fetus;<sup>21</sup> it seems right, under such circumstances, to give her the option of not consenting to fetal research even after the abortion.\*

Maternal consent is desirable, then, for all fetal research, even that begun only after an abortion. But it is most clearly required in all those studies initiated before or during pregnancy, so as to avoid the possibility of any mistake and because the procedure may affect the pregnant mother herself. (Consent by the father, on the other hand, while doubtless something which would be taken for granted in a close relationship, ought not to be required, just as it is not required for abortion itself.)\*

# C. Maternal Consent to In Utero Research

If a pregnant mother, planning to have an abortion, consents to an experiment involving some risk to her fetus, and initiated before the abortion, then several problems may arise:

- (1) It will be harder for her to change her mind about the abortion, should she wish to do so. Yet, no one should be forced, or even mildly coerced, into an abortion. She may feel there is now a new reason--possible fetal damage--added to her previous reasons for wishing to have an abortion, even though these previous reasons--say an unhappy marriage or an illness--may no longer be present. And, she may feel that she, by consenting to the experiment, is somehow "under contract" to have the abortion; that she might disappoint the investigator and impede "science" by changing her mind.
- (2) Her pregnancy may be unduly prolonged. If the investigator wants to study the effect of a drug, for instance, given to the mother ten days or two weeks before an abortion, her pregnancy may have to last that much longer. This is even more risky as the interval lengthens or as the research takes place later in pregnancy. This is most undesirable, from the point of view of increased mortality and morbidity associated with late abortions.\*\* It is also undesirable from a moral point of view, as an early abortion is in itself a more justifiable act than a late abortion, given the reasons to protect life listed on page 2-6.

<sup>\*</sup>I strongly disagree, therefore, with the suggestion in the British Report on Fetal Research that asking for maternal consent should not be required since it could be an unnecessary source of distress to the mother. No empirical evidence suggests that such is the case; should there be such concern for a particular mother, it would be better not to use her fetus in a study.

<sup>\*\*</sup>See C. Tietze, Induced Abortion, A Factbook. 22

In those experiments undertaken so late that the actual abortion is delayed past the eighteenth week, real problems having to do with the borderline between nonviability and viability will arise.

Very few women would voluntarily submit to carrying an unwanted pregnancy past that point if they could abort earlier. The explanation for the fact that experiments have been done at that late time in pregnancy, in Scandinavia, for example, is that, up to recently, it was so difficult and time consuming to obtain permission for abortions that women were often forced to wait past the trimester. With changing abortion laws, the availability of late pregnancies for experimentation and subsequent abortions may be expected to diminish drastically.

As a result, I believe that all experiments initiated during pregnancy in anticipation of abortion should be subjected to the strictest regulation, though I do not advocate that they be ruled out. Such regulation could be carried out by a local Committee on Human Experimentation, keeping the following safeguards in mind:

- Experiments should take place, if at all, as early in pregnancy as possible, and those experiments which delay abortions past the eighteenth or twentieth week ought to be ruled out.\*
- The investigator ought not to be the physician in charge of the pregnancy or abortion.\* And all decisions about the pregnancy ought to be made independently of the needs of the experiment. Thus, the timing of the abortion, the method used in the abortion, and other factors should not interfere with requirements for maternal safety and well-being.
- Women who are hesitant about wanting an abortion should not be asked to participate in fetal research.
- Drugs given should have been accepted as safe for adults.
- All elements of informed consent should be carefully attended to.
- Mothers should be allowed to withdraw from the experiment at any time, and to change their minds about going ahead with the abortion.
- Insurance for harm to the baby through the research should be available should the mother decide to carry on with her pregnancy.
- Carelessly planned experiments, incapable of yielding valid results, should be ruled out.\*\*

<sup>\*</sup>With the exception of experiments done to benefit the fetus or its family, as in antenatal diagnosis.

<sup>\*\*</sup>Such experiments are, in my opinion, also highly questionable when, as is often the case, they are performed upon animals, and involve suffering.<sup>2,24</sup>

- Experiments which might induce women to become pregnant in order to submit them to research unrelated to their needs or those of their fetus should be ruled out.\*

These safeguards\*\* would protect women against the two dangers mentioned: that of possible coercion to go ahead with an abortion no longer wanted, and that of a prolongation of the pregnancy for the sake of the research but to the detriment of the mother. With such safeguards, important experiments, such as that which established the risk to the fetus of vaccinating a pregnant woman against Rubella, would continue to be possible.

## D. Other Forms of Consent

Similar consent by local Committees on Human Experimentation should be required for all research involving living fetuses. For all research, these committees should debate carefully whether all safeguards against abuse and spread to late pregnancy and abortion are provided. (These safeguards will be discussed in Parts V and VI.) Finally, such Committees must safeguard the interests of the pregnant women, over and beyond the point at which they themselves have given consent to participating in such fetal research as affects them.

#### 4. Answer

The answer to the question whether there should be any experimentation on fetuses which is not in their own interest can, therefore, be "yes." At least some experimentation consistent with the safeguards listed can be undertaken in order to seek knowledge not otherwise available. Fetal consent is irrelevant, while maternal consent and careful study of each protocol by institutional Committees on Human Experimentation are required.

Moreover, as long as the nontherapeutic research in question involves a risk, it ought to be undertaken only on abortuses or fetuses which are to be aborted. In much experimentation, the time comes to test a new measure on individuals who may not themselves benefit therefrom. It is an agonizing process to decide how to go about this and how to provide for appropriate consent, especially in the case of children, where consent is already so problematic. It is only in the case of abortuses or fetuses about to be aborted that this question of consent does not come up. Therefore, there is a clear obligation to do all research which has to be done upon them, rather than upon those for whom no abortion is planned.

<sup>\*</sup>Such experiments are, in my opinion, also highly questionable when, as is often the case, they are performed upon animals, and involve suffering.

<sup>\*\*</sup>These safeguards will be seen to relate to the dimensions listed in the Chart on page 2-4 numbered: 3,6,2,7,8,9,b,d,f.

#### V. WHAT SAFEGUARDS ARE NEEDED?

Even if it is agreed that some forms of early nontherapeutic fetal experimentation should be permitted, the problem of how to prevent an undesirable spread of such research will arise. Clearly, it cannot be permitted on infants, children and adults without stringent protection and provisions for consent. Where, then, must a line be drawn which protects society against a spread of nontherapeutic research which could endanger newborns and children, and ultimately all of us? And how can we be sure that such a line won't be crossed?

#### 1. What Risks are of Concern? What Dimensions are Involved?

In order to answer these questions, it is necessary to look once more at the chart on the Dimensions of Fetal Research, and at the factors according to which different kinds of fetal research can vary. Those factors which are ethically relevant and capable of clear-cut distinctions have already been limited by the safeguards suggested on pages 2-9 and 2-10. Others are more fluid and therefore possess features presenting special line-drawing problems.\*

The risks which are of greatest concern are those in that fluid category. They are the risks to society which could stem:

- a. From moving along the continuum of experimenting on the previable and, then, the viable fetus without intending to benefit it, but rather others;
- b. From the brutalization which could stem from any evidence that substantial pain is inflicted on fetuses in such research;
- c. From the brutalization of the participants in such research and of the public which could come from using fetuses near viability.

All these risks are real, I believe, unless fetal research is restricted so as to take place only well before viability (unless, as mentioned earlier, the health of the fetus itself is at stake).

# 2. Viability

It is well known that viability is a fluid and shifting concept, dependent not only on the state of knowledge at a particular location where a birth or abortion takes place. 18,23 A fetus that has a 1 in 100 chance of living, therefore,

<sup>\*</sup>I have described<sup>3</sup> the ways in which such fluid dimensions sometimes present possibilities for a "slippery slope" or "entering edge of the wedge" development, and the conditions which encourage or prevent such a development.

or a 20 in 100, or an 80 in 100, ought not to be experimented upon nontherapeutically, because of the real danger of a slippery slope development. I would recommend that the United States, at the very least, follow the guidelines set by the Peel Commission in Great Britain:<sup>23</sup>

- 2. The minimal limit of viability for human fetuses should be regarded as 20 weeks of gestational age. This corresponds to a weight of approximately 400-500 grammes.
- 4. The use of the whole previable live fetus is permissible provided that: "ii. only fetuses weighing less than 300 grammes are used."

It would be preferable, I believe, given the difficulties of determining gestational age, and the possibility of mistaken estimates, to use the lower weight in paragraph 4 above as well as the gestational age of 18 weeks as a safer cutting-off time in fetal research. In addition, for experimentation undertaken in utero, on mothers with the intention to abort, the experiment should not be undertaken unless the abortion can take place during the first 18 weeks. Naturally, these restrictions should be reviewed at regular intervals so as to remain consistent with advances in supportive techniques and special policy.<sup>2</sup>

With such a limitation in gestational age, I believe that the risks of:

- a. Experimenting on the viable fetus,
- b. Causing pain to the fetus,
- c. Brutalizing participants and society,

can be avoided altogether.

#### 3. Dangers To Society

The following argument is often advanced against such a conclusion. It holds that we must guard against even the least likely threats to our society which could come from a spread of fetal research, by banning it altogether. Infanticide, euthanasia, cruel experiments without consent of the kind perpetrated in Nazi concentration camps—these are all held out as possible and more likely once we allow abortion and fetal research. Such an argument in fact, then, advances the fourth reason for protecting life\* as crucial even with respect to fetal research in the first weeks of gestational life—that to take such lives would pose threats to all of society.

It is important to see here the distinction between a logical and a factual argument concerning the risk of undesirable consequences from permitting fetal

<sup>\*</sup>See page 2-6.

research. The logical argument holds that since no clear line can be drawn in gestational age between newly conceived humans and newborns, we endanger the rights of newborns by permitting inroads on the rights of fetuses. This argument has failed to convince many responsible members of our society including a majority of the Supreme Court. And a consideration of the reasons for supporting life, outlined in Part III of this paper, shows that distinctions can be made which permit abortion and fetal research up to a point in gestational age, but not thereafter.

This logical argument, however, is often confused with a factual argument, holding that fetal research will in fact predispose doctors, researchers, or society as a whole to violate the rights of children and other persons. It is clear, however, that such a factual argument is only as good as the facts on which it relies for evidence.

Taken as an empirical argument, it must be seen for what it is—an inflammatory toying with human fears totally unrelated to any development seen to have taken place in societies permitting abortion and fetal research. To the best of my knowledge, available data do not bear out such dire predictions. The societies which have permitted abortion for considerable lengths of time have not experienced any tendency to infanticide, euthanasia, or Nazi-style experiments on children or adults. The infant mortality statistics of Sweden and Denmark, for example, are extremely low, and the protection and care given to all living children, including those born with special handicaps, is exemplary. It is true that facts cannot satisfy those who want a logical demonstration that dangerous developments cannot under any circumstances come about. But if they are also trying to warn of actual risks, the burden of proof rests upon them to show some evidence of such developments taking place before opposing a policy which will mean so much to children and their families, and also to show why it would not be possible to stop any such development after it begins to take place.

The fear of slipping from abortion and early fetal research towards infanticide, therefore, is not supported by any available evidence. It ought no longer to be exploited for political purposes.

# 4. Fetal Death

Within the first 18 weeks of gestational age, ought researchers to be permitted to attempt to keep fetuses wholly or partially alive for a period of time, even though there is no chance that they might live permanently? And, secondly, ought researchers be permitted to take action which could in any way bring about death of such a fetus? The British Peel Commission allows both of these, given all other safeguards.<sup>25</sup> The proposed DHEW guidelines<sup>12</sup> limit the first and rule out the second:

46.307 (d) Vital functions of an abortus will not be artificially maintained except where the purpose of the activity is to develop new methods for enabling the abortus to survive to the point of viability and

(e) Experimental procedures which would terminate the heartbeat or respiration of the abortus will not be employed.

Because of the absence of the reasons to protect fetal life in the early weeks of gestational life, I believe that these DHEW restrictions are unnecessary. The permission granted by the Peel Commission is to be preferred, so long as all safeguards including the time limitation are observed. In exceptional circumstances, (d) should be permitted even after such a time limit, so long as the greatest care is exercised to avoid pain to the fetus and to protect any fetus capable of surviving such a process.

# 5. Experimentation and Therapy

Much of this paper has dealt with research done upon a fetus in order to benefit, not that fetus, but other fetuses and babies, even adults. But it is important to consider also the kind of experimentation which is conducted in hopes of benefiting the fetus, the mother, or the "maternal-fetal unit". Here, of course, the strictest guidelines for consent and protection of subjects must obtain. But a great deal of haphazard experimentation is conducted without such high standards, where physicians experiment with the care they give to pregnant mothers, using different diets, drugs, and procedures, without relying on valid documentation or setting up scientifically valid protocols submitted to Human Studies Committees. Similarly, mothers often engage in experimentation of the same kind, perhaps without the benefit of medical advice at all. I believe that the most important task in protecting fetuses is to stress the risks to which they are subjected through such casual experimentation and therapy. And it is through fetal research that we are coming to know just how great these risks are, and learning to forestall them. 16

In addition to such casual experimentation and therapeutic practices, there are also many experiments done to study pregnancy and its processes without a real understanding of the fact that fetuses can be harmed thereby. Studies altering the metabolism of pregnant mothers, for instance, must clearly affect the fetuses as well. We must severely restrict such experiments, therefore, and not allow many of the routine studies performed on pregnant mothers until we can be sure they have no harmful effect on the fetus.

# VI. CONCLUSIONS

Some have argued that the babies who will suffer and die from the illnesses which fetal research could have alleviated or cured are not properly speaking the responsibility of those who wish to ban such research. They hold that no matter how important the ends are, evil means cannot be employed to reach them. This refusal to take responsibility for the illness and death which could be alleviated through research becomes untenable, however, when the means are shown not to be evil, as I hope to have shown in this paper.

A combination of a ban on fetal research protocols and the continued casual therapy and experimentation in medical practice and self-medication would mean

a reckless abandon of foresight for our society. Far more moral and humane, I believe, is a program of carefully planned experimentation with proper safe-guards, combined with a renewed caution in treating and supporting pregnant mothers and newborns.

A Commission genuinely concerned to protect fetal and childhood development, therefore, could make a great difference for health and well-being by issuing a strong statement:

- Setting forth the risks to fetuses from improper maternal use of drugs, sprays, creams and harmful procedures;
- Calling for a halt on drug use (including nicotine and alcohol) not shown to be clearly needed by women who might be pregnant;
- Calling on health professionals, drug companies and pharmacists to exercise leadership and genuine concern in these respects;
- Setting forth a coordinated policy of fetal research with the following safeguards:
  - That all experimentation on a viable or marginally viable fetus over 18 weeks of gestational age or 300 grammes in weight, be ruled out.
  - 2. That the only exceptions to such a ban, where permitted by a hospital Human Studies Committee, be:
    - (a) Those research protocols which seek to benefit the fetuses used as subjects or their families.
    - (b) Those protocols which seek to develop new techniques for helping prematurely born infants to survive.
    - (c) Those protocols which seek to test new diagnostic techniques not possible at an earlier gestational age.
  - 3. That approval of experiments be sought from Local Human Studies Committees passing on the nature of the consent, the validity of the research, the competence of the investigators, the availability of alternative kinds of research, and the risks and benefits involved.
  - 4. That consent be sought from mothers of the fetuses studied, and no pressure be exercised in favor of abortion.
  - 5. That the earliest possible time in pregnancy be sought for all such research.
  - 6. That compensation be available to mothers having agreed to research in anticipation of an abortion, should they change their mind and give birth to a baby harmed by the research.

- 7. That methods of abortion and determination of gestational age, weight, and viability rest with attending medical personnel rather than with the investigator (except for 2a above).
- 8. That no drugs be administered, or procedures undertaken during pregnancy which are known to be harmful to fetuses and/or others.
- 9. That no experiments be undertaken which might induce mothers to become pregnant purely for experimental purposes.
- 10. That these safeguards be periodically reviewed.

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#### DIMENSIONS OF FETAL RESEARCH

## I. Application Relatively Clear-Cut

#### 1. Intended Fate of Fetus

Definite support (no abortion planned
Definite abortion
Conditional abortion (e.g., after antenatal diagnosis)

# 2. Actual Fate of Fetus

Birth Spontaneous abortion Induced abortion

#### 3. Person Doing Research

Physician in charge of pregnancy Another investigator Others (mother, etc.)

#### 4. Intended Beneficiary

Fetus (subject of experiment)
Fetus (subject of experiment),
depending on diagnosis
Future individuals
No beneficiary now foreseen

## 5. General Purposes

Therapeutic
Diagnostic
Other (use of tissues, learning
techniques, etc.)

## 6. Consent Given By

No one Mother Father Local Human Studies Committee National Ethics Committee

### 7. Research Planned for Fetus

Before pregnancy During pregnancy During labor After labor

#### 8. Research Intervention Initiated

Before beginning of labor During labor After end of labor

# 9. Conclusion of Intervention

Before beginning or labor During labor After end of labor

## II. Giving Rise to Line-Drawing Problems

#### a. Degree of Viability

None, given present state of knowledge and available means of support Marginal High

## b. Risk of Harm to Fetus

High Moderate Low Unknown Nonexistent

# c. Risk of Pain for Fetus

High Moderate Low Unknown Nonexistent

# d. Risk of Harm to Mother

High Moderate Low Unknown Nonexistent

# e. Risk to Others (Newborns, Society, Medical Profession, etc.)

High Moderate Low Unknown Nonexistent

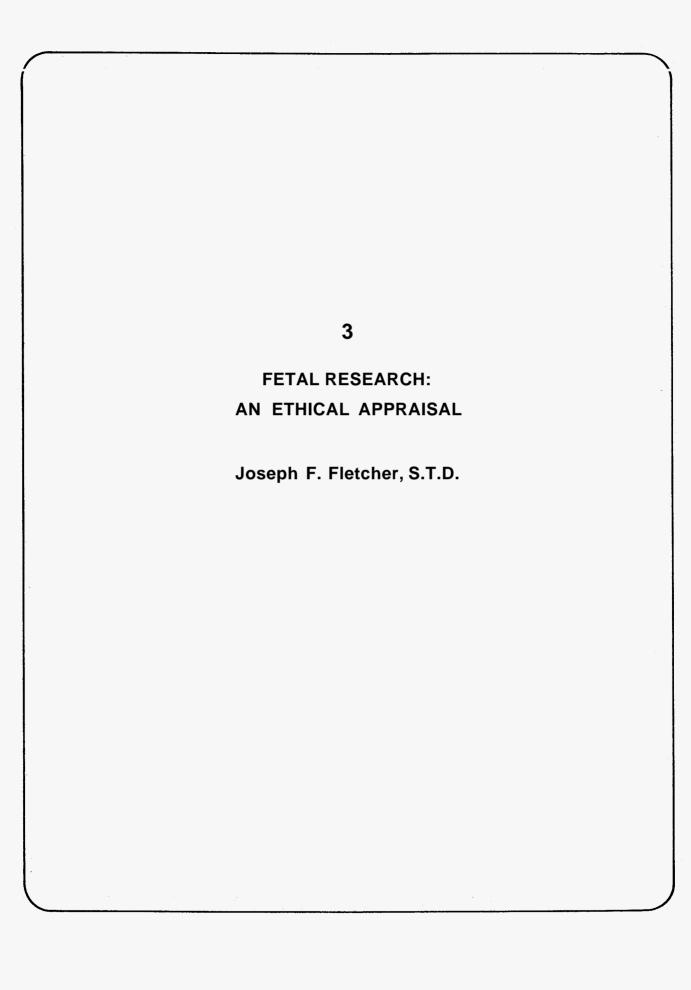
# f. Validity of Research Design

High Doubtful Nonexistent

# g. Potential Usefulness of Results of Research\*

Strong Moderate Low Unknown Nonexistent

<sup>\*</sup>A number of separate dimensions are involved here, such as immediacy with which the new information can be applied, number of persons it can help, degree of suffering or inconvenience which can be avoided.



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PD 304109-5

# Fetal Research: An Ethical Appraisal

We want our people, especially our children, to be safe from genetic and congenital disorders, uterine infections, and a host of other maladies. This means we have to learn as much as we can about controlling reproduction, for the security and quality of human life and well-being, and to be free as much as possible from the dangers of blind, natural cause and effect. Individual scientists, in addition, of course, may be moved by an intellectual itch and/or a hunger for fame.

How can we continue to achieve enormous research benefits for reproductive medicine, while at the same time maintaining a high ethical standard of concern for human subjects? It will be contended in this appraisal that fetuses are not "human beings" in the nonbiological sense of persons, even though they are potentially persons. What, then, do we owe them?

What the reasons are for an increased concern about this in the past ten years are not at all clear, or at least not aboveboard. In the past "age of faith" this concern was not very strong or well articulated. It has arisen among research scientists and physicians themselves: they have called in lawyers and ethicists and psychologists to explore it. It is reflected in the monitoring procedures of NIH, FDA and NSF, in the peer review law (PSRO), and in generally normative practice. The public's attention has been alerted by organ transplants (especially hearts), the thalidomide disaster, and by scandalous episodes such as the Tuskegee syphilis affair and the South-Mandel case of cancer cell research in New York.

Nonetheless, the need of more knowledge remains, and perceived needs proliferate as the knowledge accumulates. Virtually all that is known of some branches of reproductive medicine has come from clinical research: assets such as antenatal diagnosis, furthermore, have been acquired through fetal research in utero. The Nuremberg code is definite: clinical experimentation is justified if it can yield "fruitful results . . . unprocurable by other methods and means."

One survey of attitudes has reported that clinical researchers are "low" on ethical concern. They had put the question, What characteristics do you want to know about another researcher before entering into a collaborative relationship . . .?" The response was 86 percent "scientific ability," 45 percent "hard work," 43 percent "personality," and only 6 percent "ethical concern for research subjects." The respondents, it should be noted, were first of all concerned for competence because that is their first ethical obligation to their subjects. "If you have to do it, do it well." The fact that "concern for research subjects" does not leap to mind certainly does not mean they care nothing about their subjects, as any very wide acquaintance with physicians will show.

#### ETHICAL PRINCIPLES AND PREMISES

People often think that ethics means finding something that is "bad," as such, and then categorically forbidding it by a rule of morality. This is indeed one kind of ethics. However, in this appraisal, as John Dewey would have called it, a hypothetical rather than a categorical ethics will be employed. In this kind of ethics the moral agent says, "If you do not want such as such, then because of its consequences this or that is wrong." Rightness and wrongness are judged according to results, not according to absolute prohibitions or requirements. The ethics in this appraisal, therefore, is not categorical, based on prescriptive norms; it is not ideological nor rule-determined. On the contrary, it is based on the principle of proportionate good; it is consequential, pragmatic, and value-determined.

To illustrate, neither amniocentesis nor fetoscopy is as yet entirely without risk as a diagnostic procedure--there is some risk in the aspiration of amniotic fluid and in the use of cannulas and lens to examine fetuses suspected of being aberrant or diseased; for example, getting blood samples in a suspected hemoglobin disorder like beta-thalassemia. The procedure is still experimental, still investigative medicine. One state's law bans it as nonbeneficial risk to a live fetus. Yet three out of four times such a diagnosis would yield "all is well" or "signs negative"--a preponderantly good consequence. In this appraisal, therefore, it is held to be a good thing, because it eliminates the risk of terminating healthy pregnancies out of fear of getting a defective baby.

This particular law was passed on the ground that all nonbeneficial risks to a fetus are wrong as such, regardless of whether we could weigh up the benefits and discover that in some cases they more than make up for whatever the risks and costs might be. The fact that it would save many babies is not, in doctrinaire ethics, allowed to weigh against the categorical condemnation. It's followers would say, "All experimental risks to live fetuses are ipso facto unethical, no matter how good the consequences." (One religious moralist has even argued, in addition, that it is unethical because the fetus has not given its consent nor ever could--rather like those who condemn abortion, regardless of any good consequences to be gained.)

Pappworth puts it very bluntly. "Whether an experiment [has] gained its desired result or not is to me immaterial . . . . A worthy end does not justify unworthy means . . . . Every human being has the right to be treated with decency and that right belongs to each and every individual and should supersede every consideration of what may advance medical science. No doctor is justified in placing science or the public welfare first and his obligation to his patient second." (His italics.) Here we have a whole battery of ethical assertions, all of which will be rejected or seriously qualified in this appraisal: his radical individualism, the notion that the end cannot ever justify the means, an appeal to "rights" as if they were perfect and unconditional, and an undisclosed but obviously quite subjective understanding of "decency."

This brief discussion of ethical alternatives shows how a pragmatic ethics based on values, quality of life, and proportionate good, differs from a dogmatic

ethics of rules and categorical judgments and prejudicial decision making. It also helps the reader to know what ethical "rules of the game" are being followed here. Now let us turn to the question itself, as it is analyzed by an ethicist who is neither a biologist nor a physician.

The core question at stake in the ethics of fetal research is whether a fetus is a person. Very soon after fertilization it is apparent that the conceptus or embryo is biologically of the human species, and that it is living in the sense that cell division is going on furiously. But are we to assign personal status to a fetus, i.e., render it the regard and rights we grant to living, breathing, independently functioning individuals? The contention that we should assign human rights to the fetus is a familiar one, but definitely rejected by the Supreme Court. In Roe v. Wade (1973) it decided this question at last in terms which uphold the ethics of relative values -- namely, that fetuses are not persons, although any state may (but not must) choose to protect fetal life from termination in some cases in the third trimester, out of a "compelling interest" in the potential (postnatal) person.4 The Court itself, then, did not proscribe even third trimester abortions, as in such procedures as hysterotomies and saline induction--prior to viability. The logic of the decision is to validate not only terminating pregnancies by the induced abortion of previable fetuses but the forestalling of unwanted live births late in pregnancy--undesirable as it might be medically in most such cases.

An actual person, as distinguished from a potential one, is therefore both legally and ethically a human being who has left the maternal/fetal unit, is born alive, and lives entirely outside the mother's body with an independent cardio-vascular system. Only the pregnant patient is a "human subject" to be protected in clinical experimentation and research; the fetus is an object, not a subject-a nonpersonal organism.

A fetus is "precious" or "has value" when its potentiality is wanted. This means when it is wanted by the progenitors, not by somebody else. Hence the principle of privacy, of one's control of one's own body and its product--except that some states might intervene to do the wanting after 24 weeks of gestation. The courts have held further that if a fetus is wanted by one progenitor but not the other, then the mother has the initiative, either to carry it to term or to abort. (This last problem does not arise for asexual reproduction like cloning.)

The metaphysical or religious belief that fetuses are persons is a perfectly legitimate act of faith but there is no way to prove it or show it (no litmus paper test, so to speak); by reason of its nonempirical nature as a faith assertion it cannot be either verified or falsified. Most of us, when we look at the consequences of that belief, reject it because of what consistently acting on it would mean for the quality of life in our children and the standards of reproductive medicine. To treat live fetuses as "untouchable" is absurd; variables such as their functional condition and health prospects, costs of treatment both financially and emotionally, maternal consent, the need to "touch" them, whether they are destined for termination—these factors should enter into the decisional mix.

The fetus is not a patient. A patient is a person. The Hippocratic Oath does not recognize the fetus as a person-unless you want to infer it from the archaic statement, "I will not give to a woman a pessary to produce an abortion." The World Medical Association's reduction of the Oath leaves it out altogether, declaring only that the "utmost respect for human life from the time of its conception" should be maintained--leaving open what "respect" and "conception" are to mean.

Dr. Joshua Lederberg sees the problem in a nondoctrinaire way, as the great majority do. Speaking of governmental proposals to limit fetus research, he said, "The crux of the matter is whether one views the abortus [sic] as a person . . . "5 He was replying to Dr. Andre Hellegers, a doctrinaire moralist of the minority, whose contention was that "no one can give consent to an experiment on [a live] aborted fetus . . . It would be like asking consent from a parent who had abandoned or battered a child." 16

Here we have a moral disagreement in good faith. One side thinks vitalistically, that where there is fetal life there is a person; the other side determines personal status by quality of life. One group looks at persons as events or endowments (e.g., "infusion of the soul"), while the other sees persons as a process or achievement developmentally. This is clearly not a matter to be decided by governmental fiat. The First Amendment to the Constitution forbids any such solution in a pluralist democracy. In short, there should be no compulsory pregnancy or motherhood, and by the same token no compulsory abortion or fetal research.

The ethics of fetal research has had remarkably little discussion. For example, in the 1,154 pages of the Katz compendium on the ethics and law of human experimentation there are fewer than a half dozen pages given to fetal research. What we are to think about probing fetal life in utero and ex utero, in order to prolong the life of children yet to be born or of children already born, is still very much open to exploration and certainly open to differences of opinion and practice. Physicians and scientists will have to decide pretty largely for themselves whether to learn how to save living human beings by the use of whole fetuses, fetal tissues, or fetal materials. Each investigator, for example, will have to decide for himself or herself whether—to take a couple of examples—to perfuse fetuses to develop ways to prevent spontaneous abortions, or to prevent drug toxicity in fetuses going to term. All should be free either to participate or not to participate.

Expressed in philosophical language, as we have remarked, the question is whether a fetus is an object or a subject. If, as we suppose here, the fetus is not a subject, then it follows that "protection of human subjects" in fetal research can only mean protection of pregnant women and live-born babies, preterm and full-term, not of previable fetuses in utero or ex utero.

A related issue is whether persons or subjects have to be actual or only potential to be real--to be "in fact" human beings. The "error of potentiality" is to confuse what is yet to be or could be with what is. It supposes that because a fetus could possibly or probably become a person, it is therefore a person now. Viability anticipated converts into viability realized. This

"prolepsis" falsifies reality; in its eagerness it slips into thinking that what we want is already possessed, when in fact we are only hoping for it. In fact, a fetus is precisely and only a fetus.

There seems to be good reason to question both the validity and usefulness of the concept of viability, at least as a stage of gestation having any ethical significance. Modern resuscitation and artificial life support technologies are pushing "viability" farther and farther back towards nidation, possibly to four weeks. Marginal errors about gestational age are inevitable, in spite of such devices as ultrasound measurements of fetal head diameter. At present, infants of 700 grams are probably the baseline, even though efforts are made to save those of 600 grams if parents want it done. Yet research and development on synthetic placentas and artificial uteruses is extending the incubation period we now have for premature infants—prematurity having the greatest mortality frequency in perinatal medicine. Viability is sure to be pushed back until its relevance to speculations about humanness and personhood will have become absurd. Those who are hung up on the "resemblance" of the fetal morphon to a live-born baby will be released progressively from that psychological trap—called the "homunculus reaction."

Such notions are always changing, as medicine's capabilities change. Viability used to mean a fetus was capable of spontaneous functioning at separation from the mother. Then it came to mean (for some, not all) being capable of functioning by artificial means until spontaneous functioning begins. Soon it will come to mean being kept going artificially at any stage beginning with fertilization. Arguments about "prima facie viability" at 28 weeks or 24 weeks or 20 weeks are superficial and increasingly irrelevant to the question of survivability of fetal life. The good intention of one government official, who said, "If you have a viable fetus you are in precisely the same position as you would be with a minor child," is more and more taking on the appearance of the grotesque. Throughout the centuries the term viability meant, literally, "ability to live"—to live apart from maternal/placental support. No artificial support was available. But now, with respirators and the new biochemistry of lung inflation, who is to say what the word will come to mean, as to either the fetus' development or its independence of the human uterus (ectogenesis)?

The temporary guidelines recently laid down by NIH, trying to avoid the pitfalls of viability's definition, made it a matter of simple heartbeat and respiration, and then required that no "harm" be done to fetuses regardless of head size, gram weight, physiological development, genetic diseases, congenital anomalies—just whenever and simply because the heart beats and it breathes. This disregard of quality-of-life factors is very upsetting; it is unacceptably undiscriminating and inhumane. The question is not whether a fetus has vital signs but whether it should be brought to live birth. If not, surely research and experimentation are in order. A Tay-Sachs fetus in utero is alive; so is a massively lesioned myelomeningocele prematurely expelled, ex utero. With proper consent, learning from such false starts should be allowed as entirely ethical, if in the first case abortion is chosen and if in the latter respiration is foregone.

In America's pluralist society variety and difference of belief and values are essential. They provide the creative abrasion of competition and inquiry. Such disagreements, ethical as well as religious and cultural, are vital to the progress of reproductive medicine, as they are to all other human enterprises. Homogenization of opinion would be a disaster to science as well as to medical care and treatment if any particular set of pre- or metaethical assumptions about personhood and humanhood in fetal life were to be given a monopoly force by law or by funding work done exclusively according to only one system of ethics and its rules for obstetrics, gynecology, perinatology, and pediatrics.

Quite apart from its being wrong to impose such rules, they would surely be evaded and violated, thereby encouraging the dishonesty which always grows up under a Big Brother and Authoritarian policy. Many people's belief propositions are entirely visceral, not rational--witness, for example, the repugnance some people feel at perfusion of a separated fetus head while feeling none at the perfusion of its kidney. Where we start from is essentially important in understanding our own moral judgments, and others', but to force us all into the same value mold would be a moralistic dictatorship.

#### ETHICS IN FETAL RESEARCH

Our most searching ethical question has to do with live fetus research, not the use of abortuses and fetal tissues and materials. After vital signs are gone fetuses are in the domain of autopsy and pathological examination. The issue is drawn by temporary regulations of NIH (DHEW) banning all nontherapeutic live fetus research in utero, whether the fetus is viable or previable, and even if the fetus is destined for abortion and the research has the patient's consent. These "regs" ban the use of artificial life support for research purposes, even when a fetus is determined to be not viable, because it would be (obviously) non-therapeutic and not to "save" the life of the fetus.

Here we have an instance of a dogmatic or doctrinaire condemnation of something as intrinsically wrong, and regardless of any extrinsic consideration of the benefits to be gained. Common sense, in any case, does not allow that a fetus which is inviable or to be terminated can be "harmed" or "injured" or "insulted," since acts of battery and mayhem presuppose a living, independent individual biologically. Invasive treatment of a fetus, in either therapy or experimentation, might come under the heading in law of mutilation, as of a corpse, but would not be an injury (injure or injustice). An injustice predicates a person. The only injury could be to the maternal patient, and with the appropriate consent even that becomes null.

In a way NIH is therefore in the position of assigning "rights" to a fetus in utero whether the patient wants the experiment or not. If, as this appraisal maintains, a fetus is without personal status, the ban in effect assigns human rights to a nonperson, which is precisely what the Supreme Court has set aside. It is a repudiation of the judiciary by an agency of the executive. The legislative branch of our government has also rejected the Court's judgment, by endorsing a blanket denial of research funds, even though only temporarily, to all live fetus research "unless such research is done for the purpose of assuring

the survival of the fetus."

Its effect practically is to downgrade a great deal of our knowledge of fetal physiology and medicine to anecdotal observation instead of the genuine research which is vital to completely verified and reliable lifesaving information. This is a serious matter, since almost 50 percent of all biomedical research is funded through NIH.

As a part of this temporary policy, a ban is also laid on keeping fetuses going ex utero by artificial supports for a few hours (seven or eight at the most), even though the fetus is not ultimately viable -- in the original sense of being or becoming able to function independently of the maternal womb. same mood in which they banned the use of artificial support systems to help fetal life keep going, artificial systems to get life started are also banned-in the case of in vitro fertilization and implantation. (The 1972 "Peel Report" of an advisory group on fetal research in Great Britain also asserted, in a somewhat sweeping fashion, that it is "unethical" to do any fetal research in utero aimed at "ascertaining the harm" drugs and procedures might do. 12 Their ban did not extend to studies of fetuses ex utero, however; they allowed use of such fetuses as, simply, "previables." Their opposition, by the way, was not based on any assertion of fetal "rights" but on the danger to experimenters of law suits in torts by disappointed or disgruntled patients.)

But what is of the most urgent importance is that the NIH rules do not disclose to those thus regulated any explanation at all of the prohibitions, nor of the assertion that such research is unethical. In a civilized, democratic society it is unthinkable that regulations and prohibitions may be laid upon scientists and healers in fiat form, without any disclosure or defense of the reasons for them. Ethically speaking, this is a point of critical significance. Rules without a rationale cut straight across the principle of "due process" and are, as lawyers like to say, "arbitrary and capricious."

The tension between lifesaving research in genetics, fetology, and general medicine, on the one hand, and prohibitions of fetal research on the other, is very real. There is a considerable body of information needed, which is to be gained only from experiments and investigations with live fetuses in or ex utero; abortus research does not meet the need. We have to know more about detecting diseases in pregnant mothers, how to reduce the hazards of induced abortion, which donor-fetal tissue--thymus, liver, spleen, and so on--will save deficient newborns (for example, agammaglobulinemia children), and to study abnormalities.

It has been argued (consequentially) that fetal research would have a brutalizing effect on us all if it were to be countenanced, but surely the reply is that it has been done without that effect, before it was brought to a halt; a more brutalizing effect would be the result of refusing to do what we could to avert fetal disorders and to avoid bringing disordered babies into the world knowing that we could prevent such misery. Live fetus research can help to prevent the 20 to 30 percent of wanted pregnancies lost in spontaneous abortion. Experiments with maternal/fetal patients whose pregnancies are to be aborted can achieve impressive gains for life and health, For example, tests of rubella vaccine by injecting the mothers who consent are necessary, and drugs to know what substances a fetus can absorb or can cross the placental barrier.

Fetal experiments ex utero should be done to develop incubator procedures for prolonging the life of possibly viable premature fetuses, to carry them along until they can survive enough to enter the nursery; to find treatments for asphyxiated newborns (e.g., by complete perfusion); to test artificial placentas to help a newborn with respiratory distress syndrome; to learn about fetal physiology; to fight birth defects, diagnose disorders, and reduce neonatal mortality and morbidity.

Furthermore, research with nonviable live fetuses could lead the way to therapeutic gains such as thymus for "Swiss type" agammaglobulinemia, donor transplant tissue, fetal organs for biochemistry, tissue cultures for vaccines, liver-lung-and-spleen tissue for measles and polio vaccines, and to increase the accuracy of amniocentesis. The "Peel Report" in Britain listed 51 specific in utero and ex utero experiments and research goals with live fetuses of importance to reproduction and general medicine.

The moralistic temper which strives for ever more restrictive antenatal regulations comes from an ethical stance in which life qua life, regardless of its quality, is the first order value. Many of us, on the other hand, opt for quality, not quantity, with the value judgment that sometimes "life is not worth living." Only if we are "sacralists," investing life with a sacred entelecty of some kind, would we want to put a taboo on direct human control over life. We see this issue underneath both the fetal research debate and the terminal care debate. The issue runs through nearly all biomedical policy--transplants, determination of death, triage, and many other problems. Quality or value ethics requires us to transvaluate our values; we cannot dogmatically put "being alive" as the highest good. Life is a value to be perceived in relation to other values. At best it is only primus inter pares. Without life, of course, nothing else is of any value to us, but--by the same token--without some other things life may be of no value either.

It is a curious aspect of the consent problem that compulsory motherhood seems to be a part of the present temporary rules, if the requirement to save a viable fetus is taken seriously. For example, if a woman's abortion came very late and the fetus was artificially supported up to viability, it would mean making her a mother against her will. As it is, in these rules, the patients's consent to live fetus research in utero and ex utero is nullified in spite of her and her physician's hopes and choice.

Dr. Robert Goodlin's work at Stanford on live previable fetuses, including the product of hysterotomies (one fetus was kept alive for 11 days) was as successful as it was because so many patients asked him to do their terminations, wanting some good to come of their unpleasant experience. The present NIH prohibitions--unreasoned and unexplained--would certainly nullify such compassionate efforts to help save fetuses born with immature and uninflatable lungs. This is a serious invasion of free consent, and especially serious since it is a policy imposed by those who otherwise make a great parade of respect for consent as a requirement which should always be enforced.

One of the lurking ethical issues in fetal research is the means-ends controversy. Is risking or damaging fetal life always wrong, an intrinsically evil

act? A categorical moralist might see it that way. Presumably, if fetal life is personal such acts in research and experimentation would be looked on as mayhem, battery, or even felonious assault. But looked at hypothetically and pragmatically, whether doing intended or unintended damage to a fetus is wrong would depend upon such variables as whether it was to be terminated anyway, or whether the good to be gained would outweigh the sadness of the means. In a nondoctrinaire ethics, proportionate good or "a favorable cost-benefit ratio" would decide it. (For those who do not believe a fetus is a person there is no question of "murder" or "manslaughter" or "unlawful death" in abortion or fetal research, but only of choosing to lose or forego a potential person.)

As the editor of The New England Journal of Medicine once expressed it, to be right "the desired end should always be of sufficient value to justify the means . . . "14 In every responsible profession serving human needs we have to weigh up the good and bad relatively; ethical analysis is a matter of choosing between competing alternatives; the moral agent is a chooser in the clinical or case-focussed spirit, not a straight-down-the-line follower of pre-fabricated decisional rules. When Dr. Pappworth, as quoted earlier, says that whether an experiment gains the desired results is "immaterial" to him, because a "worthy end does not justify unworthy means," we have to part company; his categorical rigidity is ethically irresponsible.

There are a certain number of people for whom value-tied decision making is too flexible; they are more comfortable with a rule-tied approach to ethical problems. Their identity is quickly discoverable because their objection to letting decision makers judge what is best is never given in the basically doctrinaire terms which undergird it but in a variety of objections called the "slippery slope" or the "thin edge of the wedge." Where there is a trade-off between protecting fetal life and saving "born" life or learning how to do it, they complain that a "domino effect" will go into play and that if they are allowed such medical studies will end up in a reenactment of the "Nazi situation" or Brave New World or 1984. (The Nazi atrocities perpetrated in the name of "medical research" were, of course, blatant and ruthless experiments carried out on involuntary and uninformed subjects.)

This parade of horrors is not logical or rational analysis ethically; it is a mood objection, not a reasoned one. There is hardly a single advance in scientific know-how which could not conceivably be turned to stupid and malicious misuses and abuses. A maxim in the classical tradition of Judeo-Christian ethics provides an adequate retort to this particular anxiety syndrome. The retort is, abusus non tollit usum, abuse does not bar use. (There is no "answer" because there is no analyzable question posed.)

The "fallacy of necessity" lies behind the wedge objection; the notion, that is, that because we can do something it is certain that we will do it. Or, more carefully expressed, we will do it uncritically and undiscriminatingly. Prudence, an ancient and essential virtue, very often turns us against an experiment or research study in fetal medicine because the gain would not be proportionate to the cost--"the flame is not worth the candle." That is prudence. The wedge objection, on the other hand, as in the case of live fetus research

or invasive therapy, is imprudent or antiprudent, since it rejects all responsible ethical judgment with a blanket ban, ab initio. It repudiates critical analysis in favor of taboo.

#### ETHICAL JUDGMENTS

Our problem is a political one as much as ethical. How are we to "live and let live" in American medicine, which functions in a pluralist society composed of varying and even contradictory beliefs and values?

Shall we who are pragmatic and value-oriented compromise with the "prolifers" who are doctrinaire and rule-oriented, or should we follow laissezfaire? We might put the question in another way: How are we to show our concern and tolerance for minority sentiments, by compromise or by full freedom of conscience on both sides? Shall we show our acceptance of difference by banning some categories of live fetus research and allowing others, or should it be not by "class actions" but by individuating cases--allowing the minority moralists to choose for themselves in every case whether they will participate or not.

The NIH (DHEW) rules now in effect temporarily have simply meant a capitulation to rule ethics and the prohibitionists--with no explanation or rationale. Having once controlled society openly, the churches now must try to do so by tactical political maneuvers--because we have moved in policy making from "Ask the church" to "Ask society." As psychiatrists concluded in a study about objection to the abortion as wrong, "we do not believe that their belief should limit the freedom of those not bound by identical religious convictions . . . . General rather than specific guidelines should be instituted."15

Antiresearch elements would probably prefer a compromise, banning some kinds of experiments if all kinds cannot be stopped. They would not be satisfied simply to be honored as committed to one point of view. Their strategy will be to object to all live fetus research, hoping thereby to get at least a big part of it eliminated. Their method will be to build consequential and slippery slope arguments, to support their basically ideological objections. They are sure to favor completely banning or interdicting whole categories of live fetus research, rather than to leave the decision whether to participate up to the individual researcher. Thus many in their school of thought want an amendment to the Constitution, prohibiting all permissive or voluntary abortion, and all live fetus research. Since they are not apt to win a success as sweeping as that, their task will continue to be to harass and minimize live fetal research as much as possible.

Unhappily but necessarily, if rules are imposed by law or public agencies somebody is sure to be frustrated; one group or the other. In matters of this kind there is great wisdom in the old adage, the best government is the least government. The issue cannot be resolved satisfactorily to all. Ethically regarded, the minority viewpoint should have to concede, comforted (if at all) by the reminder that they would not have to engage in any research that violates their consciences. (One tart suggestion is that we ought to compile a list for

them of all the drugs and procedures that have and will be derived from live fetus research, so that they can avoid using them for the protection and health of their own children. Antifetal research agitators are as inconsistent on this score as the antivivisectionists.)

The ethical appraisal outlined above takes us to five summary conclusions about fetal research. Put in terse propositions, they are:

- (1) It is justifiable, depending on the clinical situation and the design, to make any use of abortuses or dead fetuses--whole, tissues, or uterine materials--whether from voluntary or therapeutic abortions, and with or without maternal consent.
- (2) It is justifiable, depending on the clinical situation and the design, to make any use of live fetuses ex utero, previable or viable, if survival is not purposed or wanted, and if there is maternal consent.
- (3) It is justifiable, depending on the clinical situation and the design, to make any use of live fetuses in utero, if survival is not purposed or wanted, and if there is maternal consent.
- (4) It is justifiable, depending on the clinical situation and the design, to use live fetuses *in utero* even if survival is intended, if there is no substantial risk to the fetus, and if there is both maternal and spouse-paternal consent.
- (5) As a fifth finding we may add the point already discussed, that regulations by the public authority are unethical if the reasons for them, the ethics they are rested upon, are not disclosed fully and frankly.

To say that the best government is the least government does not mean that government is wholly evil, nor even that it can be called a "necessary evil." Necessary, yes, but not evil. Fetal research and experimentation should not be radically individualistic nor a laissez-faire program carried out by personal whim without any kind of monitoring and control.

The problem is what kind of monitoring and control. Should it be under institutional peer review and design committees, or governmental? The thrust of the ethics in this appraisal seems to favor the institutional rather than the governmental model. Power politics will enter into either structure, but far less in the institution (a hospital or university medical center, for example) than in government politics. It is, therefore, preferable. As Thomas Jefferson once remarked, the people fear the government in a democracy, and the government fears the people in an autocracy. For medicine's sake we must prevent any polarization of freedom and responsibility.

It is presumed to be the proper business of legislatures to frame laws for the greatest good of the greatest number--the aggregate good and the widest

benefit. This ethical question—to whom do we owe our prior obligation, to the few or the many, the one or the several?—affects live fetus research. Absolutizing or tabooing fetal life, even when a fetus is not wanted, is an obvious form of radical individualism (selfishness and narcissism), because it would deny the research use of a live fetus which could provide lifesaving substances for living persons or yield lifesaving information. We can see this individualism in a past Pope's claim that the individual may not be subordinated to community needs, as in medical experiments, because "man [the individual] is not finally ordered to usefulness to society. On the contrary, the community exists for man [the individual]."

When related to fetal research a dictum of this kind raises the issue not only of the general welfare—e.g., perinatal medicine's gains at the "expense" of an unwanted fetus—but the basic question whether a fetus is a "man" at all, in any sense.

There is an uncomfortable tension between the individual's interests and the community's, with authentic claims on both sides, but a balanced ethics would not finalize the individual (certainly not a fetus) regardless of the cost to society. Bertrand Russell made this interesting observation: "Christian ethics is in certain fundamental respects opposed to the scientific ethic . . . Christianity emphasizes the importance of the individual soul, and is not prepared to sanction the sacrifice of one innocent man for the sake of some ulterior good to the community. Christianity, in a word, is unpolitical, as is natural since it grew up among men devoid of political power."

In this appraisal, in any case, a fetus would be held to be expendable if it yielded the medical knowledge wherewith to help many other fetuses, live children, and adults.

Dr. R. H. Moser, editor of *The Journal of the American Medical Association*, went to the heart of ethical issues like this one when he advised us succinctly to decide moral questions according to the case or situation, rather than by universalizing rules and laying down categorical prohibitions.<sup>13</sup> The wisest ethical method is situational; nondogmatic, flexible, particularized, value-oriented. In fetal research, whether with live or lifeless fetuses, what we are after is the ability to save life and lift its quality. Our goal is useful medical knowledge.

Two physicians a year or so ago wrote letters to *The Journal of the American Medical Association* to protest against a previously published paper affirming fetal research; their complaint was that the writers of the paper had sold out to "an ethic of expedience"--which they rejected because it "favors utility above principle." Apparently without realizing it they put their fingers precisely on the main issue; categorical rules versus weighing pros and cons. If "principles" block medicine's healing task, so much the worse for such principles. Medicine must be delivered from the kinds of ethics which follows principles when following them means we have to condemn and nullify the acquisition of useful know-how in medicine's effort to save and improve human life.

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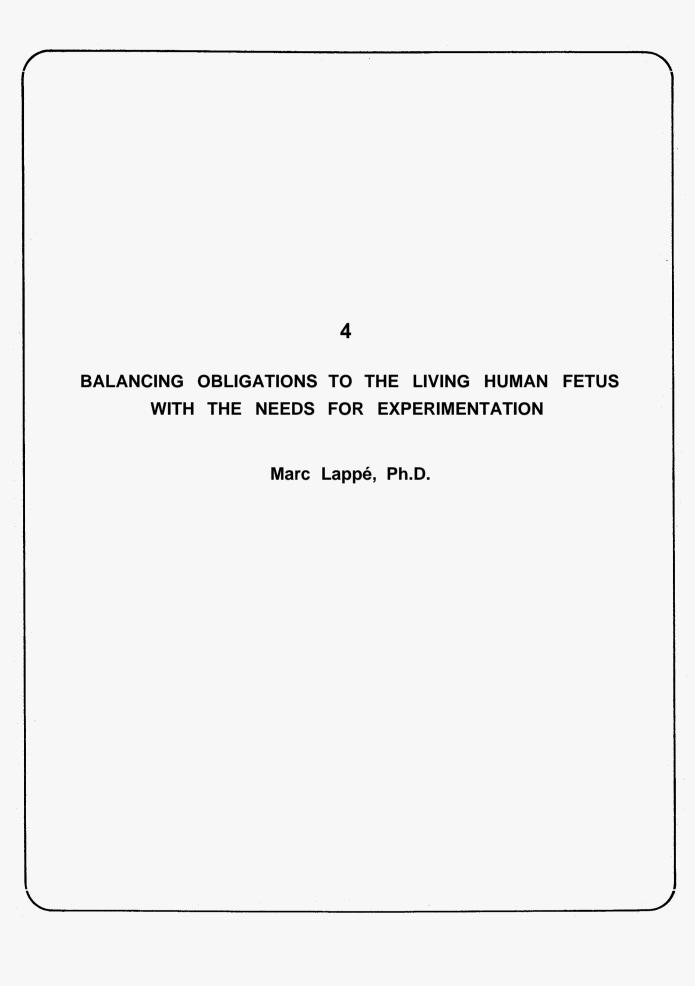
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# Balancing Obligations to the Living Human Fetus with the Needs for Experimentation

I start from the premise that there are moral "goods" which the nature of fetal development itself enjoins us to acknowledge. In defending this proposition, I will be arguing from a "natural law" perspective. The first principle I derive is that the previable (as well as the viable) human fetus is deserving of protection from harm and willful neglect in utero; the second, that the deservedness of the fetus to our protection is an absolute principle, unmodified by the societal decision to permit abortion during specific periods in pregnancy; the third, that the facts of the abortion process for a given pregnancy, radically change the ethical argumentation appropriate for sustaining the protection of that fetus, and that the circumstances of abortion logically and ethically make limited experimentation justifiable; fourth, that the "costs" of doing such experimentation are to be counterbalanced by the goods which are returned to fetuses as a class so as to as nearly as possible approximate a "therapeutic" model of experimentation; fifth, that the definition of death of a fetus, an event which opens many avenues for potential experimentation, is to be made independently of the needs of the experimenter. Finally, I will list a series of policy recommendations which would move towards implementing these principles.

#### 1. The Human Fetus Deserves Protection From Harm In Utero

The nature of the dependency characteristic of intrauterine fetal lifethe fetus's unique vulnerability to environmentally derived and indigenous insult, its need for certain critical metabolites and anatomical conditions at different phases in its relationship with its maternal host!—all give force to the fundamental moral charge to respect, protect and nurture the well-being of wanted fetuses to the fullest possible extent. It is neither the "innocent nature" of fetal existence, nor its projected "human worth" which move me to this position: it is the bald evidence derived from the study of perinatology which reveals that fetuses deprived of the conditions necessary for their normal development do fail to fulfill their full genetic potential, and if exposed to injurious substances will be born with handicaps which limit the approximation of their potential as human persons. In making this argument, I accept the value judgment that it is a fundamental good to ensure, within reason, full expression of human potential.

I would argue that the other assertions which might militate against this judgment and its corollary, that the previable human fetus has a claim on us, are not compelling. For example, one argument that the fetus is exempt from our moral duty to respect it is that the fetus cannot be regarded as a "moral agent" because it does not have the capacity to enter reciprocal moral agreements which

entail rights, claims, duties and obligations. A second argument is that the fetus is not to be granted the status of a "human being." Because it is not yet human, it lacks the necessary precondition of protection—a recognizable equality of social worth. The legal view derives from Justice Blackmun's majority decision in Roe v. Wade that the previable fetus is not recognized by the law as "a person in the whole sense" and therefore, the rights of the mother for privacy in her reproductive decision making override those of the fetus prior to the acquisition of its full potentiality for independent life.

Reasonable persons may differ as to the proper interpretation of the concept of "moral agency" or "person"; and legal scholars have contested the Court's "actual" intent in denying recognition of the fetus's standing. The question of personhood is clouded by the distinction we might give to "personhood" as an emergent property defined by the psychobiology of the organism and "personhood" as a relational property defined by the social nature of persons.<sup>2</sup> For example, Morris<sup>3</sup> uses a sociological basis for defining personhood in observing:

When we talk of not treating a human being as a person or 'showing no respect for one as a person' what we imply by our words is a contrast between the manner in which one acceptably responds to human beings and the manner in which one acceptably responds to animals and inanimate objects. When we treat a human being merely as an animal or some inanimate object, our response to the human being is determined, not by his choices, but ours in disregard of or with indifference to his." (p. 490)

By this analogy, we might recognize the biological personhood of a fetus, yet justify responding to it as if it were an animal.

I find this and similar approaches totally unsatisfactory because they are either untestable (e.g., verifying that the fetus is a "nonperson"); inconsistent (e.g., the proposition that although the fetus is not a moral agent, it has some of the rights which we associate with moral agency); or irrelevant (e.g., the assertion that the fetus does not have standing in the eyes of the Court may be taken to pertain only to its claims as they conflict with those of its mother for privacy, but not to fetal research).

Where then do I derive the notion that the previable fetus has a legitimate claim on us for protection? From those socially sanctioned and institutionalized activities that are universally acknowledged to be desirable and which we already perform during pregnancy. For example, where we have been able to identify specific causes of fetal disability during pregnancy (e.g., maternal infection with rubella or exposure to established teratogens such as thalidomide), we have rapidly instituted programs to bring those agents under control. The actions taken, if scrutinized, will be seen to be directed at preserving fetal and not necessarily maternal well-being during pregnancy. For example, the idea of mass vaccination of school age children against rubella to create a "herd" immunity against a potential pool of contagion is primarily to benefit the fetus, as are the regulations which now prohibit the prescription of drugs which might be beneficial to the mother, but of doubtful safety to the fetus. It is well known

that the Food and Drug Administration has strict policy guidelines which are scrupulously followed by most, if not all, drug companies which enjoin patients against the use of a very large proportion of potentially therapeutic agents during pregnancy (i.e., therapeutic for the mother) for the express purpose of protecting the previable fetus.<sup>4</sup>

The tacit recognition of the needs of the fetus give substance to the claim that we already behave towards previable fetuses (as distinct from their mothers) as if they were deserving of protection. We can test, along with moral philosopher R. M. Hare, the measure of our obligation by asking ourselves how we would wish others to have behaved toward us. The answer is straightforward and unambiguous: We consider ourselves deserving of such protection because we would wish others like us to have received the same protection. ("Others like us," however, does not include those potential human beings whose existence has been terminated through abortion.)

# 2. The Deservedness of the Fetus to Protection Is not Altered by Societal Acquiescence to the Need for Abortion

As I understand it, the decision to allow a woman, in conjunction with a medical practitioner, to remove a previable fetus from her body for whatever personal reasons so motivate her was based on a balancing of constitutional claims of the fetus to its emergent potentiality for independent existence against those of the mother for privacy in her reproductive decision making. Simply because the Court made a decision which allowed a woman to make the autonomous decision that a fetus will no longer receive her protection, it does not follow that others in society are similarly enjoined. The fetus, theoretically, still retains those other nebulous "rights" which the Court alluded to in allowing that during the second trimester states may assert their interest in potential life beyond the protection of the pregnant woman. Unfortunately, the Court offered no guidance as to what constituted proper medical conduct in removing the fetus from the mother—and more importantly, how the fetus was to be treated once out of the womb.

Because some of the abortions performed late in the second trimester will necessarily bring some fetuses close to the established point for viability, many fetuses have been aborted alive (witness the recent Edelin case). Once out of the womb, these fetuses have claims on our duties to afford them protection from experimentation by virtue of our basic medical tenets to preserve life. However, the procedures we can institute to protect potentially viable fetuses ex utero depends in part on how carefully we have considered the methodologies used to abort them.

Space will not allow a complete treatment of the full range of techniques which are being developed to permit abortions to be done with relatively low risks of maternal morbidity and mortality. The most commonly used mid-trimester technique through the early 1970s, saline abortion, underscores part of the dilemma. The concentrated salt solution which indirectly induces cervical dilation (laminaria tents may be used) and uterine contractions, was originally

chosen because of its relatively low incidence of maternal morbidity. The fetus, however, is apparently exposed to severe damage, including salt poisoning and intravascular clotting.

Considering fetal experimentation in this context illustrates the cross-purposes at which we now find ourselves. By the choice of abortion techniques which completely disregard the potential physiological needs of the fetus, we utilize procedures which may so damage the fetus as to preclude meaningful debate on restoring conditions ex utero which would permit continued normal development.

As long as the objective of a pregnancy was generally recognized to be the delivery of a live, nutritionally sound, physically intact (i.e., a "healthy") fetus, experimentation during the prepartum period was firmly bound to the Hippocratic tradition of sustaining life and primum non nocere (above all else, do no harm). We were constrained to limit any intrusive or potentially harmful experimentation in keeping with the principles which guided experimentation on other nonconsentual persons whose well-being we had at heart. It is logical that once that constraint was abridged for the purposes of the radical experiment of abortion, the ethical obligations owed to that class of persons potentially subject to minor experimentation become less tenable. I believe that the abortion decision, while not related to the general charge to respect the rights of fetuses to protection, does condition the debate concerning those individual fetuses which are themselves subject to abortion.

# 3. The Conditions Under Which We Respect the Fetus's Right to Protection are Compromised by the Decision and Actions Taken to Abort It

In a purely physical sense, the technique we elect to perform that abortion, itself selected on the basis of maternal and not fetal considerations, delimits the range of moral concern which we may logically continue to show to the fetus once it is aborted. I cannot accept the view, morally sound as it may be, that we must continue to treat the abortus as if it were a potential human life.

In an ideal world, perfect moral scrupulosity would protect the fetus throughout its gestation—and all fetuses would be born intact and wanted. There is a moral consistency to those who would deny both the acceptability of abortion and the permissability of research on the fetus. At the same time, it is morally inconsistent to accept our "right" to destroy the fetus but to reject any case which might be made to utilize that death for humanitarian purposes. The inconsistency stems from the failure to balance concern for the severity of abortion techniques and utter disregard of the fetus in effecting its abortion against concern for protecting the fetus from abuse after it is aborted.

A middle ground, one which I advocate, is to include in the guidelines for fetal experimentation controls over the nature of experimental abortifacient research, such that the development and utilization of new technologies which subject the fetus in utero to "extreme violence" or other grossly unacceptable procedures may be controlled. Moral concern for the fetus would dictate the

choice of procedures which not only subjected the mother to small risks of morbidity, but would expeditiously expel the previable fetus--and ideally, simultaneously render it incapable of extrauterine survival. Thus, the purportedly elective choice to defer abortion in patients at 13-15 weeks gestation for abortion by intra-amniotic saline at 16 weeks or later not only poses greater risks of morbidity to the mother, but also places at risk a potentially sensate fetus (ganglia extend fibers into body organs and skin, and the spinal cord and brain form their first connections around 20-22 weeks of gestation) which previously (at 13-15 weeks) did not likely have the biological basis for perceiving pain.

The development and use of prostaglandins is apparently unregulated by the temporary ban of fetal research (see reference 7, for example). Such research poses extreme ethical problems for fetal experimentation (even though the intended subject is the mother) because of the increased likelihood of "natural" patterns of labor which pose less likelihood of fetal distress and intrapartum death, and therefore result in the birth of more living previable fetuses than accomplished by previous techniques. Concern for the treatment of these fetuses postabortion (abortuses) should be evinced by this committee's recommendations.

To reemphasize a critical point: The fact that we allow the abridgment of the rights of the fetus for some purposes (e.g., respecting the claims of the mother for privacy in reproductive decision making) does not dictate the abridgment of our responsibility for other protective acts towards the fetus. In this, I am in agreement with the original NIH policy proposal on fetal research that "the decision of the Supreme Court on abortion does not eliminate the ethical issues involved in research on the nonviable human fetus." However, once we have incurred the costs of doing abortion, the moral universe in which we have to operate is in fact changed, and we acquire new moral duties. One of those new duties is to act in ways which prevent mass abortion from eroding our moral sensibility to wanted fetuses and newborns; another is to rectify the costs of doing abortion by ethical behavior, both in the manner in which abortions are done, and in the uses to which aborted fetuses are put.

# 4. Balance the Costs of Doing Fetal Research With the Resultant Goods

The fine line to be drawn in any attempt to redress the balance of moral goods and wrongs in fetal research is to ensure that the proposed solutions do not add to any moral wrong which has already been committed.

Paul Ramsey has addressed this dilemma at length in his book on fetal research. Where there is a question of medical experimentation on a fetus preor postabortion, the "fact" of abortion forces us to examine two conflicting
moral choices. We may either resist, in Paul Ramsey's words, the temptation
"to wrest some good out of guilt-laden harmfulness to unborn life" (his view of
abortion); or we may, in Willard Gaylin's and my own view, "endow the process
of abortion with human values it would not otherwise have had."

When Gaylin and I make the case for intrauterine research on a still-living human fetus, $^{10}$  we do so on the basis of an ethical calculus which balances

the moral harm of acting against the moral harm of not acting (not only the accrued good of those acts). For example, we justify preabortion in utero research of attenuated viral vaccines intended to protect the fetus against congenital malformation or death by citing the good of minimizing the potential harm done to a larger population of fetuses which are at risk for defect, and the moral weight of having to consider abortion for additional wanted fetuses. It is an oversimplification to state that we have appended a lesser moral wrong to a greater one (as Ramsey insists). What we have done is add a moral good to a morally tragic situation. We would not, for example, want to justify additional abortion-related research which did not have the intention of aiding fetuses, but neither would we have our "good" case justify more abortions to give more subjects for research.

Abortion should not be construed to give license to any and all experimentation (and here I agree with Ramsey). The fact of imminent demise does not provide a sufficient rationale for experimentation on the still-living fetus. The ethical rationale for research involving the living fetus preabortion must include a consideration of potential harm and risks to the fetus and mother, but the determination that the procedure is risk-free, as it would were it to be in the ethical domain of acceptable experimentation for nontherapeutic purposes on nonconsentual persons, need not be made. (Recall that I have not based my argumentation on the unascertainable fact that the fetus is a "person," but rather on our collective understanding of the different duties we owe the fetus as a potential person.)

A minimum of two conditions would seem to be required for any preabortion experimentation. The legitimate purposes of the experimentation must be established, and defined within a methodology that does not offend our moral standards, And, secondly, the mother must retain the right to refuse to allow herself (and her fetus) to be experimented upon.

Assuming for the moment the validity of the research procedure, the problem of consent is one that gives us most difficulty. Even were the fetus accorded the rights of personhood, it would obviously not be capable of granting its own consent, and it is problematic to do as in other conditions where an individual is deemed incompetent to stand for himself, and delegate a proxy. In the cases of a child, the parent is the usual proxy. But in the case of the fetus-to-beaborted, the parent cannot be said to have the interests of the fetus at heart.

Even here there are limitations, depending on the nature of the experiment. Roughly speaking, experimentation can be divided into two classes: The first is experimentation to perfect or develop as yet unproven therapies which involve using a drug or procedure before it has been adequately proved out on an individual often as a last desperate measure in the treatment of a condition which is threatening to life. The purpose of such research may be to help the subject as well as to do research or it may be a complex mixture of an intent to aid with the need to perfect the therapy such that it will be more efficacious next time.

The second category may be thought of as philanthropic. The subject offers himself for humanitarian purposes to be the subject of an experiment which may

harm him and which serves no personal selfish interests. Many of us have felt that, with rare exceptions, no nontherapeutic form of philanthropic experimentation may be permitted on a proxy basis. I have assumed that while it is a noble thing to offer oneself to science it is somewhat less generous to sacrifice someone else. Were the fetus regarded as worthy of all the rights of personhood, it would fall into this classification, and be immune from nontherapeutic experimentation. But were the fetus so regarded, we would not be free to take its life, and indeed there lies much of the covert opposition to this research.

That group which cannot reconcile itself to the Supreme Court decision (and therefore the law of the land) will logically oppose any activity that builds on the right to abortion even if (particularly if) it allows the abortion to contribute to some common good. They do not want to risk the legitimation of what they consider "legalized murder."

In establishing a minimal case for experimentation on the living fetus, we should first eliminate all research which could just as well be done on laboratory animals as on the fetus. Unfortunately, this is all too common in current practice. The fetus must never be seen as a convenient or inexpensive laboratory animal. The insensitivity of certain researchers in conducting precisely such experimentation has been responsible for generating much revulsion in the field. Secondly, we would draw an arbitrary line between in utero and ex utero research, recognizing that a whole set of new considerations and new moral dilemmas are created when we extend the life of a fetus outside of the womb for purposes of experimentation. And thirdly, we would distinguish research done on the expendable or replenishable by-products of conception, notably those cells shed into the amniotic fluid, or the fluid itself, recognizing that contingent upon adequate demonstration of the safety of obtaining these materials through "amniocentesis," this research raises special problems other than violating the integrity of the fetus.

The most justifiable experiment would seem to us to be that which is closest to the therapeutic model. Of course, in the abortion model it cannot help the fetus to be experimented upon since it is doomed to death anyhow, but perhaps it can ennoble that death by utilizing it to serve its more fortunate fellows, i.e., a research designed to help in preserving the life, health or integrity of untold wanted children. If the doomed fetus could be utilized to supply the information that could permit those same parents, or similar parents, a greater opportunity for a healthy, wanted child it would be a persuasive argument for experimentation. The classic example would involve: a disease which is lethal or damaging to the gestating child; a vaccine or drug which would prevent the disease in an expectant mother; the vaccine has been proved harmless or the drug efficacious to adults; its effect on the developing fetus is unknown, i.e., it may be harmless, or therapeutic, or it may be more destructive than the disease.

# 5. The Definition of Death of a Fetus, Which Is the Potential Subject Of Experimentation Is to be Made Independently From Any Eventual Use

I recognize that the question of when it may be acceptable to perform certain types of fetal experimentation will be contingent upon whether or not it

has been possible to determine incontrovertibly that the fetus is in fact "dead." The definition of "death" presupposes that one understands the distinction between "alive" and "dead" in physiological terms, and more important, that one understands what it is that "dies."

A fetus (from the Aryan root, bheu meaning to become) is distinguished from the child, or adult, by virtue of the fact that its "living" is simultaneously a "becoming": It is defined in terms of what it will be as well as what it now is.

Death for a fetus or an embryo may be physiologically distinct from death for a child, since, for example, embryonic and fetal tissues have a much higher tolerance to anoxia (reduced oxygen levels) than do those of the infant. When a fetus dies is further complicated by the question of when it becomes meaningfully alive. It is one thing to speak of "the death of a person," but another to speak of the death of something which is not yet a person.

For example, the body of a human being is not a person. Even when, by the brain definition of death, a body has a pulsing heart, an active endocrine system, a functioning hematopoietic system, and respiratory exchange, it is nonetheless no longer a person. It is therefore subject to the kind of experimentation, dissection, exploitation and abuse that we do not allow to a living person. This, in part, is why the question of personhood appears to be crucial in any treatment of the fetus—if we wish to argue symetrically we would be forced to ask if the fetus is to be denied personhood until cortical activity starts, or only after it achieves the capability of some semblance of human interaction. But as I have stressed, such reasoning is inherently suspect; a person—potential or real—cannot be measured by biology alone any more than it can by religious standards.

The ethical considerations for determining that a potential human organism is in fact no longer alive include at least the following:

- A. That the criteria chosen should be completely independent of the ultimate uses to which that organism is to be put, if any: and
- B. That the deliberations and conclusions used to decide upon the time of death of a fetus should not be influenced by the ultimate research needs.

These positions, as enumerated in a report from the Task Force on Death and Dying at the Hastings Institute, included the arguments that the choice of criteria for pronouncing a person dead, as well as the procedures, criteria and the actual judgment in determining the death of that one human being, should "not be contaminated with the needs of others, no matter how legitimate those needs may be." Therefore, according to the signatories, it is ethically imperative to have a universally agreed-upon test for determining that death has occurred.

To summarize our previous recommendations as they would apply to the fetus:
(1) the criteria should be unambiguous and involve assessment of the presence or absence of recognized indicators of aliveness, e.g., heartbeat; (2) the tests should be simple, such that they can be done easily and conveniently by nurses or physicians of ordinary competence; (3) the test should include a measure of the permanence of loss of any vital functions; (4) more than one function should be included among the criteria. (My own recommendations follow from here):
(5) the attempt to ascertain absence of cortical activity need not be made in the case of the fetus; (6) attempts to ascertain the presence or absence of vital signs in an aborted fetus should not themselves be resuscitative; (7) in the absence of spontaneous signs of life, no resuscitation should be attempted.

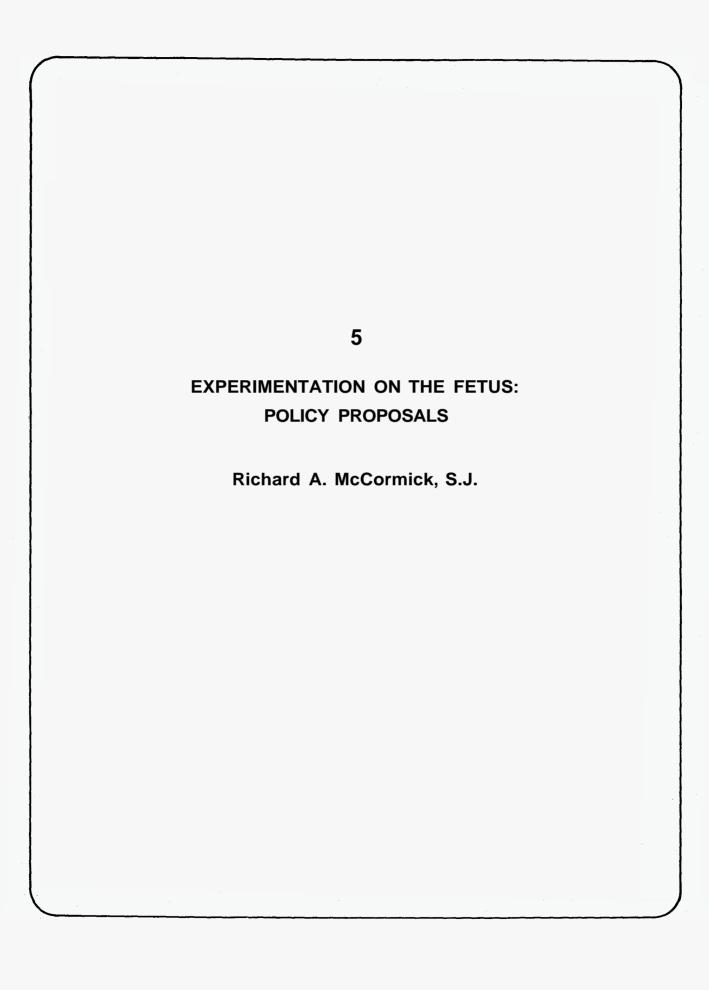
## POLICY RECOMMENDATIONS

- That the committee affirm its commitment to protect fetuses while in utero from injury, willful neglect, or undue harm.
- 2. That such statement be made morally congruent with the general need for such regard during pregnancy, so as to include concern for classes of abuse or neglect that are outside the experimental model, including:
  - Controllable maternal exposure to potentially injurious agents
  - Choice of abortifacients.
- 3. That the committee permit only very limited research on viable fetuses in utero which are subjects of abortion, such research to be guided by the following principles:
  - That nontherapeutic experimentation is permissible where it involves no risk of harm or defect or no increase in risk to the subject in its immediate preabortion state
  - That the objective of the experiment be to obtain knowledge which affords fetuses as a class protection from potentially life-threatening or defect-producing agents.
- That research intended to benefit society generally or other basic studies be performed on the previable fetus after ascertaining that it has died.
- 5. That the ascertainment of death be made by criteria which separate the purposes of experimentation from either the technique chosen for abortion, or the methodology for ascertaining that death has occurred.

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- 2. The newborn, for example, would be given such standing because it rapidly undergoes a mutual process of socialization with its mother which appears to be a necessary concomitant to its orderly neurological, psychological and physical development.
- 3. Morris, Herbert, "Persons and Punishment," The Monist 52: 475-501, 1968.
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# Experimentation on the Fetus: Policy Proposals

## 1. DEFINITION OF TERMS

By the term "experimentation" as used here, I understand all procedures not directly beneficial to the subject involved. (There is little moral problem and should be little policy problem where procedures are experimental but represent the most hopeful therapy for an individual.) By the term "nonviable fetus" I understand a fetus incapable of extrauterine survival. (Attention in this study will be restricted to the nonviable fetus because I shall suppose that in all decisively relevant moral and policy respects touching experimentation, the viable fetus should be treated as a child.) The nonviable fetus, as an experimental subject, could be further subdivided as follows:

#### In Utero

- No abortion contemplated
- Abortion planned
  - prior to abortion
  - during abortion
  - after abortion\*
    - living
    - dead

#### Extra Uterum

- Spontaneous abortion
  - living
  - dead
- Induced abortion\*
  - living
  - dead

(\*Probably identical in all decisive respects)

## 2. MORALITY AND PUBLIC POLICY

Before sound public policy proposals can be developed, the relationship between public policy and morality must be clarified. Morality concerns itself with the rightness or wrongness of our conduct. Law or public policy, on the other hand, is concerned with the common good. Clearly, then, morality and public policy are both related and distinct. They are related because law or public policy has an inherently moral character due to its rootage in existential human ends (goods). That is, the common good of all persons cannot be unrelated to what is judged to be promotive or destructive to the individual (sc., moral or immoral). They are distinct because it is only when individual acts have ascertainable public consequences on the maintenance and stability of society that they are the proper concern of society, fit subjects for public policy.

Once this point has been made, several additional clarifications are in order. First, what actions ought to be controlled by policy is determined not

merely by the immorality of the action, but beyond this by a single criterion: feasibility. Feasibility is "that quality whereby a proposed course of action is not merely possible but practicable, adaptable, depending on the circumstances, cultural ways, attitudes, traditions of a people . . ." Feasibility, therefore, looks to questions such as: Will the policy be obeyed? Is it enforceable? Is it prudent to undertake this or that ban in view of possibly harmful effects in other sectors of social life? Can control be achieved short of coercive measures? And so on. The answer to the feasibility test depends on the temperature of a society at any given moment in its history.

I make this point in discussing fetal experimentation because the feasibility test is particularly difficult in our society and will profoundly affect the Commission's policy proposals. Ultimately public policy must find a basis in the deepest moral perceptions of the majority or, if not, at least in principles the majority is reluctant to modify.<sup>2</sup> This means that it is especially difficult to apply the feasibility test where fetal experiments are concerned, for the good itself whose legal possibility is under discussion is an object of doubt and controversy. That is, the moral assessment of fetal life and value differs.

A second point to be made is that policy will not infrequently go beyond morality. Concretely, while one might morally justify this or that experimental procedure on the fetus, the danger of abuse or miscalculation might be so considerable as to call for a policy ban, or safe-side regulatory cautions. It is one thing, for instance, to justify morally a single sterilization on a mentally retarded girl in her own best interests. However, when one sees five years later that his moral reasoning has been used to sterilize 100,000 indigent blacks, then an exceptionless policy may be called for, or at least safe-side regulations to prevent such abuse.

#### MORALITY AND FETAL EXPERIMENTATION

The literature on this subject (to be reported below) is very sparse.3 what does exist has drawn attention to the analogies with experiments on children. However, at least two things must be noted about this analogy. First, whether the question of fetal experimentation approximates, and indeed, is in most crucial respects identical with experimentation on children, depends on one's assessment of fetal life. If one regards the fetus as "disposable maternal tissue" or as "potential human life" only, then the questions are sharply different and will yield a different moral conclusion, and ultimately a different public policy. If, however, the nonviable fetus is viewed as "protectable humanity" or a "person" with rights, then the problems are quite similar. Secondly, the nonviable fetus (whether abortion is contemplated or not) is in a dependency relationship, its health and growth being linked more or less to maternal health. This relationship can be read in a variety of ways in terms of its ethical yield. But one thing all would agree on is that whatever fetal experimentation is judged to be warranted, it must take account of maternal health.

Thus while there are possible differences in these two problems (experiments on children and fetuses), there are important continuities. If one judges

all experimentation on living children (even if they are dying) to be an abuse and immoral and at the same time regards the nonviable fetus as a person in his own right (even though within a dependency symbiosis), it is safe to say that he will condemn (morally) all experimentation on living fetuses in whatsoever condition they be. Contrarily, if one morally justifies some experimentation on children, it is quite possible, though not inevitable, that he could and would extend this justification to fetuses.

There are two identifiable schools of (moral) thought where experimentation on children is concerned. The first is associated with Paul Ramsey¹ and is supported by William May.⁵ The second is the position of Curran,⁶ O'Donnellⁿ and McCormick.⁶ Ramsey argues that we may not submit a child to procedures that involve any risk of harm or to procedures that involve no harm but simply "offensive touching." A subject can be wronged without being harmed. This occurs whenever he is used as an object, or as a means only rather than also as an end in himself. Why is this so? Ramsey argues as follows: "To attempt to consent for a child to be made an experimental subject is to treat a child as not a child. It is to treat him as if he were an adult person who has consented to become a joint adventurer in the common cause of medical research. If the grounds for this are alleged to be the presumptive or implied consent of the child, that must simply be characterized as a violent and false presumption." Therefore Ramsey concludes that no parent is morally competent to consent that his child be submitted to any nontherapeutic experimentation.

Thomas O'Donnell accepts the moral validity of vicarious consent where the "danger is so remote and discomfort so minimal that a normal and informed individual would be presupposed to give ready consent." Charles Curran has drawn a similar conclusion, but without supporting moral reasoning. He states: "I would maintain that children can be used in experimentation if there is no discernible risk to them, and their parents consent."

I have attempted to argue for a position that would allow experimentation on children where there is no discernible risk or undue discomfort." The position departs from Ramsey practically only if he disallows any give and play with the term "discernible risk." More importantly, it is at one with Ramsey's analysis in rejecting any utilitarian evaluation of children's lives that would submit their integrity to a quantity-of-benefits calculus far beyond any legitimately constructed consent. The heart of my argument is this: if we analyze proxy consent where it is accepted as legitimate (sc., in the therapeutic situation) we will see that parental consent is morally legitimate because, life and health being goods for the child, he would choose them because he ought to choose the good of life. In other words, proxy consent is morally valid precisely in so far as it is a reasonable presumption of the child's wishes, a construction of what the child would wish could he do so. The child would so choose because he ought to do so, life and health being goods definitive of his flourishing.

Once proxy consent in the therapeutic situation is analyzed in this way, the question occurs: Are there other things that the child ought, as a human being, to choose precisely because and in so far as they are goods definitive of his well-being? As an answer to this question I have suggested that there

are things we ought to do for others simply because we are members of the human community. These are not precisely works of charity or supererogation (beyond what is required of all of us) but our personal bearing of our share that all may prosper. They involve no discernible risk, discomfort or inconvenience yet promise genuine hope for general benefit. In summary, if it can be argued that it is good for all of us to share in these experiments, and hence that we ought to do so (social justice), then a presumption of consent where children are involved is reasonable and proxy consent becomes legitimate.

The moral reasoning outlined above yields a conclusion that is shared, at a practical level, by Curran, Beecher, Ingelfinger, the Helsinki Declaration, the Archives of Disease in Childhood and others. Yet it has built into it rational limits and controls not always present in merely practical statements.

With this as a background we now turn to fetal experimentation itself. What one judges to be morally appropriate and acceptable where fetal experiments are concerned depends above all on his evaluation of the fetus. Here there are two general schools of thought. The first would regard the fetus as a nonperson or as "potential human life." These terms are used in the moral, not the legal sense, though it is clear that one who is not a person morally should not be considered such legally. At any rate, one who is not a moral person, who is morally a nonperson——andtherefore not the subject of rights and claims——seems to present little problem where experimentation is concerned. One who holds this position ought to conclude, if his moral reasoning is consistent, that experimentation on the fetus is legitimate and desirable, or if there are to be restrictions they are rooted in values other than the fetus itself in its present state.

The second general school of thought is that the fetus is, indeed, protectable humanity, and an appropriate subject of rights. Within this school of thought, three distinct tendencies or subdivisions are identifiable: fetus is protectable humanity but to be valued less than a viable fetus or born infant. This school would probably tolerate experiments if the benefits are great, but no literature has made this conclusion explicit. (2) The fetus is a fellow human being and must be treated, where experimentation is concerned, exactly as one treats the child. Just as the child may not be exposed not only to harm and risk, but also to "offensive touching," so the fetus may not be exposed to any risk or even to "offensive touching." This would seem to be the position of Ramsey.16 Concretely, at one point the nonviable fetus is to be likened to an unconscious patient; at another point the nonviable living fetus (after instances of spontaneous or induced abortion) is to be likened to a dying patient; prior to an induced abortion the fetus is to be likened to the condemned. Since it is immoral to experiment on the unconscious, and, without their consent, on the condemned or dying, it is immoral to experiment on the fetus -- andthis would apply even to "offensive touching." In logic Ramsey ought to conclude that no experimentation on living fetuses is morally warranted. (3) The fetus is a fellow human being and ought to be treated, where experimentation is concerned, exactly as one treats the child. However, experiments on children, where no discernible risk or discomfort is involved, is morally legitimate if appropriate consent is obtained and if the experiments are genuinely necessary (trials on animals are insufficient) for medical knowledge calculated

to be of notable benefit to fetuses or children in general. This is an extension to the fetus of the moderate position on children outlined above. It is, I believe, a defensible moral position--but the way the position is defended is utterly crucial (I shall return to this below) if sufficient protection of human subjects is to be assured.

The position just outlined is the one I would attempt to defend and the one I would propose to the Commission as the basis for its policy proposals. But since the fetus can be in a variety of postures or situations, this general approach must be carefully applied to this variety of postures. I emphasize here that I am discussing for the present a moral position (not immediately what public policy ought to be) and one that reflects my own views.

For purposes of clarity and precision, the original outline under definition of terms will be followed.

## A. The Fetus In Utero

- (1) No Abortion Contemplated. Theoretically, if there is no discernible risk or discomfort to the fetus and to the mother, and appropriate proxy consent is obtained, such experimentation could be defended as morally legitimate—on the same grounds that identical experiments on children could be defended. Practically, however, one must question the necessity of experimentation here (a factual matter). If fetal material is otherwise available, experimentation here would be inappropriate precisely as unnecessary.
- (2) Abortion Planned. Here a preliminary general reflection is in order. It applies to the fetus prior to abortion, during abortion, and after abortion (whether the fetus be living or dead). It is the issue of cooperation. If one objects to most abortions being performed in our society as immoral, is it morally proper to derive experimental profit from the products of such an abortion system? Is the progress achieved through such experimentation not likely to blunt the sensitivities of Americans to the immorality (injustice) of the procedure that made such advance possible, and thereby entrench attitudes injurious and unjust to nascent life? This is, in my judgment, a serious moral objection to experimentation on the products of most induced abortions (whether the fetus be living or dead, prior to abortion or postabortional). It is especially relevant in a society where abortion is widely done and legally protected.

However, I have no confidence that a society that does not share the underlying judgment on most abortions and is so highly pragmatic as to be insensitive to the issue of cooperation will be impressed by this moral consideration--factors that must be taken into account where public policy (feasibility) is concerned. That is, public policy must root in the deepest moral perceptions of the majority, or at least, in principles the majority is reluctant to modify. Since there is such profound division on the moral propriety of abortion, the moral notion of cooperation in an abortion system will not function at the level of policy.

- (a) Prior to Abortion. One cannot approach the position of the If the planned abortion is morally legifetus without a further distinction. timate, we might say that the fetus is in the situation of the tragically but justly condemned individual. In this instance, if the proposed experimentation will involve no discernible risk to the fetus, I believe that proxy consent (of the mother) would be a defensible construction of fetal wishes. If, however, the proposed experimentation will involve discernible risks to the fetus, then proxy consent is an invalid construction. If the planned abortion is not morally legitimate, we might say that the fetus is in the situation of an unjustly condemned individual. In my judgment, this is the case with most abortions now being planned and performed. In this instance, the full moral weight of the cooperation issue strikes home--but once again, not at the policy level, as stated above. Secondly, there is the issue of consent and its validity. The consent requirement is premised on the fact that the parents are the ones who have the best interests of the child (here the fetus) at heart. But does such a premise obtain when an abortion (presumably immoral) is being planned? Does a mother planning an abortion in the circumstances described have the best interests of the fetus at heart? I think not. Thirdly, there is the possible change of mind of the mother. Allowing experimentation prior to abortion -- that is, experimentation that is potentially risky or harmful to the fetus--prejudices the freedom of the woman to change her mind about the abortion, and thus constitutes an infringement on fetal rights for this reason alone, if for no other. To those who do not share my evaluation of fetal life, these considerations will, of course, seem marginally relevant at best.
- (b) <u>During Abortion</u>. Once again, a distinction: If the abortion is morally legitimate, then granted appropriate proxy consent, experimentation could be legitimate if it left the fetus in no worse position during its dying than it is in as a result of the abortion. If, however, the experimentation leaves the fetus in a worse position (e.g., pain), then it is equivalent to illegitimate experimentation on the dying. If the abortion is not morally legitimate, then experimentation on the fetus raises two of the points mentioned in the above paragraph, namely, cooperation and invalidity of consent. The question of "discernible risk" seems meaningless morally, since it seems meaningless to speak of exposing to risk one who has already been inserted into a lethal situation.
- (c) After Abortion. The fetus may be either living or dead. If the fetus is still living and the abortion was morally legitimate, then experimentation seems morally legitimate if it induces no pain or discomfort. For if the fetus may be constructed to consent to experiments where no discernible harm is involved, and if he is in a situation (lethal) where the difference between discernible harm or risk is meaningless, then he may be legitimately constructed to consent--given appropriate proxy consent. If the fetus is still living and the abortion was morally illegitimate, then the above issues (cooperation, consent) could intrude to prevent any morally legitimate proxy consent.

## B. The Fetus Extra Uterum

(1) <u>Spontaneous Abortion</u>. The fetus may be either living or dead. If it is dead, there should be no moral objection to experimentation. If the fetus is living, the same conclusion obtains providing experimentation imposes no pain;

for the fetus may be legitimately constructed to consent to experiments involving no discernible risk, and he is in a situation (lethal) where the distinction between no discernible risks and discernible risk is meaningless.

(2) <u>Induced Abortion</u>. Here the same things are to be noted that were stated above about a fetus *in utero* after abortion.

In summary, then, within the parameters of my evaluation of fetal life, fetal experimentation would be clearly justified, with appropriate safeguards, distinctions and consent, where the abortion is spontaneous or has been justification, induced. Where it has been induced without moral justification, I believe there are moral objections of various sorts against experimentation. However, since these objections are premised on the moral character of the abortion, and since this is a difficult (at times) determination in itself, and since the ultimate judgment will hardly be shared by a majority, these objections will be extremely difficult, indeed impossible, to formulate in policy proposals on fetal experiments. Moreover, one can question whether restrictions on fetal experiments rooted in such considerations is the best way to highlight the moral illegitimacy of the abortion.

Where experimentation is morally justified, it is so because of the legitimacy and sharp limitations of proxy consent, extrapolated from the legitimacy of proxy consent where children are concerned. I wish to emphasize this point here. If proxy consent (with the clear limitations on the validity of this consent) is not the basis for the moral legitimacy of experimentation on fetuses, then the integrity of the individual will be "protected" not by soundly reasoned constructions of what the fetus--or any human being--would consent to because he ought, but by a very unpredictable and highly utilitarian assessment of his value and worth as over against great (alleged) scientific and medical benefits for others. Such an assessment does not provide but erodes -- in a highly technological, pragmatic society -- individual protection. Thus the DHEW's original but tentative version of "Protection of Human Subjects, Policies and Procedures"17 stated: "The investigator must also stipulate either that the risk to the subjects (children) will be insignificant, or that although some risk exists, the potential benefit is significant and far outweighs that risk." such thought and language is the germ--and even more--of the subordination of the individual to the collectivity. That germ is in the conclusion, to be sure; but it is far more insidiously present and threatening in the very way of thinking, in the form of moral reasoning undergirding it. We call it utilitarianism. And whatever the policy proposals this Commission recommends, it will have only gotten mired in the cultural status quo if its conclusions root in a utilitarian assessment of the value and integrity of man, fetal or otherwise.

Avoidance of this trap will not be easy. For if notable medical benefits do not justify all experimentation, they are the only things that justify any experimentation. And once that is said the tendency will be to give medical benefits the preference. Furthermore, if fetal individuality and dignity do not prohibit all experiments, they certainly prohibit some. It is the first task of this Commission to discover the form and structure of moral reasoning on which alone the proper protective balance can be based and spelled out in policy proposals. That form and structure centers around proxy consent, its legitimation and limitations.

## 4. ABORTION POLICY AND EXPERIMENTATION POLICY

I raise this issue prior to an explicit consideration of policy proposals because I presume that legal or policy consistency is, at least to some extent, a desideratum. From a moral point of view fetal experimentation and abortion are in some respects separable issues. That is, even though a particular abortion is judged to be morally justifiable, one could maintain that experimentation on the living abortus is illegitimate experimentation on the dying. And that is a different question from the morality of the abortion itself. There are those who would convert such separability as follows: even though the abortion was illegitimate, it does not follow that experimentation on the abortus is also illegitimate. (I do not believe the matter is that simple, as noted above.)

However, there is a point at which these issues converge, particularly in the popular mind. This convergence is best seen at the policy level. existing abortion law (Roe v. Wade, Doe v. Bolton) fetal life enjoys no protection during the first two trimesters of pregnancy, and even in the third the compelling interest of the state is qualified by maternal health so broadly defined that it would be difficult to convict anyone of an illegal interruption of pregnancy anytime during pregnancy. The rationale for this policy is the predominance of maternal interests, especially privacy, over "potential human life." Now clearly, if fetal life is so totally unprotected with regard to its very existence and survival, and on the grounds that it is only "potential human life," then any policy restrictive of fetal experimentation must find other grounds (other than present fetal humanity and rights) for its restrictiveness-at least if legal consistency is to be preserved. For it is patently ridiculous to stipulate that fetal life may be taken freely because it is only "potential human life," and yet to prohibit experimentation on this same "potential human life," especially when great medical benefits may be expected from such experimentation. For such a prohibition would imply that the privacy or other interests of one woman are of more value than the survival and health of perhaps thousands of fetuses and infants.

I see no way out of this impasse where this Commission is concerned--except to say that perhaps even legal inconsistency has its values. But the only value perceptible to this commentator in such inconsistency is that it may be a first step toward reassessment of the Court's "potential human life." That may be a salutary step, but it reflects what appear to be the only two options open to this Commission: to reaffirm, by implication, the Court's philosophy (as in the dicta) in Roe v. Wade, or to establish proposals (restrictive in character) that are at some point inconsistent with this philosophy. This latter alternative is, in my judgment, the way to go.

## 5. POLICY ON FETAL EXPERIMENTATION

In attempting to develop sound policies (what is feasible) on fetal experimentation, I suggest that the Commission must keep two points in mind: moral pluralism, and cultural pragmatism. A word about each:

## A. Moral Pluralism

Fetal life is variously evaluated, as the abortion decision shows. Even though abortion and experimentation are separable, they are closely related as I have pointed out. Therefore the Commission is in a very delicate position and is faced potentially with another Roe v. Wade decision. In a sense the commission cannot win in its conclusions. If it allows fetal experimentation without sufficient grounding and controls, it will alienate and galvanize those identified with right-to-life positions. If it disallows fetal experiments without sound and consistent reasoning, it will alienate and galvanize the "liberal" and research communities. If it tries to walk a middle path with a utilitarian sliding scale of costs and benefits, every decent ethician in the country will be up in arms.

The only way out of this bind (and one which avoids utilitarian costsbenefits theory) is tied to the notion of proxy consent. In other words, that measure of proxy consent regarded as valid for children, should be the measure of acceptable fetal experimentation. Where children are concerned, proxy consent is legitimate where the experimentation involves no discernible risks, discomforts, or inconvenience—in human judgment. Beyond that the individual must be free to consent for himself. Analogously, the same is true with the fetus. If the experimentation involves no discernible risk, or, if the nonviable fetus is dying and there is no pain, proxy consent may be regarded as legitimate. (There is a moral problem, of course, with the legitimacy of proxy consent where the fetus is about to be aborted or has been aborted. However, since the moral legitimacy of the abortion itself is a highly disputed point in our society, the legitimacy of proxy consent in these cases cannot be decisive at the level of policy. Sc., it is not feasible.)

This practical policy structure (centering on permissibility and controls grounded in proxy consent) has the advantage of speaking to all segments of a divided community. To those convinced of fetal humanity and protectability, it says: nothing more or less is allowed on the fetus than on the child. To the "liberal" and research community, it states the legitimacy and need of fetal experimentation. To the ethical community it states that the legitimacy and control of fetal experimentation is neither capricious nor utilitarian in character, but soundly and rationally based in and controlled by an intelligible principle.

## B. Cultural Pragmatism

Our culture is one where technology, even medical, is highly esteemed; moral judgments tend to collapse into pragmatic cost-benefit calculations; youth, health, pleasure, and comfort are highly valued and tend to be sought and preserved at disproportionate cost; maladaptations (senility, retardation, aging process, defectives) are treated destructively rather than by adapting the environment to their needs. These factors suggest that the general cultural mentality is one that identifies the quickest, most effective way as the good way. Morality often translates into efficiency. This mentality constitutes the atmosphere in which the Commission's policies must be shaped. They are, I believe, calculated to be threatening and inimical to a careful implementation of proxy consent at the fetal-research level. Therefore, I believe that the Commission will best serve the community if it bends toward more protection of individuals, rather than more freedom for experimental research. The culture will bend this latter way, and the proposals ought to be conceived as a balancing influence, not simply a reinforcing one.

If the above reflections are accurate, the task of the Commission (once it has accepted the proxy-consent rationale for experimentation on fetuses) is twofold: first, to spell out insofar as is possible what degree of risk may be regarded, in broad human terms, as equivalent to "no discernible risk"; and second, to detail the procedural demands that will best assure that this determination is realized in individual protocols.

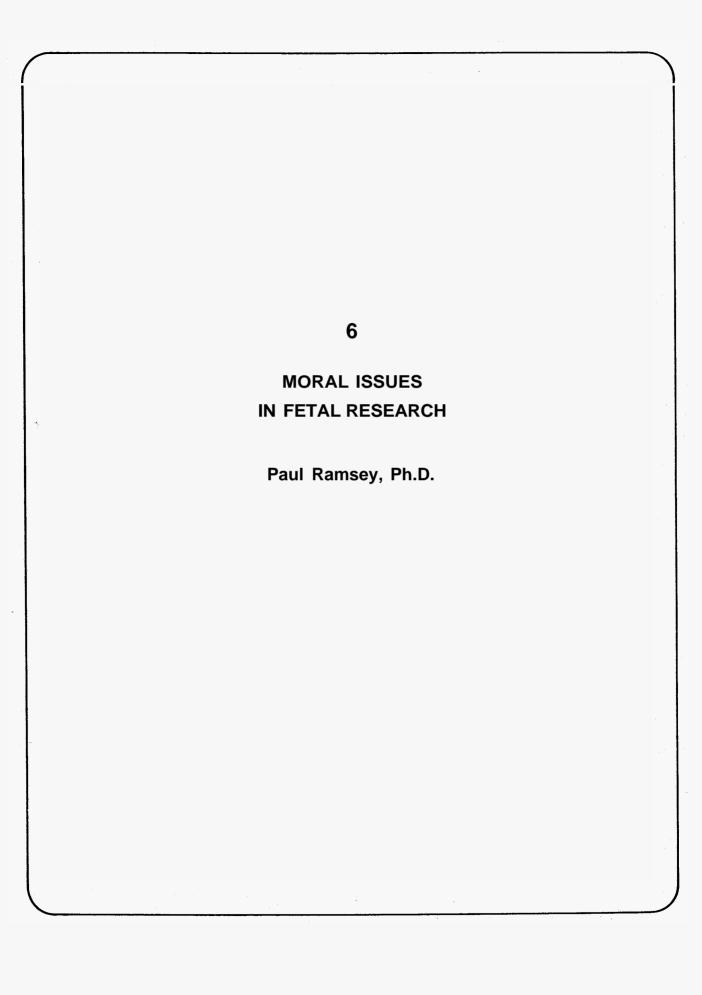
The following points are suggested as an attempt to bring this twofold task to the level of concrete proposals.

- (1) The experiment must be necessary. Use of animals and dead fetal tissue is not sufficient; the experiment is not repetitive (of work being done elsewhere); proportionate benefits are reasonably anticipated.
  - (2) The onus of showing necessity is on the experimental researcher.
- (3) There must be no discernible risk for the fetus or mother, or, if the fetus is dying, there is no added pain or discomfort. (This excludes all experiments that are aimed at determining what harm might come to the fetus, and all experiments that prolong the dying process of the fetus).
- (4) The onus of showing no discernible risk is on the experimental researcher.
- (5) The above demands must be secured by prior approval and adequate review of all fetal experiments. The reviewing group ought to include at least some members outside of the research community. (There is a tendency, as the literature shows, for researchers to minimize risk not only in terms of prospective benefits, but also in terms of the ability to "handle complications" that may arise.)

If these policies appear to some to be too restrictive, it must be recalled that we shall only know whether they are unduly restrictive if they are tried. It is always possible to liberalize; it is much more difficult to retrench—and retrenchment occurs only after rights have been exposed or violated. Where the rights of others are even and only possibly at stake, the part of wisdom and humanity is to try the less obvious, perhaps the more arduous but more conservative (of rights) way.

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# Moral Issues in Fetal Research

We are asked to give some attention to the concept of fetal death. I take the Commission to mean that until we define what we mean by a fetal human subject that is "living" yet "previable" we cannot even begin to discuss whether or in what manner such a being ought to be used in human experimentation. Here there seems to be an unfinished task of first importance: a conceptual task, the task of defining the fetal human subject.

The parameters needed to locate this new potential subject (whether of ethical or unethical human experimentation) must consist of a baseline and an outer limit. The subject must be circumscribed before and after. On one side, physicians need to tell the difference between a dead fetus and a live one. On the other side, they need to tell the difference between a previable fetus/abortus and a possibly viable infant. We need agreement in general about those indices or signs of life which physicians should use in rightly stating that a fetus/abortus has died (a declaration of death) no less than physicians need to know how best to tell the onset of viability, and where the latter line should be drawn for research purposes. In responding to the question of fetal death, I shall address myself to both sides of the descriptive definitional problem.

These are practical questions--about vital signs and viability signs. One line only--the viability line--does not define a class. (Neither does the life line.) One cannot make salvageability do work for both sides of the parameters needed. To declare that a fetus or abortus is not viable is never the same thing as to declare that a living previable fetus/abortus has died.

This the Commission has recognized in asking for comment on the concept of "fetal death." In context, I take that not to be a query about the "meaning" or definition of life and death in any ultimate sense. Rather the question is a practical one, namely, how to tell the difference between a dead fetus/abortus and a live one when we are thinking about bringing the latter under procedures that entail classifying it as a human research subject.

The answer seems clear enough: the difference between the life and death of a human fetus/abortus should be determined substantially in the same way physicians use in making other pronouncements of death. To adopt in this instance other criteria, or to ignore the vital signs (if present in the fetus) ordinarily consulted in other such declarations, would open the medical research profession to charges of ad hoc-ery, special pleading, and bad faith for research purposes.

Dr. Bernard N. Nathanson gave the only intellectually coherent reply that can be given to the Commission's question to us. He wrote (on another but related issue):

"The Harvard Criteria for the pronouncement of death assert that if the subject is unresponsive to external stimuli (e.g., pain), if the deep reflexes are absent, if there are no spontaneous movements or respiratory efforts, if the electroencephalogram reveals no activity of the brain, one may conclude that the patient is dead. If any or all of these criteria are absent—and the fetus does respond to pain, makes respiratory efforts, moves spontaneously and has electroencephalographic activity—life must be present."

Nathanson was not arguing that these criteria would put the living fetus into the class of infants. He was rather citing the indications for believing that the fetus/abortus before viability is reached was already "human life of a special order" readily distinguishable from an entity that has lost those signs (fetal death), or never had them.

True, the 1973 NIH proposed guidelines studiously refuses to speak of the previable fetus as "living" or having "life." But one cannot contrast our subject with a dead fetus without presuming to know signs of life and to recognize their absence before viability. Moreover, this document's twin prohibition of experimental procedures which artificially maintain or which of themselves terminate heartbeat or respiration in a fetus judged to be previable, reaches back to prevent intervention upon one of those vital signs that must surely be used to distinguish fetal life from fetal death, namely heartbeat. I shall not comment here on the inclusion of respiration except to say that I thought capacity to expand the lungs was a chief indication of possible viability. By studiously refusing to speak of a previable fetus/abortus who may still be medically "alive" and by leaving the determination of viability entirely to the discretion of physician researchers (not even excluding abortuses with respiration from being deemed previable and entered into experimentation), the American guidelines can be faulted for lack of definitional clarity. Indeed, if and only if the previable fetus is human, unique for certain purposes, and alive in significant medical respects -- i.e., if it is not dead -- could claims be made that researchers need the knowledge uniquely to be gained by using the fetus/abortus while it is still living, growing and reacting as a tiny, whole fetal human being or entity. Finally, the 1974 DHEW-NIH revision, of these guidelines -- for all its continuing austere definitional reluctance to say "life" or "alive"--refers to "the whole fetus or abortus, functioning as an organism with detectable vital signs." This is enough to show the way to a proper concept of fetal death.

The guidelines developed in Great Britain and the United States have all-in differing ways--recognized the need to define this novel human research subject by distinguishing it both from a dead fetus on the one side, from a viable baby on the other. The "Peel Report" in force in Great Britain distinguishes a live fetus from a dead one by stating that before viability the former "shows some but not all signs of life." The 1973 proposed NIH guidelines excluded the following from the meaning of abortus research (to which question, regulations

were addressed for the protection of "human subjects"): "the placenta, fetal material which is mascerated at the time of expulsion, a dead fetus [sic], and isolated fetal tissue and organs excised from a dead fetus." Impliedly, a distinction can be made between a certainly previable abortus and a dead one. It can be made in practice by reference to vital signs ordinarily used in findings of death, with the addition of tests or findings that may be unique to the practice of fetal medicine.

I assume then--with Nathanson--medicine's ability to determine fetal death in ways that are not inconsistent with other findings of death. I want next to remark upon the other side of the definitional task, the viability line to be drawn in defining this new human research subject.

The "Peel Report" states that no fetus of more than 20 weeks gestational age or more than 300 grams (3/4 lb.) in weight shall be eligible to be made a research subject. That was a definition on the safe side of viability; a definition of viability for research purposes. During 1971-1973 (it was disclosed in April 1973), NICHD's Human Embryology and Development Study Section had under discussion a proposal that a fetus eligible for research "must meet at least two out of three criteria: it must be no older than 20 weeks, no more than 500 grams (1.1 lbs.) in weight; and no longer than 25 centimeters (9.8 inches) from crown to heel."5 It is of first importance that we go back to the beginning and reinstate one or another of these descriptions of our new research subject on the safe side of viability. I suggest that the Commission's first task is simply this definitional one of locating the subject of its deliberations between fetal death, on the one hand, and on the other, viability defined for research purposes on the safe side of the line or span of possible viability that physicians use in decisions relevant to promoting the life of the fetus/ neonate.

In the August 1974 revision of the NIH guidelines, Secretary Weinberger stated that "the Department does not believe that the use of weight, size, gestational age and/or cortical activity is a valid substitute for the judgment of a physician" in distinguishing between a viable and a nonviable fetus.

But the issue is not viability for general medical purposes; rather the need is for a definition of viability for fetal or abortus research purposes. Of course, the fetus is generally viable at all stages unless it is removed from its natural environment. In face of that actual viability at all stages of development, in abortion practice we define viability in another and an artificial way. In the matter of research practice we need another, more or less artificial, definition of viability: eligibility and noneligibility for research purposes defined at an upper limit safely short of the span of possible or actual viability.

Researchers should be the first to insist that abortuses eligible to be entered into medical experiments be defined on the safe side of possibly viable birth weight, crown-rump length, or gestational age. They should want to be seen always to do right by not even proposing research with fetuses except within an outer limit on the safe side of viability (itself to be updated with future progress in medical technology).

Nor can it be good public policy or good intraprofessional medical policy to leave standing any possibility that medical researchers could be (or could seem to be) experimenting on possibly "viable" babies in the ordinary and permeable meaning of that expression. The point is not the meaning of viability for the purpose of decisions promoting the saving of life or allowing to die or undertaking investigations connected with diagnosis or treatment in the practice of fetal medicine or pediatrics. On those matters, doubtless, as Secretary Weinberger said, there is no "valid substitute for the judgment of a physician." The point is rather drawing a line on viability/eligibility for research purposes. The point is the completion of the definition of this new class of proposed legitimate research subjects. There is nothing morally at stake in building such a fence--except that it should prevent any researcher from doing nonbeneficial experiments with a viable infant by mistake, and it would establish in public and medical policy the assurance that this will never be done.

I do not say that, below stated weight, crown-rump length or gestational age, abortus research is justified. I do suggest that we need measurable limits beyond which it clearly is not. I have simply suggested the completion of the definition of this new class of proposed human research subjects--on the side next to infancy and some distance away from the line that can be drawn between a living fetus/abortus and a dead one.

Such are the parameters properly circumscribing the living yet previable fetus/abortus. To state these dimensions or sketch of the class of possible human research subjects we are talking about is only the beginning—the preconditions—of a proper analysis of ethical practice in fetal research. As that analysis proceeds in the Commission's deliberations and in the public forum, some sorts of experimentation ought surely to be excluded. Perhaps many research designs may prove incompatible with protections due the fetus. Perhaps all experimentation should be forbidden except for controlled observation or interventions foreseen to bear no risk of harm, etc. But none of these upshots from serious ethical reflection and from careful drawing of lines between the morally permissable and the morally impermissable are any excuse for not first defining what we are talking about using in research.

In short, the parameters tell us nothing yet about the accompanying regulations for the protection of this potential new class of human subjects. The first parameter acknowledging the livingness of a previable fetus only keeps us from confusing the issue before us with what should or should not be done with a dead fetus or fetal organs and tissue (an entirely different question). second parameter only keeps us from doing by mistake something we meant not to be talking about, namely nonbeneficial experimentation on possibly viable neonates. To define previability on the safe side for research purposes need not mean that then all is permitted, or that anything is as yet permitted. We have as yet said nothing about what should be done between the parameters, between the dead/living fetus line and the previable/viable line. On the latter, I simply urge that we need some numerical or measurable definition on the safe side of viability even if then we go on to say that, to be ethical, research ought never to prolong or directly terminate vital signs, or ought not to be done to ascertain harm to the fetus, or ought not to be done if there is any discernable risk--or if we go on to say that between the parameters there are

no limits to what may be done with the live previable human fetus/abortus except those limits upon research procedures that stem from promising benefits to come.

The more I study the paragraph in which the 1974 DHEW-NIH revised policy reaffirmed the original 1973 view that "heartbeat and respiration are, jointly, to be the indicators of viability," the more I am persuaded that the Department and its respondents are making the same simple mistake. Both are trying to make the viability line do the work also of the life/death line in determining the parameters of this potential new class of human research subjects. Consider the following summary:

"Some respondents suggested specific criteria such as birth weight, crown-rump length, or gestational age, similar to those used in Great Britain, such criteria to be reviewed and reissued periodically by the Department . . . Some respondents urged that presence of fetal heart beat be definitive (whether or not there is respiration) while others urged that identifiable cortical activity be specified as an alternative sign of viability. Others objected strenuously to any distinctions as to the nature of fetal life, holding that the physician's obligation should be the same to any fetus regardless of weight, size, or age of gestation."

Now, that passage strongly suggests that everyone has fallen prey to a play on words. "Viability" in its current meaning is only one of the meanings given in the Webster's New International Dictionary (Second Edition): the "quality or state of being viable" (the latter word defined as born alive or capable of being born alive). However, another meaning reads: "ability to live, grow and develop; as the viability of certain grains under dry conditions." Evidently, the first is the meaning of "viability" when the word is currently used as a term of medical art. Evidently also the foregoing statements play on a confusion of that with the second meaning.

By studiously refusing to speak of the previable fetus/abortus as "alive" or having "life," the Department subtly insinuates that a viability line can also do the work of a life/death line. Then, in order to oppose salvageability looming here as the beginning of a physician's obligation to the fetus, some respondents were led into a similar, if opposite (and also verbal) error. want to draw other lines on the beginning of life in the fetus (in the relevant sense of the beginning of or a new stage in the physician's duty to protect the fetus from harm), and they are reported to have done this by suggesting alternative definitions of "viability." Some said fetal heartbeat should be definitive--as an alternative sign of "viability." While certainly heartbeat alone is no test of "viability" in its going meaning, that might reasonably be taken to be among the determinants of fetal life or death. Some suggested cortical activity. Again, if EEG shows not only brain activity but also the beginning of cortical brain activity during fetal development, that was to locate another determinant of fetal life or death. (If full development of the cortical regions of the brain was meant, it was a determinant of infant life or death, and an indicator of death not yet adopted in the case of other human beings.) who strenuously objected to any measurable criteria for viability/eligibility for research purposes were really saying that only the life/death line matters.

Where there is life, whatever its size or age, there is hope, and physicians are unqualifiedly obliged to save, aid and protect that life from harm. Only those who proposed to follow the British precedent may have had in mind the need for both parameters in circumscribing and defining this potential class of new human research subjects.

Citing Nathanson, I have urged that the criteria for fetal death cannot be inconsistent with the indicators of death applicable to other forms of human life. There may be additional tests, or variants of the common criteria, which fetologists may propose. But in the present instance, "not inconsistent with" other declarations of death is well-grounded in the fact that the fetus is more like a human infant than it is like a human embryo, blastocyst or zygote. The Commission is not called upon at this time to jump into the nettle of determining embryonic life or death, or the death of blastocyst or zygote.

Moreover, those who argue that a physician's obligation is the same at all stages of fetal life were not arguing that fetal death does not cause that obligation to cease. In opposing the adoption of an outer parameter of viability for research purposes, they were stating a view about the impermissability of many or all forms of human research between those or other parameters. It is true that they and they alone of all the respondents need only a life line; they need no other parameter to state their views on fetal research. The rest, as we have seen, fall into the error of using only a proposed viability line (blurring the need for a different life line also) in order to open the door wide to fetal research before viability without having to do some difficult thinking about medicine's duty when considering this form of human life as a potential experimental subject.

I urge, however, that a clear and safe outer boundary serves only a practical function, to be sure a very important one. It need not be question-begging or value-laden for what may subsequently be deemed morally permissable research using human fetuses that while not yet dead fall within that outer boundary.

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My proposals to the Commission draw upon our extant medical ethics, including the British "Peel Report" and the paragraphs on fetal research in the 1973 and 1974 versions of "The Protection of Human Subjects" generated by DHEWNIH.

1. U.S. medical research policy should contain a provision that "no procedures be carried out during pregnancy with the deliberate intent of ascertaining the harm that they might do to the fetus" (Peel). Ethically, that seems to me clearly a different research intention and action than "a medical practitioner may carry out procedures on the mother with the deliberate intent of ascertaining the benefit these might do to the fetus, even though the fetal research subject is not likely to benefit because its abortion is in prospect." For one thing, since both interventions—the beneficent one as well as the

harm-ascertaining one--are bound to carry some additional risks, the total harm-fulness may reasonably be expected to be greater from the latter than from the former procedure. That is an objective morally relevant consideration.

Still the choice between these alternative provisions rests mainly on a subjective morally relevant consideration, namely, the intention (and not alone the action) of the researcher. The "virtues of the moral agent" is an important part of general ethics, and not "action guides" alone. Likewise, the "ethical physician" is an important consideration for medical ethics, and not "codes of conduct" alone. "Do not harm" encompasses also "intend to do no harm." How can harm to the fetus be ascertained without a deliberate intention to do harm to ascertain it?

2. The foregoing regulation in force in Great Britain is paralleled in the apparently categorical prohibition of fetal research in utero in anticipation of abortion in the first (1973) version of "Protection of Human Subjects"--which however, opens up the question to which I believe the Commission must address itself, namely the determination of a permissible degree of risks of harm even from procedures a beneficent researcher may undertake for beneficent goals.

The 1973 NIH guideline states that "no experimental procedures entailing risk to the fetus be undertaken in anticipation of abortion."

I have elsewhere argued that the experiments at Boston City Hospital testing which of two antibiotics would be the more effective in protecting from syphilis the fetuses of future mothers with penicillin allergies was ethical research under either the "Peel" rule or the proposed American regulation of fetal research in utero. Still the subjective British rule needs to be supplemented by the objective weighing and limitation of risks suggested by the American guideline. Both should be included in U.S. public medical policy.

Here lies a creative frontier for the Commission's leadership -- in spelling out the meaning of this second provision so far as it is possible to do so--if fetal research policy is to be based on sound moral grounds, and is to maintain contact with our tradition of medical ethics. After all there is a difference between experimental procedures having "no discernible risk," those having "no discerned risk," those having "discernibly no risk," and those having only "negligible risk" or "no conceivable risk." And how statistically negligible must a "negligible risk" be to be morally negligible? Even the Commission's choice of language (if no one can go further) will be exceedingly important in bracing the ethical researcher to the standard he should hold himself to in conscience, not to speak of Ethical Review Boards. Carefully drawn, protective language is needed--if for no other reason than to provide a benchmark against which to "measure" the justifying reasons found (such often is the claim) in exceedingly great benefits expected to come. Otherwise the human fetus will become the most unprotected "primate" in medical research. (I refer to the perturbation aroused among the generally nonantivivisectionist part of our population from viewing primate experiments on public television; the troubling question awakened was: Has anyone even asked the question how important must the benefits be to warrant doing such things to another living being close to us in nature and resemblance?)

3. It is in order for me to insert here a parenthetical paragraph indicating the appeals and warrants cited by the British committee and by the drafters of the 1973 U.S. guidelines in support of proposals (1) and (2) above.

The "Peel Report" appealed at once to the criminal law to support its view that "the protection afforded to the fetus is continuous and is not abrogated by the fact that it may be the intention at the time of the affliction of the injury that the fetus should be prevented by a subsequent abortion from attaining life." Therefore, "even if the mother is willing to consent to such an experiment," that too would not abrogate the protections afforded the fetus.

The 1973 U.S. guidelines appealed directly to our tradition of medical ethics to obtain the same foundation for its rule. "The recent decision of the Supreme Court on abortion does not nullify, so far as medicine is concerned, the ethical obligation to protect the developing fetus from avoidable harm," even if that harm is lesser than the planned abortion. Why not? Answer: "Respect for the dignity of human life must not be compromised whatever the age, circumstances, or expectation of life of the individual. Therefore, all appropriate procedures providing protection for children as subjects in biomedical research must be applied with equal rigor and with additional safeguards to the fetus" (emphasis added).

In my opinion the philosophy of ethics and the medical ethics undergirding the Commission's recommendations should be consonant with the foregoing. Some indirect consequences of adopting these or similar fundamental principles are pointed out in the footnote.

4. <u>Live Abortus Research</u>. The 1973 NIH proposed policy states two parallel prohibitions: "If the [attending] physician determines that the fetus is not viable, it is not acceptable [for the researcher] [1] to maintain heart beat or respiration artificially in the abortus for the purpose of research. [2] Experimental procedures which of themselves will terminate respiration and heart beat may not be undertaken."

In the 1974 revision only the second of these provisions remains: "Experimental procedures which would terminate the heart beat or respiration of the abortus will not be employed." The first provision is reversed to read: "Vital functions of an abortus will not be artificially maintained except where the purpose of the activity is to develop new methods for enabling the abortus to survive to the point of viability."

Everything depends on the meaning of "the abortus" in the last statement. Does "the abortus" mean that particular abortus, the subject of that research effort further to develop lifesaving techniques? If so, the provision allows the artificial maintainance of the life of an abortus only in the case of investigational therapy, i.e., experimentation related to efforts to promote the life of particular abortuses with whom this may be learned. There is no ethical objection to be lodged against such experimental treatments, except to say that physicians ought not to take extraordinary affirmative action to save prematures at cost of their grave injury from the procedure (and here there truly is no substitute for the discretion of the physician).

But "the abortus" in the statement above could mean abortuses as a class. In that case the new methods of saving prematures to the point of viability (otherwise expressed: new methods of pushing back the viability line still further) would be sought solely for the sake of abortuses other than the human research subject. There would be grave moral objections to be lodged against that. I will mention only one. Such nonbeneficial research extending an abortus' life is bound to do it damage. The protocols would have to stipulate that once the procedure is perfected to the point of prolonging the life of the subjects for, say, a week or two the experiment should be stopped, and the technique thereafter should be used only in trial therapeutic efforts to save abortus subjects that already are close to viability.

In short, stopping the procedure would have to be a part of the experimental procedure, if benefit to abortuses or prematures as a class is the main objective. But then the revised guidelines prohibit that: "experimental procedures which would terminate the heartbeat or respiration of the abortus will not be employed." The planned termination of an experimental procedure—to avoid bringing a procedurally damaged abortus to the point of viability—cannot be excluded from the meaning of that statement. If the 1974 revised guidelines were adopted, we can anticipate a number of salvage experiments in which cannulas "inadvertantly" slip and the subject dies.

If benefit to prematures as a class was meant, I rather think it would be better, candidly, also to allow experimental procedures that terminate vital signs in the human abortus subject. Was that prohibition retained only because the public would not "understand" or accept the direct killing of still-living abortuses for research purposes? It also seems likely that on the other reading--"the fetus" meaning a particular fetus submitted to therapeutic investigational efforts to save it--a number of experiments will also "inadvertantly" come to an end, if the lure of research benefits to other prematures comes to outweigh caution about serious damage to the particular abortus under a physician researcher's care.

I would urge that the two parallel prohibitions in the 1973 NIH guidelines be adopted, or else that the ambiguities and dilemmas introduced by the 1974 revision should be removed by a clear statement that the development of salvage procedures, which maintain vital signs that otherwise would cease, can be researched only with a physician's patients as aborted or premature experimental subjects in connection with efforts consistent with the promotion of their lives.

5. It was certainly a symbolic flaw, and a flaw of some practical consequences, that the Senate bill's reference to fetal research "whether before or after induced abortion" was retained in the final language of the National Research Act which established the Commission. For it is only in the quantity of experimental subjects made available, and here rather than abroad, that there is significant linkage between current abortion practice and the moral issues involved in using living human fetal subjects in medical experimentation. The products of spontaneous miscarriages, if previable and not yet dead, place the same (or no) moral claims upon medical practice and upon the human community generally.

Even fetal research in utero can be done and apparently has been done in cases where the women were not planning abortions. The early pages of Dr. M.H. Pappworth's Human Guinea Pigs<sup>10</sup> describe some rather astonishing imposition of risks upon the fetus in situ and upon pregnant women that was not done in anticipation of abortion. Undoubtedly, however, the wide practice of abortion has freed up experimental designs especially in the case of fetal research in utero with abortion in prospect.

In cases of live abortus research ex utero, however, a simple "thought experiment" may help to separate the question of the morality of such research from the question of the morality of abortion. One can imagine that abortus research ex utero is proposed to be done only on products of spontaneous abortions and on living abortuses that result from entirely justifiable abortions. Let the abortion be just and necessary, however tragically necessary, e.g., to save the mother's life, or whatever any member of the Commission happens to believe is the sort of, or occasion for, abortion he or she would entirely back doing morally. This is one way to keep these issues separate, as they should be. For the question of the morality of fetal research is what, if any, moral claims should rightfully be made in behalf of the fetus, even-perhaps especially-while it is dying from spontaneous abortion, and even-perhaps especially-when it is already condemned by an abortion decision or is dying from that decision already set in course.

For these reasons, my own view is that the ethical standards applicable to fetal research are the same as we would subscribe to in the case of proposed research on the unconscious, on the dying (in cases of spontaneous abortion) or on the (perhaps justly) condemned (in cases of abortion) or in experimentation with children. (The latter was in fact the position taken by the original or 1973 NIH policy.) My argument that these are the applicable standards is in the public forum and available to the Commission.

Let me, instead, cite in conclusion the best recent article by an ethicist who favors, more than I do, placing uncomprehending subjects at some degree of risk, namely, Richard J. McCormick, S.J., "Proxy Consent in the Experimentation Situation." Father McCormick uses the expression "vicarious" consent for situations in which parents or another proxy authorize operations or investigations connected with treatment. That is not at issue in fetal research; at least in my view no objection can be lodged against fetal research related to promoting the life of the fetus. I mention it only to point out that, as an ethician, Father McCormick wishes to say that "vicarious" consent is valid not because the child would want investigational therapy, but because he should do so. Likewise, in the case of "presumed" consent to nonbeneficial experimentation, he believes that is valid if proxies correctly construe not what the uncomprehending human research subject would want or does desire, but rather is something he should will to do.

The question, then, in regard to research with children and with the fetal human subject (if "all appropriate procedures providing protection for children as subjects in biomedical research must be applied with equal rigor and with additional safeguards to the fetus" and if we ought not to regard respect for human life as a variable functioning with "expectation of life"--1973 NIH policy)

translates into the question: What ought those subjects to want, as social beings for the long or brief time they have in the human community?

I draw the Commission's attention to this important article because any theoretical differences between Father McCormick and myself (important as we theoreticians fondly believe they are) has only quite narrow consequence in indicating the range of practical action guides the Commission is charged to formulate. The consent Father McCormick would "presume" or "construe" (based on what the -- in some sense--living human subject ought to want) is simply experimentation beneficial to others that involves "no discernible risks, no notable pain, no notable inconvenience, and yet holds promise of considerable benefit" for other humankind. He quotes -- in Latin, no less -- parum pro nihilo reputatur ("very little counts for nothing"). While I myself tend to believe that any use of the fetal subject, children, the unconscious, the dying or the condemned would be an abuse, I grant that there may be degrees of "no discernible risk" that closely approximate my position. Apart from that refinement, the signal thing to note is that Father McCormick and I agree that "one stops and should stop precisely at the point where 'construed' consent does indeed involve self-sacrifice or works of mercy . . . The dividing line is reached when experiments involve discernible risk, undue discomfort, or inconvenience." Concerning a child--and I add, the fetal human research subject--McCormick says that "he need not ought to want" real dangers; that awaits charitable selfsacrifice which no one should presume to exact of another.

The moral basis legitimating "presumed" consent which McCormick endorses leads precisely to my own location of the chief task of the Commission in formulating fetal research policy (paragraph two above). I respectfully suggest that if the Commission follows the 1974 DHEW-NIH revision in making the facticity of abortion crucial in its deliberations, that can only amount to seizing the "golden opportunity" afforded by abortion to exact--and falsely to "presume"--acts of charity from the fetus as a human research subject. That can only mean a terrible distortion of medical ethics to date, and of the Jewish-Christian tradition which was the foundation of its regard for the sanctity of human life regardless of its age, condition or "expectation of life."

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- 1. "Deeper Into Abortion," New England Journal of Medicine 291 (No. 22): 1189-1190, November 28, 1974.
- By this and similar expressions I refer to the first published version of "Protection of Human Subjects," Federal Register 38 (No. 221): 31738-48, November 16, 1973.
- By this and similar expressions I refer to "Protection of Human Subjects," Federal Register 39 (No. 165): 30648-57, August 23, 1974.
- 4. "The Use of Fetuses and Fetal Material for Research," Department of Health and Social Security, Scottish Home and Health Department, Welsh Office, London: Her Majesty's Stationery Office, 1972.
- "Proposed Grant Code for Experiments on 'Viable Human Fetuses,'" Ob-Gyn News, April 15, 1973.
- Ramsey, Paul, The Ethics of Fetal Research, New Haven and London: Yale University Press, 1975, p. 68.
- 7. A routine answer to this question will no longer suffice. In Helling v. Carey, 519 P. 2nd 981 (Wash. 1974), the Supreme Court of Washington held physicians responsible for negligence despite uncontradicted expert testimony that it was the universal practice of ophthalmologists not to administer glaucoma tests to patients under age of 40 because the incidence of glaucoma below that age is in the neighborhood of 1 in 25,000. While "standard medical practice" holds that degree of risk to be negligible, the court ruled to the contrary: "that one person, the plaintiff in this instance, is entitled to the same protection, as afforded persons over 40, essential for timely detection of the evidence of glaucoma where it can be arrested to avoid the grave and devastating results of this disease." The court held physicians accountable to "a standard of reasonable prudence, whether it is usually complied with or not." "Reasonable prudence" may not be the same as "common prudence," since "a whole calling may have unduly lagged . . . " Thus the court reached out to protect patients under 40 for whom risk of 1 in 25,000 was formerly deemed "negligible."
- 8. First, the Commission thereby would avoid lending support to astonishingly inept extrapolations from the Supreme Court's abortion decision that are widely believed. It is often said that by that decision the Court opened the door to any and all experimentation on the fetus or abortus in the

### REFERENCES (Continued)

first and second trimester, In that decision, however, a woman's constitutional right of privacy was brought against restrictive State legislation. It is very poor legal reasoning to say that a woman now has a quasi-constitutional right to deliver an abortus into the hands of a researcher or to cause potentially harmful experiments to be done on her fetus in utero in anticipation of abortion or on her abortus if delivered alive. Nor is there a constitutional right to the benefits of medical progress; nor is a class action in behalf of anonymous future benefitees apt to be brought, or succeed. The Commission is free to affirm the foregoing principles of medical ethics. Indeed, an invitation to the Commission to do so can be found in the fact the law is quite capable of deciding one thing for one purpose, another in another connection. What the law is when it is a matter of the fetus versus a woman's constitutional rights is one question. What the law might say or ethics should say in the matter of the fetus or abortus versus research is a quite separate question.

Second, by reaffirming our tradition of medical ethics and basing its recommendations on this (as did the 1973 NIH proposed policy), the Commission would incidentally give needed leadership to the medical profession in closing a gap that has been left wide open in recent years. I have in mind the ambiguity and uncertainty about the responsibility of physicians toward potentially viable human life. In this uncertainty a number of sticky legal cases have arisen, as is well known, and widespread doubt in the public mind concerning what physicians deem their responsibility to be toward viable lives that may fall under their care as a result of abortion procedures.

The Commission's lead in reaffirming medicine's obligation to life regardless of expectation of its longevity (plus a definition of viability on the safe side), would have important influence on the grey area into which the near-viability fetus has fallen in the practice of medicine generally.

I quote from an important legal analysis of one of the Boston cases:

"The Edelin prosecution may be explained as the result of a perceived breakdown in professional self-regulation in late-term abortions . . . Thus Dr. Edelin can hardly argue in defense that his effort to shut off the fetus' blood supply before removal was justified as standard medical practice, for it is the ethics of such practice which is being challenged. Resort to the legal system occurred because of the unwillingness or inability of the medical profession to engender sufficient consideration of fetal interests in late-term abortions . . . If [Dr. Edelin] disregarded the interests of the fetus altogether, or made a judgment that even if viable, its future was poor, then we may question his

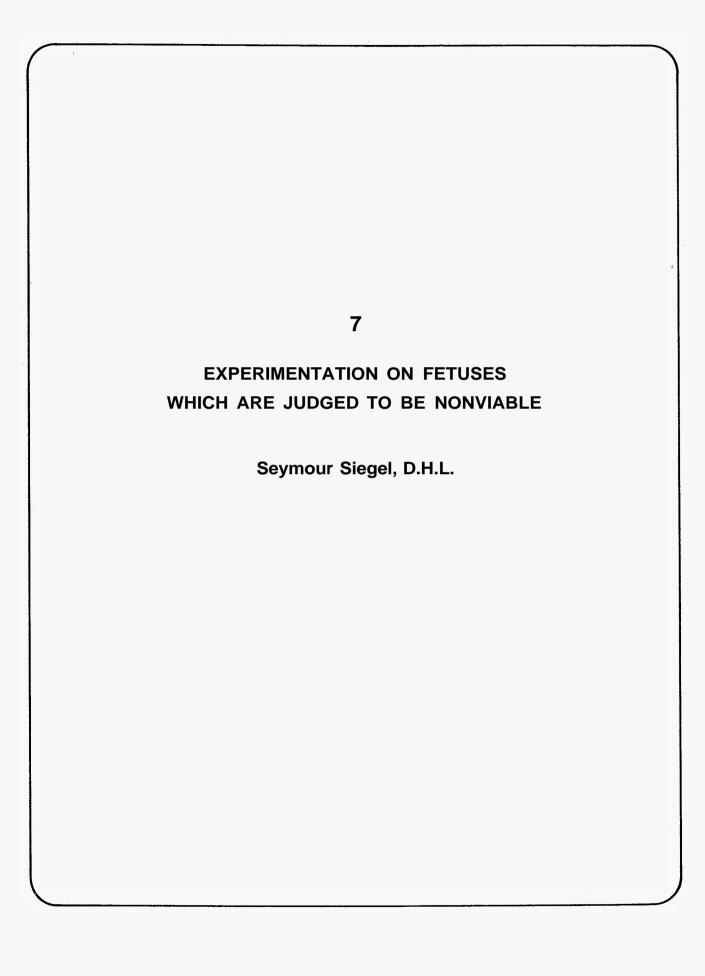
## REFERENCES (Continued)

ethics, the profession's inability to resolve such questions, and find law an appropriate instrument to protect such interests."

-John A. Robertson, "Medical Ethics in the Courtroom," Hastings Center Report 4 (No. 4): 1-3, September, 1974.

Third and finally, it seems clear to me that only by affirming paragraphs one and two above, along with the philosophy of ethics cited in my paragraph three, can the Commission avoid the utter disarray and incoherence in ethical and public policy reasoning that characterizes the 1974 revision of "Protection of Human Subjects." Perhaps I may cite chapter 9 of my The Ethics of Fetal Research (New Haven and London: Yale University Press, 1975, pp. 75-87), for a full documentation of the disguised confusion in saying that experimentation that will harm may be done if "part" of an abortion procedure, in claiming still not to allow fetuses for whom abortion is contemplated to be placed by research at greater risks than fetuses in general while writing that into the Secretary's "exception"-making power, and in published "corrections" that manage to say the same thing. It does seem to me the Commission should show more perserverance in rational analysis and greater rule-making prowess.

- 9. "The Human Fetus as Useful Research Material," Case Studies in Bioethics,
  Hastings Center Report 3: 8-10, April 1973; Ramsey, Paul, The Ethics of
  Fetal Research, New Haven and London: Yale University Press, 1975,
  pp. 37-40.
- 10. Boston: Beacon Press, 1968.
- 11. Perspectives in Biology and Medicine 18 (No. 1): 2-20, Autumn, 1974.



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# **Experimentation on Fetuses**Which Are Judged to be Nonviable

In analyzing the ethical dimensions of the problem before this Commission it is necessary to affirm certain basic principles:

## 1. A BIAS FOR LIFE

The most general principle which should inform our decisions in these crucial matters is a "bias for life." This "bias" is the foundation of the Judeo-Christian world view as well as the motivating force which undergirds medical research and practice. It flows, for most people, from a theistic belief. However, it has been and can be affirmed by those whose views of reality do not include the existence of God. The "bias for life" requires that all individuals--most especially those involved in the healing arts--should direct their efforts toward the sustaining of life where it exists; that means and procedures which tend to terminate life or to harm it are unethical; and that where there is a doubt, the benefit of that doubt should always be on the side of life. Another implication of this "bias" is that any individual life which claims our efforts and attention, and which is before us at this moment, has precedence over life that might come afterwards. In certain situations, individuals are called upon to sacrifice their lives or their comfort for future generations. This is part of our character as members of the human race tied to those who came before us and to those who will come after us. However, the burden of proof is always upon those who wish to subordinate the interests of the individual presently before us for the sake of those who will come later. for the "good of medicine" or for the sake of the "progress of knowledge" are not automatically legitimated, if they cause harm to people now, because someone in the future might benefit. What comes in the future is what the Talmudic literature calls "the secrets of the Almighty." This does not mean that we have no responsibility toward the future. However, we have a greater responsibility to those who are now in our care. These reflections do not, of course, preclude the scientist's search. These are intended to make him more cautious in his search.

This "bias for life" is exercised whatever the status of the life before us is. The fact that the life is certainly to be terminated, that it is flawed, or doomed does not preclude the activation of the "bias." This idea is expressed in the 1973 U.S. Guidelines published by the Department of Health, Education and Welfare: "Respect for the dignity of human life must not be compromised whatever the age, circumstance, life expectation of the individual." [Emphasis mine.]

#### 2. THE INDETERMINANCY OF THE FUTURE

Even the most expert scientific intelligence cannot predict the future with certainty. This is especially true of medical science. Medical science is replete with instances where certain experiments and treatments were administered to human subjects with the expectation that these procedures would be positive in their effect—only to turn out to be harmful. That means that when a decision is made to permit experimentation on human subjects, there must be present the utmost caution. Some of the experiments proposed would involve the mother as well as the fetus. It is not impossible to predict that these very procedures would have so changed the mother's organism as to preclude further births or to have other untoward effects.

In speaking of the future effects of experimentation we should not overlook the social consequences of policies in this area. Already the public is beginning to believe that physicians are not merely the saviors of human liferbut also its destroyers. While this allegation is, of course, unfair, it is still important to keep the social effects in mind when making policy in this very sensitive field. This century has seen the consequences of the breach of the notion of the sanctity of life. The Nazi horrors began with the legitimation of the destruction of "useless" life and concluded with the most horrible phenomenon of this or any other century. The ethicist, LeRoy Walters, has stated: "An unexamined premise of both the British and the American policy statements on fetal experimentation is that the consequences of such research will be medical and that they will be good . . . it is equally plausible to argue that serious social consequences will follow such experimentation and that these consequences will be mixed, at best."

#### 3. THE NUB OF THE PROBLEM: THE FETUS

In approaching our problem, the nub of the issue is the status of the fetus. This problem can be approached medically, metaphysically and ethically. It would seem that the two extreme positions which have been expressed in the literature and public debate on this issue--though having much to commend them--do not seem plausible.

The fetus does not seem to be identical with an infant. This is the view of many religious and ethical traditions—including the rabbinic tradition. It is supported also by common sense. The fetus has no independent life—system and is literally tied to the mother. It has not developed the social and personal qualities generally assumed to be part of being a full human being. This is not a self-evident principle. B.A. Brody, in a recent article says: "the status of the fetus and of whether destroying the fetus constitutes the taking of human life . . . seems difficult, if not impossible to resolve upon rational grounds."4 Yet, it would seem that the weight of common sense is on the side of those who wish to distinguish ontologically and ethically between a born infant and a fetus. This means that feticide is not the same as homicide—that is, before viability.

However, this does not mean that from an ethical standpoint there is no difference between a fetus and a tooth or a fingernail of the mother -- to be disposed of as the mother wishes. It is indeed part of the mother's body--but a unique part of the mother's body. It is only part of the mother's body which is destined to leave the mother's body in order to take upon itself individual and independent existence as a human being. This special status gives the fetus certain rights that other organs of the mother do not possess. This is expressed in the fact that Western religious thought has "ascribed a high value to prenatal human life." Nor should we forget that even if we were to conceive of the fetus as merely a limb of the mother, this does not imply that society has no responsibility for what the mother does with her limbs. No civilized community would allow individuals to capriciously cut off limbs from their own bodies -- even if they wished to do so. Of course, limbs can be amputated for the sake of the whole individual. But this must be justified by the "interests" of the individual, and this "interest" must stand the test of common sense as well as medical opinion.

What then is the status of the fetus, if it is not a whole individual or mere tissue. The answer must be that the status of the foetus is that of "potential human life." Both Aristotle and Thomas Aquinas and many medieval thinkers saw human life as a developing process from step to step. In the case of the ancients it was from vegetative to animal to rational levels. However, it is clear that successive stages of human ontogeny contain within themselves the future stage. That is to say, that all "higher" stages are present in potentia in the "lower" stages.

The character of the fetus as "potentially human" raises it above the level of "mere tissue." It therefore evokes within us a sense of responsibility for its welfare as well as the welfare of the mother. Because it is not yet fully human, the fetus has less rights than it would have if it were fully born. When the fetus presents a threat to the mother's life or to the lives of its potential siblings, then the mother has a right to protect herself against the fetus. That is why most religious traditions permit abortion under some circumstances. When one harms the fetus, however, "potential life is being thwarted."

### 4. THE RIGHTS OF THE FETUS

The fetus, then, has potential human qualities and therefore it has rights. These rights are encapsulated in the demand it can make upon us to benefit from our "bias toward life." This "bias," which makes us responsible to guard and preserve life where it exists, this responsibility, to preserve the life of the fetus, is not an absolute responsibility. In most civilized societies war is legitimate even though it means the inevitable loss of life. But it is used to serve a larger and more comprehensive aim of the society--its self-protection. In the same way the fetus' right to our concern for its life is mitigated when the fetus threatens someone elses life or health--his mother's or his prospective sibling's. However, when there is no threat then the fetus' potential humanity and his present life signs entitle him to benefit from the ethical imperative to protect and revere life. This means that even before viability

and even when in utero the fetus has a right to expect those who interfere with his own life-system to do so out of a consideration for the fetus' well-being or the health of his mother. Those who do interfere with his life-system--physicians, experimenters, or others--are ethically permitted to do so only to help the fetus sustain his life-system (unless, of course he is a threat to the mother or his prospective family). It must be stressed that this consideration involves all fetuses--whether viable or not. To declare that a fetus or abortus is not viable is never the same thing as to declare that a living previable fetus/abortus has died.

This does not mean that any kind of experimentation is prohibited. Experiment's, even when nontherapeutic, could be carried on which present no discernible harm to either the mother or the fetus. Though the fetus can hardly give consent to such experiments, those who are his guardians can give consent. Andre Hellegers¹o has described the many important experiments which could be carried on within these guidelines especially those related to amniocentesis.

It would be most unfortunate if the respect for the life of the fetus were related to the fact that he is soon to be aborted. Both the British and the American guidelines11 are insistent that a fetus in utero should not be the subject of procedures which can cause him harm even when he is destined to oblivion through abortion. Paul Ramsey warns against skewing the medical ethical issue involved here by the abortion issue.12 It is possible to be against fetal research in utero even when favoring abortion. The analogy has been drawn to a condemned prisoner who is facing execution, or someone who is in extremis. Medical ethical practice would condemn experiments on such individuals, even if they were to redound to the benefit of scientific progress, unless such experiments or procedures were designed to help the patient in some way. "Still I suggest that someone who believes that it would be wrong to do nontherapeutic research on children, on the unconscious or the dying patient, or on the condemned, may have settled negatively the question of the morality of fetal research."13

### 5. THE FETUS IN UTERO

Therefore the interventions that would be sanctioned when the fetus is in utero would be those which (1) help the mother, (2) are harmless to the fetus, or which (3) are designed to help the fetus in his own life-system. The latter would be licit even if it resulted in negative outcomes--for it is ethical to undergo procedures which have a good chance of success even when some risk is involved.

The view expressed here reflects the prevailing opinion that "no procedures be carried out during pregnancy with the deliberate intent of ascertaining the harm they might do to the fetus." (Peel Commission).

Furthermore, it has been suggested that permission to initiate procedures which will harm the fetus, even when there is an announced intention of abortion, makes it impossible for the parent to change his or her mind about the fate of the fetus. The possibility of reversal of decision about abortion should remain to the last possible moment. This is a convincing argument to my mind.

The assertion that there might be a different ethical consideration in reference to experiments carried out in the course of the abortion does not, in my mind, merit approval. The circumstances of life do not mitigate the right to benefit from our bias for life. To cite the analogy used above--even when the rope is around the neck of the condemned prisoner he cannot be used for any procedure except that which is designed to bring him comfort or well-being.

### 6. THE FETUS EX UTERO

The living fetus ex utero, even when not viable, would seem to have more rights than the fetus in utero. When the fetus has been severed from his mother's body, he can no longer pose a threat to her. There is no issue of the woman doing with her body as she wishes, or the right of privacy, or the consideration of the mother's health. It would seem, therefore, that the fetus' right to enjoy our bias for life would be enhanced when he passes out of the mother's uterus. Life is valuable wherever it exists. As such it evokes our responsibility. The fact that the abortus is sure to die--it is, after all, nonviable--does not mean that our concern for the life is diminished. Because it will never be a real child, it is not, nevertheless, right to consider it "nothing more than a piece of tissue."

We should understand "live" to include the presence of a heartbeat or any other discernible sign of life. For example the Louisiana statute on the matter reads: "A human being is liveborn, or there is a livebirth, whenever there is the complete expulsion or extraction from the mother of a human embryo or fetus, irrespective of the duration of the pregnancy, which after such separation breathes or shows any other evidence of life such as beating of the heart, pulsation of the umbilical cord or movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached."<sup>14</sup>

The prohibition against experimental procedures on live abortuses should, as the published guidelines suggest, concern both the artificial prolongation of life systems such as heartbeats for the purpose of observation or the stopping of any of the life signs. This does not mean that all experiments are prohibited. Only those should be prohibited that do discernible harm to the abortus. However, any procedure which breaches the dignity of the abortus such as prolongation of life-systems or destruction of existing life-systems should be prohibited. These considerations are in line with the guidelines suggested by both the Peel Commission and the regulations proposed by the Department of Health, Education and Welfare.

### 7. FETAL DEATH

The question of when can an abortus be presumed to be dead is a crucial issue. There are those, who were cited above, who believe that in regard to prehumans, the only meaningful distinction is viability or nonviability. For the reasons cited above, this approach is against the ethical canons of medicine--which make no distinction of the prospects of the subject in regard to

his right to be treated with dignity and concern. While the dividing line between viability and nonviability is crucial, the dividing line between death and life is even more crucial. It is life--real and potential as well as being part of the human species--that has an ethical claim upon us.

The best approach to this problem is that suggested by Professor Paul Ramsey, 15 "the difference between life and death of a human fetus/abortus should be determined substantially in the same way physicians use in making other pronouncements of death." He quotes Doctor Bernard Nathanson, who gave the only intellectually coherent reply that can be given to the question put to us by the Commission:

"The Harvard Criteria for the pronouncement of death assert that if the subject is unresponsive to external stimuli (e.g., pain), if the deep reflexes are absent, if there are no spontaneous movements or respiratory efforts, if the electroencephalogram reveals no activity of the brain, one may conclude that the patient is dead. If any or all of these criteria are absent--and the fetus does respond to pain, makes respiratory efforts, moves spontaneously and has electroencephalographic activity--life must be present."

These signs of life do not make the abortus into a viable infant. But they do make it possible for the abortus to enjoy the fruits of our "bias for life." It is interesting that the proposed DHEW guidelines do not present criteria for fetal death. The Peel Commission defines death as "the state in which the fetus shows none of the signs of life and is incapable of being made to function as a self-sustaining whole." These criteria have been criticized by LeRoy Walters<sup>16</sup> as being too vague. The last criterion, for example (being made to function as a self-sustaining whole) might determine that infants are dead. The idea of "signs of life," without designating what these "signs" are, also is too vague. LeRoy Walters writes: "As a general formal requirement for defining fetal death, I would suggest that any criteria developed for determining death in human adults should be applied, insofar as it is technically feasible, to the fetus. This requirement of simple biological consistency would rule out in advance the special pleading contained in hypothetical claims that the fetus is dead because it is about to die or that the fetus was never really alive."

### 8. CONSENT

The concept of informed consent is essential in formulating guidelines for experiments on human subjects. In the case of fetuses, this concept has doubtful application. The fetus obviously cannot give consent. The consent of the parents is made questionable by the fact that they have decided to terminate their relationship to the fetus by consenting to an abortion. The concept of consent is related to the concept of responsibility. Those who give consent must in some way be ready to bear the consequences of their decision. In the case of abortuses and fetuses this has doubtful applicability. Therefore, it would seem that for the experiments that are legitimated, a special board should give the requisite consent. This board would closely scrutinize

the proposed procedure and determine that there is no real risk in carrying it out, that all precautions had been taken, and that there be strict separation between the physician doing the abortion and the researcher.

### 9. PROPOSED GUIDELINES

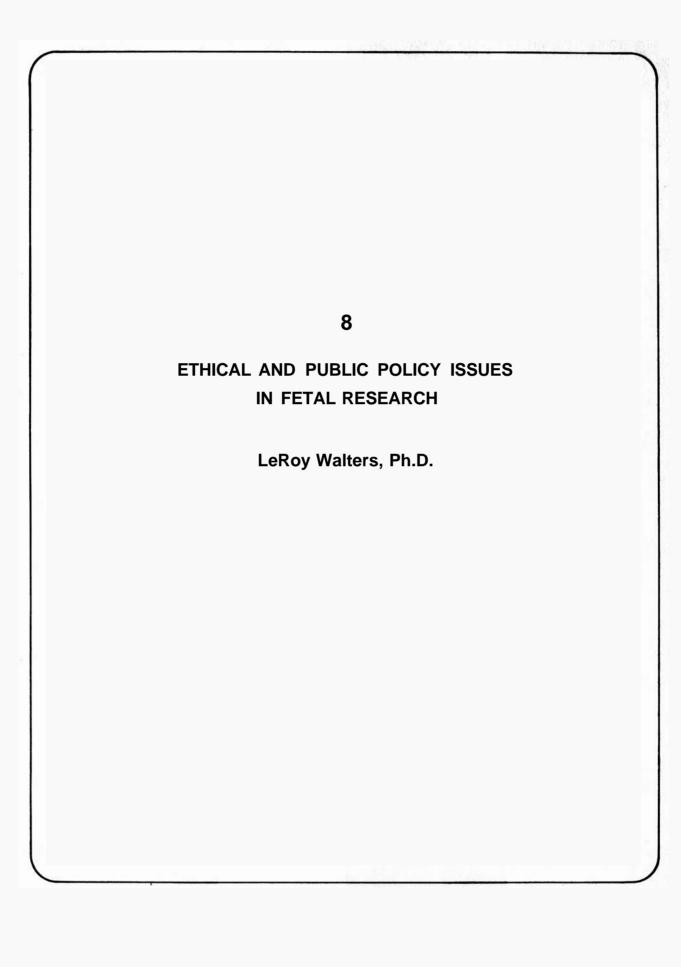
In light of the above it is recommended that:

- A. Research and experimentation on fetuses be limited to procedures which will present no harm or which have as their aim the enhancement of the life-systems of the subjects.
- B. No procedures be permitted which are likely to harm the fetus, even when the abortion decision has already been made, and even where the abortion procedure has been initiated or is in progress.
- C. When the fetus is ex utero and alive, no procedures should be permitted which do not have as their primary aim the enhancement of the life-systems of the fetus, unless such procedures present no risk to the subject. This prohibition would also apply to the artificial sustaining of life-systems for the sole reason of experimentation.
- D. Criteria for determining death in the fetus be the same as the criteria applied to viable fetuses and other human individuals.

#### REFERENCES

- The literature on this subject is enormous. For a summary of the views of the Judaic tradition see Agus, Jacob B., The Vision and the Way, an Interpretation of Jewish Ethics, New York: Frederic Ungar Publishing Co., 1966, and the bibliography cited there. It would, of course, be a mistake to believe that this principle is so obvious as to be banal. We have seen in our century whole societies based on opposite suppositions such as to "kill is good."
- Walters, LeRoy, "Ethical Issues In Experimentation on the Human Fetus," Journal of Religious Ethics 2 (No. 1): 42, 1974.
- 3. For an interesting summary of the issues involved in the status of the fetus see the work cited above by LeRoy Walters; Englehardt, H. Tristam, Jr., "The Ontology of Abortion," Ethics 84 (No. 3): 217ff, April 1974; Reback, Gary L., "Fetal Experimentation: Moral, Legal, and Medical Implications," Stanford Law Review, May 1974. For the Jewish views on the matter see Feldman, David M., Birth Control in Jewish Law, New York: New York University Press, 1968; Jakobovitz, Immanuel, Jewish Medical Ethics, New York: Bloch, 1959; and Aptowitzer, V., "Observations on the Criminal Law of the Jews," Jewish Quarterly Review, Philadelphia, 1924, 111ff.
- 4. Cited by Englehardt, op. cit.
- 5. See especially the book by Feldman, op. cit., and the discussion from a philosophical point of view by Englehardt, op. cit.
- 6. Walters, op. cit., p. 48 and the literature cited there. Walters believes that the religious opposition to abortion is based on theories of ensoulment. Though this is certainly a factor, it would seem that the intuitive feeling that we are dealing with a potential human being gave birth to the religious attitude toward abortion.
- 7. Englehardt, op. cit., while citing and generally approving the Aristotelean and Thomistic approach, however, draws the conclusion that it is not ontologically correct to say that the future effect is present in the present. He believes that each step is independent and ontologically self-contained. Thus the fetus is really like a vegetable until it develops the quality of movement. Then it is an animal until it shows signs of rationality. This argument is not convincing to me. Potentiality has an ontological status. That is: what I am to become is present in what I am, for the simple reason, it seems to me, that I cannot become what I will become unless I am what I am now. Therefore, there is an organic relationship between what I am now and what I will be later.

- 8. Feldman, op. cit., 268ff.
- 9. See Ramsey, Paul, The Ethics of Fetal Research, New Haven and London: Yale University Press, 1975. This new work will be a standard in the field of fetal research.
- 10. Statement by Andre E. Hellegers, M.D., before Senate Health Subcommittee, Senator Edward M. Kennedy, Chairman, July 19, 1974. Doctor Hellegers is, of course, a distinguished physician as well as one who is concerned with the ethical dimensions of the problems before this Commission.
- 11. These guidelines were formulated after the Supreme Court decision about abortion.
- 12. Ramsey, op. cit.
- 13. Ramsey, op. cit., p. 30.
- 14. Cited in Reback, op. cit., p. 1199.
- 15. Ramsey, Paul, Statement submitted to National Commission for the Protection of Human Subjects, 2ff.
- 16. Walters, op. cit.
- 17. Ibid.



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## Ethical and Public Policy Issues in Fetal Research

"The Commission shall conduct an investigation and study of the nature and extent of research involving living fetuses, the purposes for which such research has been undertaken, and alternative means for achieving such purposes. The Commission shall . . . recommend to the Secretary policies defining the circumstances (if any) under which such research may be conducted or supported."

"Until the Commission has made its recommendations to the Secretary . . . the Secretary may not conduct or support research in the United States or abroad on a living human fetus, before or after the induced abortion of such fetus, unless such research is done for the purpose of assuring the survival of such fetus."

Public Law 93-348, sections 202b, 213

I shall begin by stating the conclusion of this paper, so that the upshot of the following analysis is immediately apparent. A three-step argument forms the core of the essay:

- Nontherapeutic research on children should be permitted, if such research involves no risk or only minimal risk to the subjects.
- Nontherapeutic research on fetuses which will be carried to term should be permitted, if such research involves no risk or only minimal risk to the subjects.
- 3. Nontherapeutic research procedures which are permitted in the case of fetuses which will be carried to term should also be permitted in the case of (a) live fetuses which will be aborted and (b) live fetuses which have been aborted.

### I. SCOPE AND FOCUS

The legislation which created the Commission clearly focuses attention upon "research involving living fetuses." Thus, this paper will not discuss the problem of research involving the dead fetus, living tissues derived from the dead fetus, or the placenta, fluids, and membranes. As noted below, the term "fetus" will be used in a general rather than a technical sense to apply to the living human conceptus (1) in utero from the time of implantation to the time of delivery or abortion, and (2) outside the uterus from a point eight days after fertilization to the point at which the organism is clearly viable.

### II. DEFINITIONS

- A. <u>Fetus</u>: the human conceptus *in utero* from the blastocyst stage to delivery and outside the uterus from the blastocyst stage to the point at which the organism is clearly viable. Beyond this latter point, an extrauterine organism would be designated an "immature infant" or a "premature infant."
- B. <u>Live or Living</u>: possessing at least one of the standard signs of life, namely, heartbeat, respiration, movement, or, in the case of the fetus, pulsation of the umbilical cord.
- C. <u>Dead</u>: the state in which the organism as a whole shows none of the standard signs of life (in the absence of artificial life support systems) and is not capable of being resuscitated. Individual tissues and cells may live on after the organism as a whole is dead.
- D. <u>Viable</u>: sufficiently mature to be able to continue to live apart from direct connection with the mother, assuming standard neonatal care. I would recommend that for the sake of clarity this term be analyzed into three subcategories:
  - 1. <u>Clearly Viable</u>: sufficiently mature to be able to survive in virtually all cases, if no serious illness or malformation is present (suggested estimate: birth weight of 2300 grams or more).
  - 2. Probably Viable: sufficiently mature to possess a 50 percent or greater chance of survival, based on current national averages for fetal survival (suggested estimate: birth weight of 1250 to 2299 grams).<sup>2</sup>
  - 3. Possibly Viable: possessing a 49 percent or less chance of survival, based on current national averages for fetal survival. For the purposes of this definition, the birth weight of a possibly viable fetus must equal or exceed the birth weight of the smallest fetus known to have survived through well documented medical records (1975 estimate: birth weight of 500 to 1249 grams).
- E. <u>Previable or Nonviable</u>: weighing less at birth than the smallest recorded surviving fetus; clearly incapable of continuing to live apart from direct connection with the mother, assuming standard neonatal care. A graphic representation of the definitions proposed in D and E would appear as follows, according to the suggested estimates:

previable	possibly viable	probably viable	clearly viable
5	00g 12	50g 230	00g

- F.  $\underline{\text{Therapy}}$ : the use of established and accepted methods of treatment to meet the needs of a patient.<sup>5</sup>
- G. Therapeutic Research: the use of treatment methods which are not established and accepted, with the primary intent of benefitting the patient receiving the new treatment. (Whether the new treatment in fact benefits the patient is an important question but, according to the ethical codes which have addressed the problem of clinical research, it is a secondary question.)
- H. Nontherapeutic Research: the use of procedures which are not established and accepted methods of treatment, with the primary intent of gaining scientific knowledge or of benefitting persons other than the experimental subject.

### III. MAJOR TYPES OF FETAL RESEARCH

Conceptually, one can distinguish at least the following major categories of fetal research:

- 1. Research involving live or dead fetuses
- 2. Research involving fetuses in utero or outside the uterus
- 3. Research involving induced abortion or either spontaneous abortion or spontaneous delivery
- 4. Research involving previable or viable fetuses
- 5. Nontherapeutic or therapeutic (for fetuses) research
- Research involving various degrees of risk to fetuses: minimal, moderate or serious.

If one excludes research involving dead fetuses (category 1) and the risk question (category 6), one is still left with 16 possible combinations of the remaining categories, i.e., 16 distinct types of fetal research. If one includes the three levels of risk noted in category 6, this total rises to 48 potential types of fetal research. (For an attempt to display these various potential types of fetal research in diagrammatic fashion, see Appendix B.)

There is, however, a more inductive approach which can be adopted in enumerating the major types of fetal research. One can review reports or survey articles which have appeared in the medical literature during the past 15 years to ascertain what kinds of live fetus research have in fact been done. This survey will be based in part on the literature review performed by Dr. Mahoney's group.

Chronologically speaking, live fetus research seems to be done most often at four stages of fetal life: (1) when the fetus is *in utero* and will remain *in utero* for at least one week; (2) when the fetus is *in utero* and delivery or

induced abortion is anticipated within a few hours or days; (3) during an abortion procedure, i.e., after the procedure has begun but while the maternal-feto-placenta unit is still intact; and (4) following the completion of abortion, i.e., after the surgical separation of the fetus from the mother.

From a medical or biological standpoint, one can distinguish the following major types of live fetus research in the medical literature:

- 1. Prenatal diagnosis
- 2. Intrauterine therapy
- 3. Studies of fetal behavior
- 4. Nutrition studies
- 5. Studies of placental transfer
- 6. Studies of fetal physiology or metabolism
- 7. Studies of abortion techniques
- 8. Tissue studies
- 9. Studies of oxygenation or life prolongation
- 10. Studies of techniques for facilitating delivery.

Certain of these ten research procedures are likely to be correlated with particular chronological stages of fetal life.

In the following paragraphs, I shall briefly describe some of the live fetus research which has been conducted and reported in the scientific literature of the past 15 years. The studies will be organized according to the four chronological stages noted above.

### 1. The Fetus In Utero More Than One Week Prior to Delivery or Abortion

- a. <u>Prenatal Diagnosis:</u> The traditional use of x-ray has been supplemented by a series of newer techniques, including amniocentesis, 10 ultrasound, 11 fetoscopy, 12 and fetal blood sampling. 13
- b. <u>Intrauterine Therapy</u>: Intrauterine blood transfusions for Rh incompatibility have been employed for several years; more recently attempts have been made to treat adrenogenital syndrome, <sup>14</sup> fetal lung immaturity, <sup>15</sup> and a type of acidemia <sup>16</sup> prenatally.
- c. <u>Studies of Fetal Behavior</u>: Most studies seem to concentrate on fetal response to sound, 17 although some studies investigate the effect on the fetus of light and other types of stimuli. 18
- d. <u>Nutrition Studies</u>: Prospective studies involving animals have been performed, but few prospective studies on humans have been done; a major retrospective study has examined the effect of the Dutch "hunger winter" of 1944-1945 on fetal development.<sup>20</sup>

e. Studies of Placental Transfer: Numerous retrospective studies have been done concerning the effect on the fetus of drugs administered to the mother for therapeutic reasons; 21 several prospective studies of placental transfer have been performed prior to induced abortion, including two rubella vaccine studies. 22 The prospective studies are performed more than a week prior to induced abortion, so that sufficient time elapses to allow the effect of the experimental procedure on the fetus to become apparent.

### 2. The Fetus In Utero a Few Hours or Days Prior to Delivery or Abortion

- a. <u>Prenatal Diagnosis</u>: Some new techniques of prenatal diagnosis, for example, fetoscopy, have been tested on fetuses prior to abortion.<sup>23</sup>
- b. <u>Nutrition Studies</u>: In a study entitled "Response to Starvation in Pregnancy" women scheduled for abortion fasted during an 84-hour period immediately prior to the abortion procedure.<sup>24</sup>
- c. Studies of Placental Transfer: In pregnant women nearing the time of delivery, several studies have investigated placental transfer of radioisotopes, ethyl alcohol, or steroids.<sup>25</sup> In cases involving abortion, numerous studies of placental transfer have been performed. Most of these studies begin several hours prior to abortion, at which time an agent is administered to the mother intravenously. The agent, having crossed the placenta, is recovered from the fetus during or following the abortion procedure either by drawing a fetal blood sample or by examining fetal organs. Specific compounds which have been tested in placental transfer studies at the time of abortion include: erythromycin and clindamycin,<sup>26</sup> 125I-glucagon,<sup>27</sup> cortisol,<sup>28</sup> diphenylhydantoin,<sup>29</sup> and gentamycin.<sup>30</sup>
- d. Studies of Abortion Techniques: For the most part, such studies have concentrated on maternal comfort and safety; 11 recently one study has investigated the mechanism by which fetal death is produced in saline-induced abortion. 32
- e. Studies of Techniques for Facilitating Delivery: In pregnant women nearing the time of delivery, numerous studies have been conducted to test the effect on the fetus of agents which delay or induce the onset of labor<sup>33</sup> and various types of obstetrical anesthesia, e.g., paracervical block.<sup>34</sup>

### 3. The Fetus During the Abortion Procedure, While the Maternal-Feto-Placental Unit is Intact

a. <u>Placental Transfer</u>: During abortion by hysterotomy, studies of placental transfer investigate whether a compound introduced on

the fetal side of the placenta crosses the placenta and enters the maternal bloodstream. For example, two studies of fetal circulation and blood volume injected radioactive isotopes into the umbilical vein, then sought to detect the presence of radioactivity in the mother.<sup>35</sup>

b. Studies of Fetal Physiology or Metabolism: In such studies the attachment of fetus to the placenta and to the mother assures the continuation of fetal circulation. During hysterotomy procedures various researchers have investigated blood flow within the fetal circulatory system<sup>36</sup> and fetal metabolism of arginine,<sup>37</sup> sulfur,<sup>38</sup> and <sup>125</sup>I-glucagon.<sup>39</sup>

### 4. The Fetus Outside the Uterus Following Separation from the Mother, i.e., the Abortus40

- a. Studies of Fetal Physiology or Metabolism: Since the aborted fetus may continue to live for a period of time following abortion by hysterotomy or hysterectomy, it is possible to study certain aspects of fetal physiology even after spontaneous or induced abortion. One study which involved abortion-hysterectomies perfused the pregnant uteri with barium sulfate solution in order to perform angiographic studies of the circulatory system in the uterus and the placenta. Another study decapitated eight live aborted fetuses, perfused the fetal heads through the carotid arteries, and measured cerebral oxidation of a glucose substitute.
- b. <u>Tissue or Organ Studies</u>: The removal, or harvesting, of fetal organs or tissues is frequently the final step in studies of fetal metabolism which commenced prior to abortion. In some cases such organs are removed from the still-living organism immediately following the abortion procedure. Studies which have involved the retrieval of organs from the live abortus include an investigation of biosynthesis in the fetal liver and brain<sup>43</sup> and two projects which examined the enzyme response of the fetal liver.<sup>44</sup>
- c. Studies of Oxygenation or Life Prolongation: Previable aborted fetuses lack the capacity to breathe and to absorb oxygen through the lungs. Several investigators have tested the feasibility of prolonging fetal life by other means of oxygenation. One study placed fetuses in an immersion chamber and sought to discover whether "the skin of a fetus immersed in a oxygen-pressured nutrient could be utilized as an organ of absorption and excretion." 45 Another study serially attached several aborted fetuses to an artificial placenta.46

### IV. ETHICAL ISSUES IN FETAL RESEARCH

As the foregoing survey makes clear, "fetal research" is not one but many things. Several of the studies noted above were clearly therapeutic in intent,

particularly if one considers diagnosis to be a prerequisite of therapy. Other studies were not done for the benefit of the fetuses involved. The Commission will no doubt wish to formulate policy for both therapeutic and nontherapeutic fetal research. However, since it is nontherapeutic research on fetuses which seems to raise the most serious questions in the public mind, I will concentrate primary attention on the problem of nontherapeutic fetal research.

The survey of major types of fetal research also indicates that fetal research involves both fetuses which will come to term and be born and fetuses which will be, are being, or have been aborted. Here again a limitation is in order. As the legislation which established the Commission suggests, it is research which occurs "before or after the induced abortion" of the fetus which was uppermost in the minds of the lawmakers. I will therefore focus especially on ethical issues involved in research before, during, or after induced abortion. Since abortion is generally performed before fetal viability is clearly achieved, such fetuses will generally be previable or, at most, only possibly viable.

There are few published discussions of the ethical issues involved in live fetus research. The few documents which do exist reveal that the Commission is faced with a situation of ethical pluralism. So far as I am able to detect, there exists no national consensus on the question of fetal research.

In my view, four major positions have emerged on the ethics of research involving live (not clearly viable) fetuses before, during, or after induced abortion:

- 1. Nontherapeutic fetal research should not be done under any circumstances.
- Nontherapeutic fetal research should be done only to the extent that such research is permitted on children or on fetuses which will be carried to term.
- 3. Greater latitude should be allowed for nontherapeutic fetal research than for research on children or on fetuses which will be carried to term. However, certain types of experimental procedures should not be performed, even in nontherapeutic fetal research.
- 4. Any type of nontherapeutic fetal research may legitimately be performed.

Position 1 was argued by Monsignor James McHugh in testimony before the Commission last month. Position 2 was adopted by both the Peel Commission and the 1973 and 1974 DHEW guidelines with respect to the fetus in utero. Position 3 approximates the regulations of the 1973 DHEW guidelines regarding the abortus and the 1974 guidelines regarding both the abortus and fetus in utero during an abortion procedure. Position 4 may have been the view of the Peel Committee on research involving the live previable abortus; the Report of the Committee is silent regarding substantive limitations on abortus research.

In this section I shall seek to demonstrate that Position 2 is a reasonable ethical position. In the succeeding section I shall attempt to show that such a position could also be translated into a constructive and workable public policy.

One can arrive at Position 2 by extrapolating backward from a position on the ethics of pediatric research. In recent years, some philosophers and ethicists have argued that nontherapeutic research on children who cannot consent should not be performed under any circumstances. However, Richard McCormick has presented what seems to me to be a very cogent argument for including children in certain kinds of no-risk or low-risk nontherapeutic research. McCormick's central thesis is that all members of society owe certain minimal debts to society; among these debts is one's obligation to take part in low-risk biomedical or behavioral research. He concludes that parents should be authorized to consent to a child's taking part in experiments which the child should be willing to take part in if the child could understand and consent.

If one accepts this position on pediatric research, one can easily extend it to cover the prenatal period in the life of a fetus which will be carried to term and be born. The parent or parents of such a fetus can be expected to have the interests of the fetus in view, just as parents of already-born children normally consider the interests of their offspring. Thus, proxy consent for non-therapeutic research on a fetus prior to birth is both possible and ethically consistent with consent for nontherapeutic pediatric research.

In the case of a fetus which will be aborted or has been aborted, the situation is somewhat more complex. The mother has decided, perhaps for good reason, that the life of the fetus should be terminated. Because she will not be obliged to consider the interests of the child on a long-term basis, she cannot give proxy consent in the same sense as the mother or both parents of an already-born child or a fetus to be born. There is, in addition, an inherent difficulty in conceptualizing what "risk" or "harm" might mean when one is speaking of an organism which will shortly die at a previable stage of life. I suggest that it is possible to skirt these difficult problems as well as to be ethically consistent if one adopts the general rule: Nontherapeutic research procedures which are permissible in the case of fetuses which will be carried to term are also permissible in the case of (a) live fetuses which will be aborted and (b) live fetuses which have been aborted.

The fundamental presupposition of the position here advocated is that there is a substantial measure of continuity between previable fetal life and viable fetal life or pediatric life. This continuity cannot, in my view, be conclusively demonstrated by means of factual arguments. However, a proponent of the continuity thesis can point to a series of considerations which render the thesis at least not implausible. It seems clear, for example, that the living previable fetus has a qualitatively different potential from a living tissue or a living subhuman animal.50 One notes, too, that Anglo-American law has displayed a certain ambivalence vis-à-vis the previable fetus, according to the fetus some, but not all, of the legal protection enjoyed by children or adults.51 It can also be argued that in form or general appearance the 12- or 16-week-old previable fetus resembles the viable fetus more closely than it resembles the embryo or blastocyst. Finally, one is struck by both the technology dependence and the somewhat arbitrary character of the viability watershed: fetuses which twenty years ago would have been correctly classified as previable are now surviving in neonatalcare units; today the immaturity of a single organ system, the lungs, constitutes the major barrier between a 450-gram fetus and viability.

There are strong counterarguments which can be mounted against the continuity thesis and the ethical position advocated above. I shall briefly mention and comment on two. It might be argued, first, that the right to have a previable fetus aborted is firmly established in American law and that the termination of life is much more harmful to the fetus than any experimental procedures -- even highly invasive procedures -- which might be performed upon it. In response to this argument one would wish to question whether abortion and fetal research are, indeed, analogous questions and whether the moral justification of abortion entails, as well, the justification of fetal research. the case of abortion there exists a clear conflict between maternal interests and the developing fetus. The woman alleges a right to be rid of an immediate, serious threat to her previous pattern of life. This right is now quaranteed by the law for the stages of pregnancy prior to fetal viability. In the case of fetal research, however, there is, so far as I can see, no similar clear and immediate conflict between the previable fetus and society at large or any other social group. Thus, it would seem that the proponent of highly invasive fetal research must build an entirely new case for such research rather than being able to piggyback his or her case on the fact of presumably lethal abortion procedures.

A second major counterargument to the position taken in this paper is more consequential in character. This argument can be taken in any of several directions. It is asserted, for example, that if fetal research proceeds without limitation, one can expect such research to yield major advances in scientific knowledge or results of great benefit to all future fetuses and premature infants. A narrower and more limited consequentialist claim is that by performing high-risk safety-studies of new procedures on fetuses which will be or have been aborted, one can prevent damage to fetuses which will later be born and who will subsequently bear the stigma of prenatal damage throughout an entire lifetime.

These are significant arguments and deserve to be taken seriously. There are, however, several avenues of reply. It may be noted, first, that many of the benefits promised from fetal research without limitation could also be achieved by research carried on within the ethical guidelines here proposed. Second, it can be argued that the positive consequences of fetal research without limitation, desirable as they seem, are not the only consequences which need to be considered. A comprehensive social-impact statement would take into account, in addition, the possible dehumanizing effects on investigators of their performing highly invasive procedures on still-living fetuses. One would also wish to inquire whether such research would set a precedent for the performance of similar procedures on other classes of human organisms—for example, on newborns who are mortally ill or comatose elderly persons.

The safety-studies argument is perhaps the most difficult one to meet. Negatively, it seems to me that the potential problems of dehumanization and precedent-setting are pertinent to this argument, as well. More positively, if, as I have advocated, children and fetuses are to be involved in low-risk nontherapeutic research for the sake of society, then society would seem to owe such subjects a reciprocal debt. There would inevitably be accidents resulting from low-risk nontherapeutic or higher-risk therapeutic forms of

research. In my view, society would have a serious moral obligation to develop programs of compensation and care for a new class of "disabled veterans"--those wounded in the battle against disease.

### V. RECOMMENDATIONS FOR A NATIONAL POLICY ON FETAL RESEARCH

Policy-making always involves the setting of priorities, and the priorities one chooses reflect the values one wishes to maximize. Thus, there is always a significant ethical component in the policy-making process.

However, policy making takes into account certain factors which ethics generally does not. In a pluralistic society it seeks to accommodate a variety of belief-systems and interests rather than elevating the views of any single group to the status of national policy. Policy making also attempts to achieve maximal continuity with some of the generally-accepted principles within the society. Finally, policy makers, at their best, seek to ensure that national policies are formulated and expressed in terms that are clearly understandable to the public at large.

In my view, the Commission is in an ideal position to articulate a clear, well-reasoned national policy on fetal research which can become the basis for ongoing discussion and a possible movement toward national consensus. I wish to recommend that the Commission adopt a policy which emphasizes equality of treatment or equal protection for all categories of human subjects. More specifically, I would recommend that the Commission adopt a policy which approximates Position 2 in the foregoing ethical analysis. On the policy level, this recommendation can be stated in terms of three parallel propositions:

- 1. Nontherapeutic research on children should be permitted, if such research involves no risk or only minimal risk to the subjects.
- Nontherapeutic research on fetuses which will be carried to term should be permitted, if such research involves no risk or only minimal risk to the subjects.
- 3. Nontherapeutic research procedures which are permitted in the case of fetuses which will be carried to term should also be permitted in case of (a) live fetuses which will be aborted and (b) live fetuses which have been aborted.

A policy developed along the lines suggested has numerous advantages, in my view. I will attempt to list several:

- 1. It is formal and therefore flexible; it does not prohibit any particular research procedure but establishes a general test which all proposed procedures would be required to meet.
- 2. It is a mediating policy, which corresponds to moderate positions on the spectrum of current ethical opinion regarding fetal research.

- 3. The proposed policy is in continuity with past policy-recommendations by the Peel Committee and DHEW concerning research involving the fetus in utero in anticipation of abortion. Like these previous policies, it protects the woman's rights to change her mind concerning a planned abortion.
- 4. It obviates the need for a definition of viability, since the same formal guidelines apply to both previable and viable fetuses.
- 5. It takes into account the sensibilities of the large numbers of persons who object to highly-invasive research on live aborted fetuses.
- 6. Finally, the proposed policy, if adopted, would permit many valuable types of fetal research to continue. Research involving living tissues from dead fetuses would not be affected in any way by the policy here proposed and could thus continue unabated. Studies of prenatal diagnosis, intrauterine therapy, fetal behavior, placental transfer, fetal physiology or metabolism, oxygenation-techniques, and the facilitation of delivery could all be continued, provided that the various categories of fetuses were treated equally and provided that the non-therapeutic procedures would involve either no risk or only minimal risk to the subjects.

In conclusion, I should like to recommend that the Commission devote at least some attention to one other policy aspect of the fetal-research question, namely, the development of more adequate protective mechanisms for the pregnant women who are necessarily involved in fetal research. Bradford Gray's study of two research projects at Eastern University Hospital seems to demonstrate that expectant mothers or women seeking abortions are in a particularly vulnerable position vis-à-vis the health professions and that they are not always adequately informed concerning the research in which their participation is sought.<sup>52</sup> I would hope that the Commission's final policy recommendations will include guidelines for protecting the pregnant woman's right to receive adequate medical care regardless of her decision concerning possible participation in projects involving fetal research.

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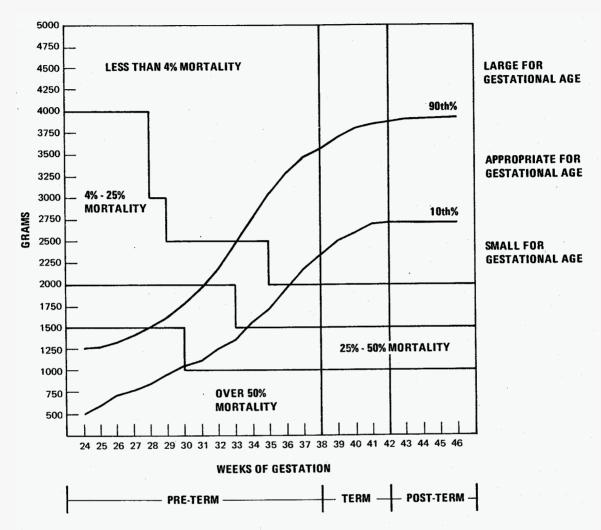
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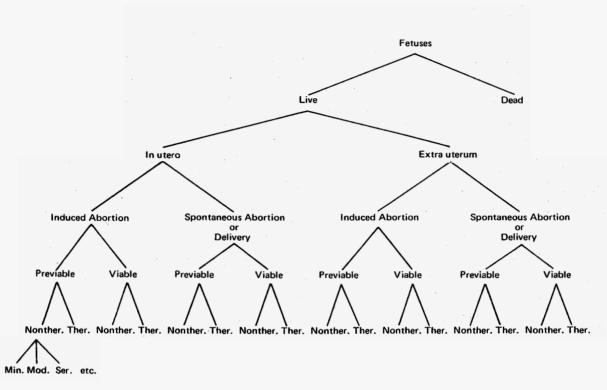
Classification of Newborns by Birth Weight and Gestational Age and by Neonatal Mortality Risk

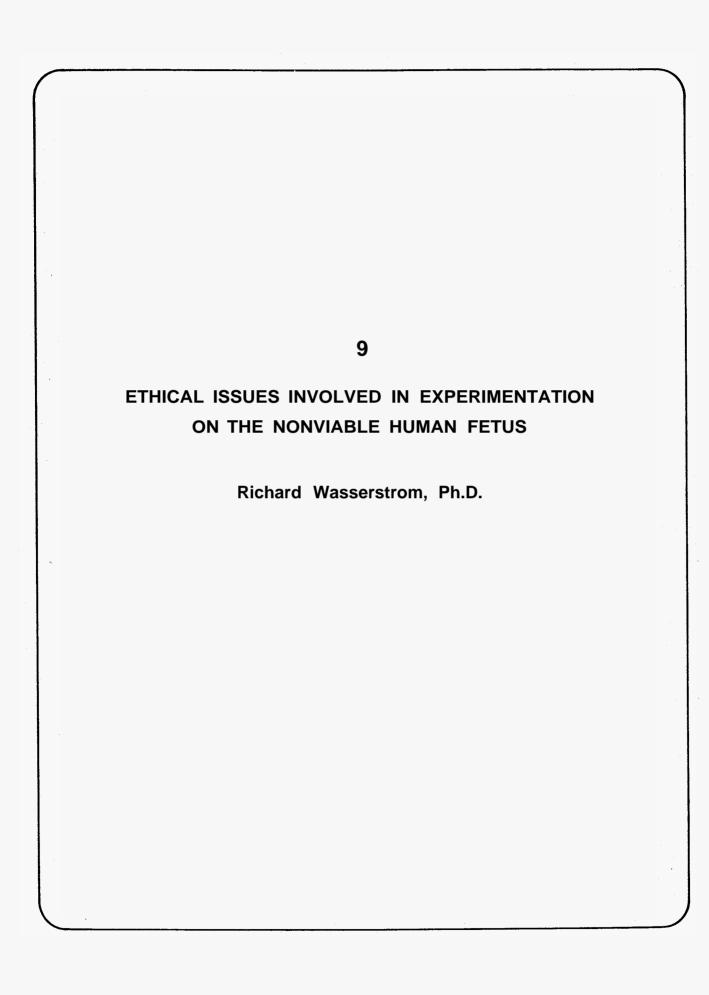
APPENDIX A



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# APPENDIX B General Types of Fetal Research





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PD 304215-5

# Ethical Issues Involved in Experimentation on the Nonviable Human Fetus

### THE STATUS OF THE FETUS

I do not believe that the question of the morality of experimentation on living, nonviable fetuses can be sensibly considered without some attention being paid at the outset to the question of what kind of an entity a human fetus is. Although some of the relevant arguments do not depend, even implicitly, upon an answer to this question, the great majority of them do. That this is so can be seen, I think, from the fact that the question of experimentation is a very different one if the fetus is thought to be fundamentally like a piece of human tissue or organ, e.g., an appendix, than if the fetus is thought to be fundamentally like a fully developed, adult human being with normal capacities and abilities.

There are four different views that tend to be held concerning the status of the human fetus. They are:

(a) That the fetus is in most if not all morally relevant respects like a fully developed, adult human being. At least two major arguments can be given in support of this position. The first is a theological argument which fixes conception as the time at which the entity acquires a soul. And since possession of a soul is what matters morally and what distinguishes human beings from other entities, the fetus is properly regarded as like all other persons. second argument focuses upon the similarities between a developing fetus and newly born infant. In briefest form, the argument goes as follows. It is clear that we regard a newly born infant as like an adult in all morally relevant respects. Infants as well as adults are regarded as persons who are entitled to the same sorts of protection, respect, etc. But there are no significant differences between newly born infants and fetuses which are quite fully developed and about to be born. What is more, there is no point in the developmental life of the fetus which can be singled out as the morally significant point at which to distinguish a fetus not yet at that point from one which has developed beyond it and hence is now to be regarded as a person. Therefore, fetuses are properly regarded from the moment of conception as having the same basic status as an infant. And since infants are properly regarded as having the same basic status as adults, fetuses should also be so regarded.

Now, of course, on this view abortion, whether before or after viability, raises enormous moral problems, since it is morally comparable to infanticide and homicide, generally. And the morality of abortion per se is beyond the scope of the present inquiry. This view is nonetheless directly relevant, even on the assumption that abortion prior to viability is morally permissible. For on this view, for instance, experimentation ex utero upon a nonviable living

fetus is to be seen as analogous to experimentation upon, say, an adult human being who is in a coma and who will die within the next few hours. Thus, on this view, the moral problems of experimentation ex utero would be thought to be similar to those of experimentation upon adults whose deaths were imminent and who were themselves unconscious.

(b) That the fetus is in most if not all morally relevant respects like a piece of tissue or a discrete human organ, e.g., a bunch of hair or a kidney, The argument in support of this view focuses upon all of the ways in which fetuses are different from typical adults with typical abilities. In particular the absence of an ability to communicate, to act autonomously (morally, as well as physically), to be aware of one's own existence, and/or to experience sensations of pain and pleasure would singly and collectively be taken to be sufficient grounds for regarding the fetus as more like an organ growing within the woman's body than like any other kind of entity. It should be noted, too, that for our purposes this view includes all those positions which regard the status of the fetus as changing from something like a human organ to something else only at or after the moment of viability has been reached. For this inquiry is concerned only with experimentation upon nonviable fetuses.

On this view there are, I think, virtually no arguments against experimentation ex utero and only a few arguments against experimentation in utero. Whatever, for example, can properly be done to a severed human organ which still has certain life capacities (e.g., it is capable of being transplanted into another human, or it still maintains some of its organ function) can properly be done to the nonviable fetus ex utero in those few hours before its life functions have ceased.

(c) That the fetus is in most if not all morally relevant respects like an animal, such as a dog or a monkey. The fetus is, on this view, clearly not a person, nor is it just a collection of tissue or an organ. It is an entity which is at most entitled only to the same kind of respect that many (but not necessarily all) persons think is due to the "higher" animals. It is wrong to inflict needless cruelty on animals--perhaps because they do suffer or perhaps because of what this reveals about the character of the human imposing the cruelty. And fetuses are, basically, in the same class.

On this view, too, there are comparatively few worries about experimentation ex utero on nonviable fetuses. At most, the worries are of the same sort that apply to experimentation upon living animals. For the most part, it is proper to regard them as objects to be controlled, altered, killed, or otherwise used for the benefit of humans--subject only to concerns relating to the infliction of needless and perhaps intentional pain and suffering upon the entities being experimented upon, and (in the case of those higher animals we most identify with) to prohibitions upon their consumption as food.

(d) That the fetus is in a distinctive, relatively unique moral category, in which its status is close to but not identical with that of a typical adult. On this view the status of the fetus is both different from and superior to that of the "higher" animals. It is, perhaps, closest to the status of the newly born infant in a culture in which infanticide is regarded as a very different

activity from murder or to the status of the insane, the mentally defective or slaves -- again in cultures which see them as less than persons but as clearly superior to animals. The case for regarding fetuses as belonging to a special, discrete class of entities rests, I think, largely on the fetus' potential to become in the usual case a fully developed adult human being. Conceding that the fetus is significantly different from an adult in respect to such things as its present capacity to act autonomously, to experience self-consciousness, and perhaps even to experience pain, this view emphasizes the distinctiveness of the human fetus as the entity capable in the ordinary course of events of becoming a fully developed person. This view sees the value of human life in the things of genuine value or worth that persons are capable of producing, creating, enjoying, and being, e.g., works of art, interpersonal relations of love, trust and benevolence, and scientific and humanistic inquiries and reflections. Correspondingly, it sees the distinctive value of the fetus as being alone the kind of entity that can someday produce, create, enjoy and be these things of genuine value and worth.

It is, I think, especially important to notice the implications of this view for the morality of experimentation upon nonviable fetuses ex utero. For it is the nonviability of the fetus that goes, I believe, a long way toward making experimentation a substantially less troublesome act than it would otherwise be. That is to say, it is evident, I think, that on this view abortion is a morally worrisome act because it involves the destruction of an entity that possesses the potential to produce and be things of the highest value. However, if an abortion has been performed and if the fetus is still nonviable, then experimentation upon the fetus in no way affects the fetus' ability, or lack thereof, ever to realize any of its existing potential. On this view especially, abortion, not experimentation upon the nonviable fetus is the fundamental, morally problematic activity.

### 2. SPECIFIC ISSUES RELATING TO EXPERIMENTATION EX UTERO

I propose now, within the context of the discussion in section 1, to turn to an examination of what seem to me to be the specific issues that arise in thinking about the morality of experimentation upon nonviable, living, human fetuses ex utero. The examination will be divided into four parts: (a) an enumeration and analysis of the arguments against experimentation; (b) an enumeration and analysis of the arguments in favor of experimentation; (c) an enumeration and discussion of some specific problems that arise in respect to the question of consent; and (d) a statement of my own view about the permissibility of experimentation.

A. The Major Arguments Against Experimentation Upon Nonviable, Living, Human Fetuses Ex Utero. The arguments can be divided in a rough fashion into two groups: those that, on the one hand, oppose experimentation because of the possible, deleterious consequences that are thought to follow from the legitimization of such a practice; and those that, on the other hand, oppose experimentation because of some feature of the situation that is seen to be itself wrong or improper. I begin with the former collection of arguments—those that concentrate upon the possible, deleterious consequences.

(1) Possible, Deleterious Consequences of Permitting a Practice of Fetal Experimentation. One general argument here is that if such a practice is permitted and well publicized then individuals and, in some related sense, the society will become less sensitive to values and claims which are entitled to the greatest respect. Thus, one specific version of this general line of attack is the argument that individuals will become less sensitive than they ought to be to the value of human life. Another specific claim is that individuals will become less sensitive than they ought to be to the rights and needs of persons who are, for one reason or other, incapable of looking after themselves, e.g., infants, the aged, and the seriously ill or retarded. Still a third, related worry is that individuals will become less sensitive than they ought to be to the claims of those persons whose deaths are reasonably thought to be certain and imminent, e-g., persons in the last stages of terminal illnesses. And a fourth, consequential concern is that individuals will become less sensitive than they ought to be to the rights of persons not to be the unwilling subjects of experimentation.

I think one thing that is of interest about all four of these arguments is that they can retain some if not all of their force irrespective of what is thought in fact to be the correct view about the kind of entity a fetus is. is to say, consider the claim that permitting fetal research may lead individuals to become less sensitive than they ought to be to the rights and needs of persons who are, for one reason or another, incapable of looking after themselves. someone who is convinced that a fetus is basically like a human organ might nonetheless legitimately worry about the inferences that individuals would mistakenly draw from the permissibility of a practice of fetal research. As long as it is reasonable to believe that persons, in any significant number, might mistakenly suppose that the principle which justified fetal experimentation was a principle which justified experimentation upon any entity that was incapable of keeping itself alive without substantial human assistance, this is a deleterious consequence of a practice of fetal experimenation which would have to be taken into account. Of course, the more one thinks that a fetus is like other persons in most significant respects, the more one is also apt to think that individuals generally may confuse the case of the fetus with the case of those other entities whose claims to morally more sensitive treatment are nonetheless distinguishable.

A rather different consequential argument goes like this. Once it becomes permissible for experiments to be done on living, nonviable fetuses, such fetuses will come to be regarded as extremely useful in medical research. The increased demand for fetuses within the scientific community will lead to the creation of a variety of subtle as well as obvious incentives for persons both to have abortions and to have them in such a way that the fetus can be a useful object of experimentation. And this is undesirable for several reasons. To begin with, unless it is the case that abortion is a morally unproblematic action, it is wrong to develop a social practice which will encourage persons to have abortions. In addition, the fact that fetuses are useful objects of experimentation might lead members of the scientific and medical community unconsciously to distort or alter their views of when persons should have abortions. Doctors might in this way take into account nonmedical reasons for advising patients to have abortions. And, finally, there is always the danger that the pressures and

inducements would operate unequally throughout the society--persons from a low socioeconomic status would be the ones who were more likely to be attracted by the incentives and subjected to the pressures.

Still a third argument, which may or may not be consequential, points to the fact that many individuals will experience revulsion and will be in psychic turmoil when they learn of fetuses being treated in this way, i.e., as objects of experimentation. The revulsion and turmoil are comparable, although less universal, than that encountered at the thought of such things as cannibalism, and the desecration of graves. If a large number of persons respond this way, then one argument against experimenation is that it will substantially impair social peace and harmony. Because they care so strongly, they will be led to act antagonistically toward the source of their discomfort. In addition, even if the numbers are not large, the severe quality of their reactions may justify prohibition simply on the ground that the gains of experimentation do not overbalance the pain and discomfort experienced by those who are so affected.

(2) Arguments for the Intrinsic or Direct Wrongness of Fetal
Experimentation. I can identify approximately a half-dozen arguments that in some direct, nonconsequential way call into question the morality of fetal experimentation upon nonviable, living fetuses. More so than in the case of the consequential arguments, the force of these arguments often depends upon the status that it is thought ought properly be accorded the fetus.

The first two arguments relate to the principle involved in fetal experimentation. One such argument is this: To permit fetal experimentation is at least to commit oneself to the principle that it is permissible to perform comparable experiments upon any living person, provided only that we have good reason to believe that the person will die very soon, i.e., within a few hours, anyway. But since it is surely wrong to experiment on persons just because they will die anyway within a few hours, experimentation on nonviable, living fetuses lacks a coherent principle of support.

The other argument is similar: To permit fetal experimentation is to commit oneself to the principle that it is permissible to perform comparable experiments on all living persons, provided only that they are no longer conscious and will not regain their consciousness before they die. But since it is surely wrong to experiment on all such persons, experimentation on nonviable living fetuses lacks a coherent principle of support.

In both cases it is, I think, clear that the force of the argument depends upon the claim that fetuses are sufficiently like other human persons so that there are no plausible, reasonably persuasive grounds upon which to distinguish the way in which the fetus is treated from the way in which other persons, e.g., the terminally ill or the unconscious, could also properly be treated. The argument appeals both to a claim that it would be wrong to treat other persons in this way and to a claim that the case of fetal experimentation cannot be readily or convincingly distinguished.

A third argument concerns the concept of viability. It is this: The concept of viability is anything but a precise one, even within medical science.

It is fundamentally the idea that the fewer the number of weeks of gestation the less likely it is that any medical means presently exist by which the fetus could be kept alive until it could function without artificial support. The problem is not just one of imaginary, theoretical possibilites. Given the present state of medical technology there will at best be a range within which it is relatively likely or unlikely that the fetus could be kept alive, i.e., is viable. This means that it is not the case that all fetuses classified as nonviable for purposes of experimentation would necessarily have died no matter what steps had been taken to try to maintain their lives. Now it is clear that once a fetus is viable it is wrong to experiment upon it in ways that are potentially harmful to it. But if this is so, then in some significant number of cases comparable experiments will be performed on fetuses classified "non-viable" but perhaps really viable.

The plausibility of this argument depends both upon the claim that deleterious experimentation upon viable fetuses would be wrong and upon the claim that a significant number of moderately developed fetuses determined to be nonviable might in fact have proved to have been viable, if they had not been the subjects of experimentation.

A fourth argument is this: We believe that fetal experiments which directly terminate either respiration or heartbeat are wrong; see, e.g., "Protection of Human Subjects: Policies and Procedures," DHEW. But there is no real difference between that and engaging in experiments in which the risk of terminating respiration or heartbeat is substantially increased. Hence, if the former is wrong, the latter must be too.

I think this argument is surely correct in its insistence upon the absence of any convincing way to distinguish experiments which directly terminate either respiration or heartbeat from those that increase the risk of termination significantly. What remains the open question, however, is whether there is any good moral reason to regard as improper experiments which directly terminate the respiration or heartbeat of a nonviable fetus.

The fifth argument concerns the general question of the relationship between means and ends in morality. Let it be conceded, so this argument goes, that good ends, e.g., the prevention of premature births, are sought to be achieved through this kind of fetal experimentation. Nonetheless, if the means used to achieve that end are morally unacceptable, it is wrong to seek that end in this way. Hence the pursuit of a good end cannot justify experimentation on nonviable fetuses.

This argument leaves two questions unanswered. To begin with, the argument assumes rather than explains the immorality of this kind of experimentation on nonviable fetuses. Unless independent grounds are offered to establish the impropriety of such experiments, the argument is at best hypothetical: if such grounds exist, they cannot be overridden by the worth of the end that is sought. In addition, the argument assumes both the possibility of separating clearly means from ends and the wrongness of using bad means to achieve a good end. Neither assumption seems to me to be unproblematic, and both would require discussion and analysis of a sort which lies beyond the scope of this inquiry.

The remaining argument relates especially to those experiments which prolong the life of the nonviable fetus, but also to some experiments which do not. The argument is that all experiments which cause the fetus more pain than it would otherwise experience are bad just in virtue of this fact. I do think that it always counts against the doing of an action that it increases the amount of pain in the world, and it always counts substantially against the doing of an action that it increases the amount of pain experienced by human beings. Thus, this argument would, I think, be a relevant argument if it were the case that it was reasonable to think that the nonviable fetus had the present capacity to experience pain, even in the sense, say that we think animals like dogs and horses do. And the argument would be an especially important one if it were the case that it was reasonable to think that the nonviable fetus possessed the present capacity to experience pain in roughly the same sense or way in which fully developed persons do.

B. The Major Arguments in Favor of the Permissibility of Experimentation Upon Nonviable, Living Fetuses Ex Utero. As has already been indicated, some of the arguments depend quite directly upon what view is held concerning the status of the fetus, and others do not. More specifically, if the nonviable fetus is properly regarded as basically a human organ or piece of tissue, little if anything more than scientific curiosity is needed to justify experimentation. In the same way, if the nonviable fetus is properly regarded as basically like a higher animal, e.g., a monkey, genuine scientific curiosity coupled with the avoidance of unnecessary suffering, if any, is all that is required.

The chief argument that applies, even if the nonviable fetus enjoys some other, more significant status, consists in a threefold claim. First, things of great usefulness vis-à-vis the preservation and improvement of human lives can be learned from these experiments. Second, things of great usefulness vis-à-vis the preservation and improvement of human lives can only be learned from these experiments. And third, to describe the fetus as nonviable is to concede that no matter what is done, all signs of life will disappear from the fetus within a very short period of time, i.e., not more than four or five hours. Thus, it is claimed, the conjunction of utility, need and inevitability combine to establish the legitimacy of this kind of experimentation, irrespective of the status of the fetus.

One important objection that this argument must confront is this: If experimentation is justifiable under these conditions, then it is also justifiable in the case of a person who is unconscious, and who will die soon without regaining consciousness, e.g., because he or she is in the last stages of a terminal illness. But because it is wrong to experiment on adults who are in this state, it cannot consistently be maintained that it is right to experiment on the fetus.

At least two responses are possible. First, it might be argued that fetuses are just in a different class from adults. To be sure, there may not be anything intrinsically wrong with experimenting on an adult in the circumstances just described. However, to permit experimentation would be an unwise

exception to the doctrine of the sanctity of human life. Because fetuses are perceived to be different entities from fully developed persons, to permit experimentation on them is not to create the same kind of dangerous exception.

Second, it might be argued that the two cases are distinguishable in that there is no analogue to the concept of nonviability in the case of the adult. That is to say, medical science cannot identify with confidence those cases in which an individual will die soon without regaining consciousness, in the same way in which it can identify with confidence those fetuses that are not yet viable.

There is one other argument in favor of experimentation that is worth noting. It is that if there is no good, moral reason to prohibit experimentation, then a decision to prohibit it encourages the practice of making social decisions on nonrational if not irrational grounds. And this is a generally unwise thing to do. That is to say, it might be maintained that experimentation should be prohibited just because it seems wrong or offensive even though no one can give a plausible account of why it ought to be so regarded. This argument is an answer to that way of proceeding. It is an argument for the importance of restricting scientific inquiry only if there are good reasons and not, for example, irrational or superstitious objections to the investigations.

C. The Issue of Consent. There is a general problem of consent that arises: namely, that the fetus will not have consented to anything. The question is whether that should make a difference. It might be argued, of course, that an experiment is always improper unless the subject of the experiment agrees or consents to being a subject. Since the fetus did not consent to being a subject, any experimentation upon the fetus is improper. The difficulty with this position is that there is no obvious way to decide whether the principle should apply to entities who are not capable of consenting, and if so, to which kinds of entities. It will depend upon the view that is taken of the status of the fetus, and the possible answers will parallel those discussed above in the first part of the paper. If the fetus is a person, then consent will be required (but so, a fortiori, should consent have been required for the abortion), etc. I conclude, therefore, that no new general problem is raised by the absence of the consent of the fetus to being the subject of experimentation.

There is, however, a related issue that is worth mentioning. It is possible, I think, to hold a variety of views about the status of the fetus and still believe that the mother, or perhaps both parents, have a legitimate claim to have their consent secured before any fetal experimentation occurs. The justification cannot, of course, be that to require the consent of the parents will protect the fetus from harm. That is because having elected to terminate the pregnancy the parents are already in a nontraditional, atypical relationship vis-à-vis the offspring. So it cannot be that the consent of the parents should be required as a means of protecting the fetus, or looking after its interest. Still, the parents may have sensibilities, attitudes, etc., that are deserving of respect--sensibilities, etc., that correspond to those of living persons toward a deceased relative. It is not exactly that they "own" the deceased, but that

they do have a legitimate claim to decide how the body of the deceased shall be dealt with. In the same way, I think, parents of an aborted fetus could still quite often see themselves as being in a similar relationship to the fetus, such that they would feel themselves injured in serious ways were the fetus to become the subject of experimentation without their agreement. For this reason, I believe that the consent of the mother (in the case of an unmarried woman) or of both parents to any experimentation should be required before the abortion occurs, and that the nature of the proposed experiments should be explained carefully and fully to them.

- D. Recommendations Concerning Experimentation Ex Utero. My own view is that the fetus enjoys the kind of unique moral status described in section 1(d) above. Hence, abortion on demand seems to me to be a very troublesome moral issue. If the morality of the abortion is not in question, however, then I somewhat uncertainly conclude that experimentation ex utero may be permissible provided the following conditions are satisfied:
- (1) The consent of the mother (if unmarried) or of both parents should be procured before the abortion, and the experiments clearly described to those whose consent is required.
- (2) It should be determined by a body independent of those proposing the experiments that the experiments can reasonably be expected to yield important information or knowledge concerning the prevention of harm or the treatment of illness in other human beings. That same body should also determine that the desired information or knowledge is not reasonably obtainable in other ways.
- (3) Those medical persons who counsel a woman concerning abortion and secure the requisite consent should not be the same persons—or affiliated directly with those persons—who will be involved in the experimentation.
- (4) No experiments should be permitted on an aborted fetus which might in fact be viable, given the state of present medical ability.

#### 3. SPECIFIC ISSUES RELATING TO EXPERIMENTATION IN UTERO

The cases that seem to me to be problematic are those in which there is a reasonable risk that the experiment will be harmful to the fetus and in which the experiments are not undertaken in order to benefit the particular fetus. Much of what has been said about experimentation ex utero applies to these cases as well. In addition, however, there are several new arguments that are relevant only in these cases.

The most significant one against experimentation *in utero* is that the fetus' nonviability has not yet been established in the same way in which it has been in the case of experimentation ex utero. That is to say, in the latter case, the abortion has already occurred and ex hypothesis the fetus cannot survive no

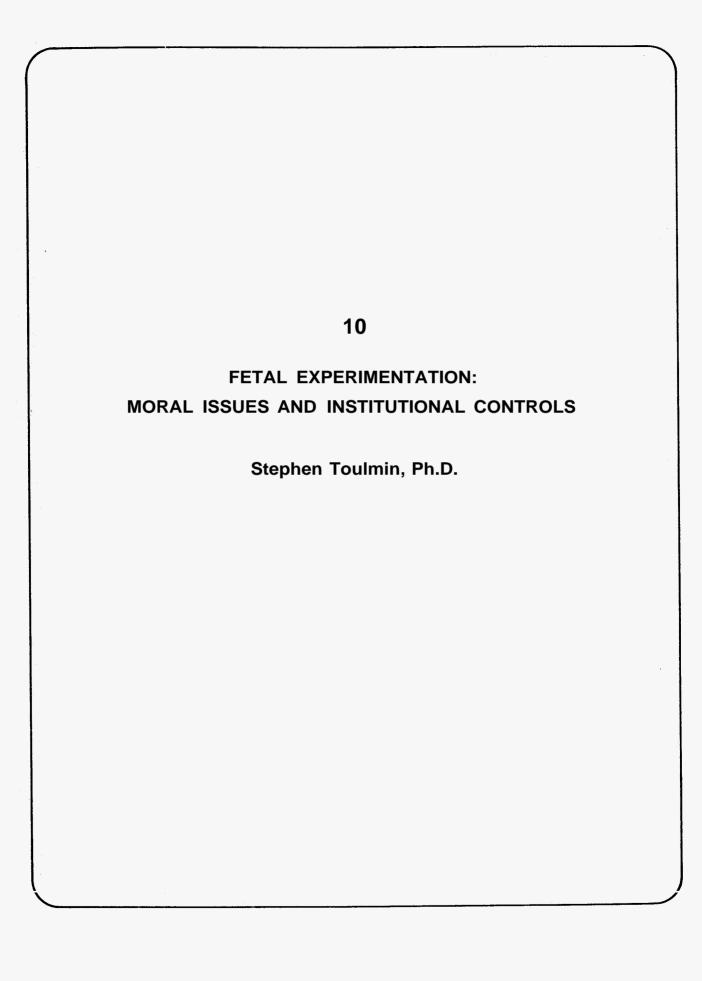
matter what is done. In the former case, however, the abortion has yet to take place, and until it does there is always the genuine possibility that the mother may change her mind and decide not to have the abortion at all.

Because this is so, the possibility of intervening injury resulting from the experimentation creates the following dilemma. On the one hand, if the mother changes her mind and decides not to have the abortion, the chances have thereby been increased that she will give birth to a child who is unnecessarily injured. It seems unfair to the child, the society, and the parents to bring into the world a child with defects or disabilities that could have been prevented.

On the other hand, if the mother is required to proceed with the abortion because the experiments have been undertaken, the state is regarding the original consent to the abortion as irrevocable and it is, in essence, requiring her to submit to the abortion against her will.

There is, in addition, a related matter. The fact that potentially damaging experiments have been performed on the fetus will itself constitute an added inducement to the mother to go through with the abortion and not change her mind. That is to say, experimentation itself makes abortion more likely because the belief that the fetus has been injured will make the mother less likely to change her mind. If abortion is viewed as the kind of serious act that ought not be "artificially" encouraged, then the intervening experimentation may be objected to as just such an "artificial" inducement or encouragement to stay with the original decision to have the abortion.

For the above (and other) reasons I think it important that the decision to have an abortion be kept easily revocable, up until the time of the abortion. And for this reason I do not think that any experiments in utero should be permitted, where those experiments involve a substantial risk of injury to the fetus.



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## Fetal Experimentation: Moral Issues and Institutional Controls

#### I. INTRODUCTION

This paper surveys concisely the range of views available in the current literature, and in the preliminary papers available to the Commission up to March 1, 1975, about the moral admissibility of fetal experimentation, and about the institutional controls that appear desirable in present circumstances to protect the legitimate rights and interests of those affected by such experimentation. It is designedly a selective, not an exhaustive survey. It focuses particularly on those questions that most directly relate to the practical tasks of the Commission, in recommending a policy and guidelines for the public licensing and control of fetal experimentation; and it considers the fundamental theoretical issues involved only more briefly, in an appendix.

The reasons for handling the issues in this way are not merely pragmatic. They reflect also the fact that the doctrinal commitments and philosophical standpoints of the different participants in this discussion turn out, in the event, to have had less influence than may have been expected on the practical recommendations they are prepared to support. To be sure, the recommendations actually offered cover the whole spectrum from an outright ban on nontherapeutic fetal experimentation to a policy of complete freedom for biomedical research on fetal material. But a substantial moderate consensus emerges, which stops short of an outright ban, and advocates a system of social controls carefully designed to limit the scope, and prevent the abuse, of fetal experimentation. This consensus cuts sharply across doctrinal lines. (It proves compatible, for instance, both with support of the thesis that a fetus is a "person," and with rejection of that thesis.) While analyzing the main lines of difference between the various positions advanced in the course of the debate, accordingly, the present paper will concentrate on exploring the nature, basis and implications of this moderate position, and on carrying further the questions it raises into some additional areas that seem to me have been neglected in the discussion to date.

The additional areas of discussion taken up here arise out of the social context of the current controversies surrounding the subject of fetal experimentation. Although the nature of this context is implicitly acknowledged in several of the papers before the Commission--e.g., in LeRoy Walters' discussion of the dangers of brutalization--it is worth bringing the delicate issues it raises into the open here. Three groups of basic social issues are involved: all of these reflect a certain loss of confidence, on the part of the public at large, in the absolute commitment of medical practitioners and their contemporary allies, the biomedical research scientists, to the immediate personal welfare of each individual patient.

- (1) There is a widespread sense that the medical advice given by attendant physicians to their patients may in some cases be directed less towards the individual's personal benefit than towards some research project to which the physician is directly or indirectly committed, and in which the patient becomes unwittingly involved.
- (2) There is a suspicion that biomedical research scientists are insufficiently hesitant to perform experiments on human subjects or human tissues, and that their experiments are, in some cases, motivated as much out of a concern for personal achievement or the satisfaction of intellectual curiosity as from the desire to improve therapeutic techniques.
- (3) There is a fear that the burden of human experimentation in general, and more particularly fetal experimentation, is liable to fall unduly on those groups in the population that are in present circumstances least likely to benefit from any therapeutic advances that result.

The point of making these fears and concerns explicit here is not to endorse them, or to suggest that they are necessarily well-founded. merely to put it on record that they exist; that their existence and currency are relevant to the political decisions which led to the Commission's establishment, and influenced its terms of reference; and--most important--that they give rise to legitimate interests, which have a moral claim to protection in the Commission's recommendations. I shall be discussing the topic in more detail later. At this point, let me just add two brief side comments. First, it was inevitable that the shift in medical attention characteristic of the 1950s and 1960s, away from general practice and individual health care and towards the newly renamed "biomedical sciences," should eventually have occasioned some critical social and political questions about the physician's contemporary role and responsibilities; and it is no surprise, given the particular delicacy of the problems intrinsically involved, that these questions should have arisen with particular force in connection with fetal experimentation. Second, we must take care not to assume--erroneously--that this loss of confidence is confined to the ignorant, the prejudiced and the ill-motivated. Anybody who was present in person at the recent public discussion on human experimentation organized by the National Academy of Sciences, or who received detailed firsthand reports on it, will know otherwise.

The discussion that follows deals, in succession, with:

- (1) The basic question, whether fetal experimentation is morally admissible at all.
- (2) The issues raised by the moderate position, which would permit a limited program of nontherapeutic fetal experimentation, subject to carefully-designed controls--specifically, with the practical balance to be struck between risks and benefits, in deciding what fetal research should be permitted, and with the consent procedures called for in order to protect all those having legitimate rights and interests.

(3) An appendix, with the underlying questions, having to do (a) with the dispute about "personhood" and related concepts--life, human potential, sentience, quickening, and also "viability," in at least two senses of a highly ambiguous term--and (b) with the need to improve our understanding of the psychology of pregnancy--notably of a woman's changing psychological investment in her issue during the course of pregnancy, as affecting the "rights" she can properly claim over the handling and disposal of that issue, when it is lost through abortion or miscarriage at different stages in the pregnancy.

### II. THE MORAL ADMISSIBILITY OR INADMISSIBILITY OF NONTHERAPEUTIC FETAL EXPERIMENTATION

Before there is any question of discussing the practical limits or controls needed in any policy for a restricted program of fetal experimentation, a prior ethical question must be faced:

Is the use of experimental procedures on a human fetus, or on fetal tissues and organs, morally admissible at all in situations where those procedures are "nontherapeutic," i.e., not immediately directed to the individual medical benefit of the affected fetus or mother?

Papers before the Commission give answers to this prior question that range all the way from advocating a total ban on all nontherapeutic fetal experimentation, by way of various carefully-qualified middle-of-the-road positions, to the view that any such research is morally admissible, provided only that it aims at improved medical knowledge. If the former view is accepted the question of practical restrictions and controls does not (of course) even arise. If the latter view is accepted there would be no need for any special controls over fetal research, beyond those that apply to all human experimentation. So, our first task here will be to look at the arguments advanced in support of these two extreme positions.

#### The Case Against Special Controls

The case for the most liberal position towards fetal experimentation is argued by Joseph Fletcher. As I understand the case, Fletcher accepts an overriding moral claim in favor of the pursuit of biomedical knowledge, and sees nothing in the obstetric situations characteristic of fetal research to limit the scope of that claim, beyond a requirement of maternal consent in the case of fetuses (whether in utero or ex utero) which are still alive:

"In fetal research, whether with live or lifeless fetuses, what we are after is the ability to save life and lift its quality. Our goal is useful medical knowledge . . . . We must be delivered from the kind of ethics which let 'principles' . . . nullify useful know-how in medicine's effort to save and improve life."

The chief thrust of Fletcher's argument is directed against those who would project such a liberal policy, and would place restrictions on biomedical research

in the name of general or universal "principles." Their argument he construes as part of a political campaign to impose on medical scientists, against their own feelings and better judgments, limitations that are required only by adherents to a "doctrinaire and rule-oriented" system of ethics. In reply, Fletcher pleads for a "pragmatic and value-oriented" approach to the issues in dispute, based not on a "categorically rigid" insistence on hard-and-fast rules or principles, but on a readiness to consider problems "situationally" or case by case: an approach that will be "nondogmatic, flexible, particularized, value-oriented." He is evidently confident that, in all cases involving a "tension between lifesaving research... and prohibitions on fetal research," such a situational approach will certainly lead us to come down on the side of medical science.

With all respect, I cannot agree that this conclusion follows, even on Joseph Fletcher's own grounds. The distinction between "rule-oriented dogmatism" and "value-oriented pragmatism" is not (as I understand it) a distinction that cuts between rival systems of ethics. Rather, it cuts between alternative ways in which any ethical system can be applied to actual cases. Whatever considerations are appealed to as morally relevant to a case in question, that is, they can be advanced in either a dogmatic or a pragmatic spirit; but the task of demonstrating that specific considerations are or are not morally relevant to a particular case is a separate matter. As a result, the case for restricting fetal research is not met by merely pointing out that advocates of restriction frequently present their case in a dogmatic or absolutist spirit. On the contrary, it must be shown that the specific considerations appealed to by the restrictionists lack the moral relevance to the fetal research situation that they claim. Otherwise, the case for restriction can equally well be advanced in a "situational" manner, and in a "pragmatic and value-oriented" spirit. (As I read it, this is just what Sissela Bok does in her paper.)

In my view, Joseph Fletcher has not succeeded in demonstrating the impossibility of arguing a case for limitations and controls in precisely such "situational" terms. The problem for his approach is that "situations" are not self-describing. With the most flexible and value-oriented spirit in the world, we might still acknowledge (e.g.) that a woman has a genuine moral stake in the disposal of her own aborted issue, even after it is unquestionably dead, and so regard Fletcher's guidelines for fetal research as disregarding her legitimate interest. Different characterizations of the fetal research situation can thus lead to different moral conclusions about the admissibility of such research, and Fletcher's argument comes to an end (it seems to me) before the operative issues have been addressed, whether in a pragmatic spirit or any other.

To put the point in Fletcher's own vocabulary, the Commission's terms of reference call for guidance, precisely, over the questions (1) which of the alternative particularized descriptions of the fetal research situation properly balances up all the values and benefits that constitute authentically relevant moral features of that situation; and (2) on what conditions the categorical present claims, benefits and interests of individuals may properly be set aside in favor of hypothetical future benefits to "science" or "mankind" in general.

#### The Case For a Total Ban

At the opposite end of the spectrum is the conclusion that fetal experimentation is justifiable only where its aim is immediately therapeutic, and so should be "limited to procedures which have as their aim the enhancement of the life-systems of the fetuses"--i.e., the particular fetuses which are being experimented on, not fetuses in general. On this view, all nontherapeutic fetal experimentation should be banned as morally inadmissible. All of the arguments advanced in support of such a ban concede that the fetus is -- at any rate, after a certain point in pregnancy--a creature of a kind that is entitled to primary rights, but otherwise they take two rather different forms. There are those that deny that any third parties can have the right to give proxy consent for such experimentation on behalf of the fetus, and there are those that deny the medical scientist's right to pry into "the secrets of the Almighty," or to "compromise the dignity" of present human life for the hypothetical benefit of future human beings. Both Paul Ramsey and Seymour Siegel advance arguments of the former type. Siegel alone puts major weight on the latter; though LeRoy Walters also argues, more generally, that there are genuine risks of brutalization involved in permitting exceptions to the rule that hypothetical and general future benefits may not be sought at the price of categorical and particular present suffering.

Let me cite Seymour Siegel's draft paper first:

"The burden of proof is on those who wish to subordinate the life of an individual presently before us for the interests of what might come later. In other words experimental procedures for 'the good of medicine' are not automatically legitimated because someone in the future might benefit. Our concern primarily should be for the person or persons before us now. The rest of what is called in the Talmudic literature 'the secrets of the Almighty.' These reflections do not, of course, preclude the scientist's search. It is intended merely to circumscribe it."

When considered in the light of its historical origin, the Talmudic appeal to the sanctity of Divine "secrets," together with Siegel's call for caution in the face of "the indeterminacy of the future," must indeed be understood--on the face of the words--as precluding not just nontherapeutic fetal experimentation, but biomedical research of all kinds. In this respect, Siegel's preliminary argument, like Fletcher's, does not seem to me sufficiently fine-grained, as it stands. Is fetal research in his view on all fours with all nontherapeutic biomedical research? Or are there special limitations on fetal, as contrasted with later medical experimentation? If the latter is the case, then what are the morally relevant considerations distinguishing the two classes of research? Do these have predominantly to do with the problem of consent, as in Ramsey's argument? Or are there other considerations? It would be helpful if he could spell out more exactly what the crucial moral factors are, on his account.

What guidance does Siegel give us, in fact, about the conditions on which fetal research might have been morally admissible, despite the general burden of proof against incautious research projects? As I read his view, adult

patients of sound mind do have the right to consent to nontherapeutic experimentation on their own bodies since the act of giving informed consent protects their human dignity from compromise. If that is the crucial factor, then Siegel's case for a ban on nontherapeutic fetal research becomes the same as Ramsey's. Both men agree that the problem of obtaining adequate fetal consent to such experimentation is insuperable, and so conclude that fetal experimentation is admissible only if its aims are directly therapeutic for the particular fetus under examination.

Taking all the available literature together, then, it is clear that the central arguments for or against a total ban on nontherapeutic fetal research are those which turn on the admissibility of proxy consent, by the mother, the father or other third parties. These arguments will, of course, be fully convincing either way only to those who accept the notion that the fetus itself can have morally relevant "claims" or "interests" in its own right. (The denial of primary rights to the "previable" fetus entails that no question of proxy consent can arise; so that, on this alternative position, only the mother's own primary consent can come up for question.) Over this central issue, the cases presented by Paul Ramsey for, and Father Richard McCormick against a total ban carry particular weight.

Rather than attempting to condense their close arguments still further, at the price of distorting them, let me simply recall the precise point at which the two men part company. Granted that it is out of the question for the fetus to give direct consent to being made the object of nontherapeutic experimentation, Ramsey holds that there is no ground on which any third party can legitimately give consent on its behalf, vicariously or as a proxy either:

"I myself tend to believe that any use of the fetal subject, children, the unconscious, the dying or the condemned would be an abuse . . . Seizing the 'golden opportunity' afforded by abortion to exact--and falsely to 'presume'--acts of charity from the fetus as a human research subject . . . can only mean a terrible distortion of medical ethics to date, and of the Jewish-Christian Tradition which was the foundation of its regard for the sanctity of human life."

Ramsey's position has the merit of cutting along a clean line. Like Siegel, he would have fetal experimentation permitted only where it was directly "related to promoting the life of the [particular] fetus." Richard McCormick, by contrast, seems prepared to allow third parties (specifically, the parents) a right to "vicarious" or "proxy" consent on behalf of the fetus, as on behalf of a child, on certain strict conditions. How, then, does his argument rebut Ramsey's unqualified case against nontherapeutic fetal research? It does so (as I understand) by claiming that vicarious consent can be justified, provided that it is directed at the question:

"What may it be presumed that the fetus ought reasonably to consent to, if it were capable of understanding what is at issue, and taking this decision for itself?"

Since the fetus is a human creature, and so potentially a rational being, there are certain things to which it ought to be prepared to consent, in virtue of that potential rationality; and suitably qualified third parties (e.g., the mother) are accordingly qualified to give its vicarious consent in these terms.

Father McCormick supports this conclusion by appeal to considerations from "the natural-law tradition" to the effect:

" . . . that there are certain identifiable values that we ought to support, attempt to realize, and never directly suppress because they are definitive of our flourishing and well-being."

As he notes, this is not a position that depends on any specifically theological dogma:

"Knowledge of these values and of the prescriptions and proscriptions associated with them is, in principle, available to human reason. That is, they require for their discovery no Divine revelation."

Nonetheless (I would comment) this is not a position that has won universal agreement. Many people would argue in reply, for instance, that we do not have a self-evident obligation to act rationally all the time, and that we cannot reasonably impose such an obligation by proxy on a fetus. Carrying this line of criticism further, Paul Ramsey himself replies that McCormick's argument actually imposes on the fetus an obligation to perform an implied act of charity that, in an adult, would represent at best an act of supererogation; and this he finds morally repugnant.

Speaking for myself, although I cannot wholly support Paul Ramsey's position, I have great respect both for his conclusion, and for the force of the arguments by which he supports it. If members of the Commission hold that the fetus is entitled to primary rights, and if they decide to recommend that the present ban on nontherapeutic fetal research be continued, they can accordingly do so with the confidence that such a recommendation can be given a firm ethical foundation.

#### The Case For a Restricted Program of Fetal Research

There remains an intermediate position, which would permit a resumption of nontherapeutic fetal research, on a restricted basis and subject to carefully designed institutional controls. Among those who have prepared papers for the Commission, both supporters and opponents of the view that the fetus can have primary rights (e.g., Sissela Bok and Richard McCormick) have argued for variants of this intermediate position; and, despite the force of Paul Ramsey's advocacy, I would personally be inclined to join with this intermediate group.

For those who deny the fetus primary rights, the case for placing restrictions and controls on nontherapeutic fetal experimentation must rest, of course, on the interests of other parties—on the direct interests of the parents in the disposal of an aborted fetus, on the agony of mind to be expected in parents

from the fear of casual experimentation on their issue, and on the general risk of brutalization in society, if medical research workers are permitted to handle human beings and human tissues in a callous or arrogant manner. Sissela Bok's paper accordingly gives prominence to the question at just what point in fetal development these dangers become realistic, so that the use of the whole previable fetus for nontherapeutic research should cease to be permissible. For those who would accord the fetus primary rights, on the other hand, it remains necessary to reply further to Paul Ramsey's arguments. In my opinion, this can be effectively done, if we make one small modification to the statement of Father McCormick's case. Instead of following him in requiring that proxy consent be directed towards the question:

"What may be presumed that the fetus ought reasonably to consent to, if it were capable of understanding what is at issue, and taking this decision for itself?"

We can alternatively pose the operative question in the form:

What may it be presumed that the fetus could not reasonably object to, if it were capable . . . ?

This emendation does little to alter the practical substance of McCormick's proposal, but it does avoid the objection of imputing "obligations" to the fetus, in virtue of its "rational nature," and it does underline the force of McCormick's requirement (in the case of nontherapeutic experimentation on children) that such research should be attended by:

"No discernible risk, no notable pain, no notable inconvenience, and . . . promise of considerable benefit."

For to declare that nontherapeutic fetal experimentation, in order to be morally permissible, must be of a kind that the fetus itself, if cognizant, "could not reasonably object to, " suggests, on the one hand, that such experimentation should be limited to (e.g.) the kinds of innocuous research investigations that might be conducted incidentally on infants in a postnatal clinic, and would, at the other extreme, certainly rule out any idea of (e.g.) stockpiling aborted human fetuses in tissue or organ "banks." Accordingly, I conclude: Whatever view the members of the Commission take about the fetus' entitlement to primary rights, if they decide to recommend that the present ban on nontherapeutic fetal experimentation be relaxed in favor of a restricted program of fetal research, subject to careful controls and safeguards, they can again do so with the confidence that such a recommendation can be given a firm ethical foundation. Either way, however, the task of striking a balance between the risks of such research, and the benefits to be foreseen from it, remains a highly delicate one; and the key task of the Commission must be to devise appropriate safeguards and controls.

For those who support a moderate position of this kind, therefore, the substantive problem immediately becomes one of striking such a balance between the risks to which the fetus, the mother, and society would be exposed as a result of nontherapeutic fetal experimentation, and the benefits that would presumably

accrue to medical science, and to humanity at large. As we shall see, this intermediate program involves a substantial measure of agreement, about practical policies and controls, between both supporters and opponents of the "primary rights" or "personhood" view. So, without at this point attacking the underlying issues about "personhood," "viability" and the rest, I shall immediately turn to the question of risks and benefits, reserving the "personhood" problem for later discussion.

#### III. IMPLICATIONS OF THE MODERATE CONSENSUS

Any policy for the licensing of nontherapeutic fetal experimentation on a limited basis must be based (1) on an analysis of the actual risks and potential benefits involved, and (2) on the establishment of appropriate institutional safeguards to monitor and control the application of that policy. The papers on the ethics of fetal experimentation that are before the Commission provide significant consensus about what we might call the "moral boundary conditions" within which any such policy should be framed, in case a restricted program of nontherapeutic fetal research is resumed. I shall draw attention to the key elements in that consensus here, while adding some additional comments of my own.

#### The Risks of Fetal Experimentation

In assessing the risks attendant on fetal experimentation, we should consider separately three groups that are apparently at risk: the fetuses themselves, the mothers, and society at large.

As to the fetuses, from certain points of view, it might appear paradoxical that we should consider their interest at all. Father McCormick's paper on "Proxy Consent in the Experimental Situation," for instance, links the exercise of parental consent partly (though not entirely) to the child's prospect of survival. Nothing should be done, by way of an experimental procedure, which might reasonably be supposed to risk having deleterious effects on the child's future welfare. To that extent (it would seem) the consequential arguments can hardly be extended, as they stand, to a fetus which is due to be aborted. Yet the papers submitted to the Commission are generally agreed that such a fetus may nevertheless be exposed to two significant types of risk. First, there is the risk of discomfort or pain during the experimental procedure, in the event that its development is sufficiently advanced; and second, there is the risk of deformed birth, in case the mother withdraws her consent to the abortion after the experimental procedure has actually taken place.

Several papers mention the risk of pain and discomfort to the fetus in passing, but none of them (in my view) pays close enough attention to the topic. It seems somehow to be assumed that the questions of sentience is directly linked to that of "viability," and discussion of fetal pain tends to switch, almost immediately, to that of the fetus' capacity for autonomy or survival. So let me underline here the fact that these two issues are, on the face of it, quite independent. The question whether or not a fetus is capable of surviving

ex utero after being aborted has no obvious or direct bearing on the question whether or not it is capable of experiencing pain and discomfort if subjected to experimental procedures either in utero, before abortion, or ex utero, after abortion, but before death. If it were clear that some fetuses are, in this respect, "sentient" by (say) the sixth month of pregnancy, then there would be an equally clear moral objection to employing painful nontherapeutic experimental procedures on them at that stage, for in these circumstances the use of such procedures would be quite straightforwardly cruel. At just what stage in fetal development sentience may reasonably be supposed present, however, is a question about which I have found regrettably little solid evidence. At what stage, for instance, is the central nervous system sufficiently consolidated for sentience to be a possibility? (Evidently much of the motor activity of the fetus is purely reflex in character; but this is presumably less completely the case the nearer the fetus approaches to full term.) I suggest that these are questions about which the Commission should obtain testimony from impartial experts. For there are certainly some kinds of fetal experimentation whose permissibility would have to be made dependent, not on the "viability" of the fetus, but on its sentience.

The other class of risks capable of affecting fetuses that are due to be aborted springs from the possibility that the mother may change her mind about the abortion after the experimental procedure is complete, and the fetuses may subsequently be born deformed. As to these risks, two different proposals have been made. Sissela Bok suggests an insurance scheme, to compensate mothers who are left with the task of bringing up a deformed child, in consequence of such a fetal experiment. Paul Ramsey refers (disapprovingly) to the view that experiments should be undertaken only as a part of a single operative procedure, designed to terminate with the abortion. This would normally obviate the possibility of the mother's revoking her consent after the experiments have taken place. Both suggestions (in my view) deserve serious consideration by the Commission, though I am personally inclined to think the latter proposal is the more satisfactory one. In a case of this kind, after all, the financial burden is the least of the agonies a mother will be exposed to, and it would be preferable to design our operative procedures in a way that spared her the other, more painful, psychological and personal burdens. At the same time, Sissela Bok's proposal does have the merit of drawing attention to the important question (also referred to by Joseph Fletcher) of who is to take responsibility for the future welfare of those fetuses, or premature infants, whose lives are preserved by medical intervention after a late abortion against the wishes of the mother, especially when they are too frail or deformed to be suitable subjects for adoption. (In a suitable social political environment, a case might be made for regarding such children as "wards of the State," and for assigning them to publicly-financed foster homes, rather than obliging their mother to raise them, even with the help of insurance benefits.)

The risks of nontherapeutic fetal experimentation to the mother are not in dispute, and it is generally agreed by the members of the present panel that the proposal to perform such experiments should never be made the reason for delaying a planned abortion. On the one hand, the experimental procedures themselves may be a direct source of pain and discomfort; on the other hand, they may have longer-term medical consequences; and, either way, any delay in the

abortion is generally undesirable. There is much to be said, therefore, in favor of Paul Ramsey's argument that—if there are to be fetal experiments at all—they should, at most, be combined with the actual abortion procedures.

In addition to the possible physiological effects of fetal research on the mother, however, these risks have another side also, to which the papers before the Commission give (in my view) too little attention. The psychological aspects of pregnancy and abortion are a subject about which too little is known; but we do at least know enough to recognize that it would be morally wrong to disregard a woman's psychological investment in a pregnancy, and in the issue of that pregnancy. Whatever the circumstances in which a pregnancy is terminated, the mother should have confidence that the issue will be handled and disposed of, both before and after death, in a respectful and humane way; and the lack of such an assurance would be a legitimate source of grief and guilt. This represents, therefore, an additional element to be taken into account in judging the potential damage to be guarded against in fetal research. (I shall return to this topic at the end of this paper.)

More attention is paid in the papers to the risks affecting society at large, in case nontherapeutic fetal research is permitted, either at all, or without being subject to adequate controls. In this respect, the fear is one of "brutalization," i.e., a fear that any relaxation in the general feelings of reverence and concern towards the tissues and remains of the dead and dying could give the color of extenuation to other forms of callousness, violence and human indifference. It may be questioned whether, as applied to fetal research in particular, these fears are in fact realistic; every apprentice physician is exposed to the disecting room as a part of his normal training and, by the time he is medically qualified, his attitudes to human tissues and cadavers will have been effectively formed and tested. So, it is not clear that a properly-regulated program of fetal research can, in this respect, have any novel effect on the attitudes of physicians and medical researchers.

On the other hand, the existance and currency of these fears is itself a matter of importance and moral relevance, as well as being a significant element in the social context of the Commission's proceedings. The sources of this fear are not hard to trace. Over the last 25 years, the public's image of the physician has changed. Traditionally, the general practitioner of medicine was one of those people--along with the local priest or minister, and perhaps the family lawyer -- to whom the individual could turn for advice, in absolute confidence that any advice he received was concerned wholly with his personal welfare. The family doctor had no perceptible conflict of interests: his whole position was dependent on his capacity to act as a fully-committed personal advisor. Even after a patient was admitted to the hospital, he could still look to his family doctor to represent his interests unhesitatingly, and to rescue him, if need arose, from the hospital's bureaucratic toils. The new alliance between attendant physicians and medical research scientists has brought that implicit confidence into question. Many people today, as a result, actively feel for the first time something less than certain whether the medical advice they get is purely directed at their own individual benefit, or whether it is in part motivated by other concerns, e.g., by the research interests either of the attendant physician himself or of his colleagues. (This uncertainty has

been only aggravated by the growing shift in the locus of medical practice, from the bedside or private consulting room, to the hospital clinic.) So the current public image of the physician is in course of being transformed from the friendly and totally trustworthy one of the "family G.P.," to the intimidating and psychologically opaque one of the "white-coated" scientist.

No doubt this transformation in public attitudes has gone too far, and I am not in any way claiming that it is justified. Still, this change itself has made it possible for public feelings about abortions and fetal experimentation to be inflamed beyond a realistic level, to the point at which the collaboration between attendant physicians and biomedical scientists can sometimes be made to appear an "unholy alliance" for promoting scientific knowledge, in disregard of patients' interests. Given the resulting disquiet, the actual fear of brutalization becomes as relevant a feature of the ethical situation as the objective risks of brutalization; and any procedures for supervising human experimentation in general, and particularly fetal experimentation, must take it into account. For this reason among others, the general public has a legitimate moral interest in being adequately represented on the ethical and human experimentation committees of all hospitals in which nontherapeutic fetal experimentation is to be undertaken. Such lay representation will, of course, not just protect the public against the possibility of overenthusiasm or malpractice on the part of research workers, but also protect the research scientists themselves against uninformed or ill-motivated outside criticism.

There is one other source of public disquiet, which takes us beyond the scope of the Commission's immediate recommendations, though not beyond its topics of discussion: let me simply mention this in passing. Some years ago, it was demonstrated at Cambridge University that a newly fertilized human zygote could be kept alive in vitro for a period of days, during multiple cell-divisions, and this demonstration drew widespread public attention. The resulting outcry about "test-tube" babies played on fears and hostilities towards science that have roots in the Middle Ages, if not in antiquity. This episode is relevant to the present controversy about fetal research. If we carry the discussion of "viability" to its final conclusion, the question indeed arises whether it will not eventually be possible to engage in "zygote culturing," and even to bring an embryo to full term outside the mother's womb. If this were ever practicable, there might well be situations in which it was both medically desirable and ethically permissible to bring a child into life by in vitro gestation. another application of the same techniques would make it possible also to massproduce human tissues and embryos for use in scientific experimentation, and it is my sense of the matter that people of most persuasions find the prospect of such "zygote farming" morally repugnant. Whatever their position on the "personhood" issues, they would see such a practice as inevitably encouraging unacceptably casual and arrogant attitudes towards the control of human life.

#### The Benefits of Fetal Experimentation

Surely, none of those who have prepared papers for the Commission on the ethics of fetal research has any doubt about the positive value of improving medical knowledge. The implication apparent in some speeches at the National

Academy of Sciences discussion, that those who raised moral objections to unsupervised, nontherapeutic fetal experimentation are "against science," is accordingly The question is not whether our medical knowledge about pregbeside the point. nancy and fetal development ought to be improved by all legitimate means at our disposal, but rather how far this is to be done without lapsing into morally unacceptable procedures. So it should go without saying, here, both that fetal experimentation holds out the promise of genuine and substantial benefits to "medical science" -- both directly, to pediatrics and obstetrics, but also to general physiology, pathology and medical therapeutics -- and that those benefits can reasonably be expected to carry over to "humanity" in general, as the new techniques of biomedical science become incorporated into actual medical practice. If ethical questions must, nevertheless, be raised about these benefits, those questions have to do with the sad yet realistic need to satisfy ourselves that these beneficial results are being achieved in fact, and not sidetracked into directions to which legitimate objection might be taken. So it is desirable to introduce, at this point, a word of caution about the intended beneficiaries of fetal research: viz., "medical science" in the first place, and "humanity" in the second.

As to medical science: the same public disquiet that shows itself in fears that fetal experimentation might encourage "brutalization" extends also to hesitations about the personal motives underlying the medical scientist's own research. The suspicion is that, in some cases, the legitimate theoretical goals of medical science may eventually become partly confused in the minds of those human agents who are personally engaged in fetal experimentation, with the satisfaction of their intellectual curiosity or the personal achievement; so that a proprietary attitude towards their own research may lead them to expose fetuses or fetal organs to experimental manipulation praeter necessitatem. (This anxiety, too, was reportedly evident in the National Academy of Sciences discussion.) Once again, these hesitations may well be groundless in all but a tiny minority of cases. But, in so delicate a field as that of fetal research--as in all matters involving the possibility of delicate conflicts of interests -- it is not enough that justice should in fact be done: it must also be seen to be done, in a visible and verifiable manner. Once again, therefore, I am led to conclude that the general public has a legitimate moral interest in being represented by lay assessors on hospital ethical and human experimentation committees. assessors could satisfy themselves, on the public's behalf, that nontherapeutic fetal experiments were being approved only in cases where it had been demonstrated that their results held genuine promise of contributing substantially to the legitimate therapeutic goals of science, and that no alternative ways were available of arriving at the same discoveries. Once again, also, the fact that experimental protocols had been scrutinized by lay assessors would protect biomedical scientists from uninformed outside criticism, as effectively as it would reassure the public about the actual conduct of fetal experiments.

The claim that better medical science is a good for humanity in general also needs qualifying in one significant respect. We may, of course, discount loose and uncritical claims of this kind when they are made by the public spokesman for medical research in their advocacy of increased funding for biomedical science; but it must be noticed that even Richard McCormick's account of "what any rational being ought to want, and so ought to be ready to promote,"

takes it for granted that the improvement of medical science is of benefit to all of humanity. In an ideal world, this might well be the case. But we should take a moment to inquire who will in fact be the primary beneficiaries of the therapeutic advances made possible by fetal research.

Many of the panel members, notably LeRoy Walters and Paul Ramsey, have pointed out the limitations to the claim that categorical suffering on the part of the child or a fetus now is justified by hypothetical benefits to children or fetuses in later generations. It is one thing for a father (say) to make a sacrifice now, of which his own children can expect to be the beneficiaries after his death; but it is quite another matter for an individual to suffer pain now, in order to do hypothetical good to some unidentifiable class of possible beneficiaries at some indeterminate future time. What is morally questionable about such appeals to charity is not just the hypothetical character of the resultant goods: we must also satisfy ourselves that there is no evident systematic differentiation between the class of those who are to suffer now and the class of those who are to benefit later.

E.H. Carr, the historian, has wisely commented on the political demand that the Russian people of the 1920s should "sacrifice their present comfort for the benefit of future generations," pointing out that all such demands are in practice intrinsically inequitable: the class that pays is always quite other than the class that benefits. If we are to justify nontherapeutic fetal research in similar terms, we must therefore be sure that we are not building any comparable inequity into our practice. At once, certain reservations suggest themselves. Suppose, for the sake of argument, that the class of pregnant women predominantly involved in fetal experimentation were taken from the poorest members of the population, while the class of those who predominantly benefitted from the resulting therapeutic advances were taken from the richest. The effect of this would be to introduce a substantial and morally relevant inequity into the actual practice of fetal research.

This supposition, whose racial implications do not need to be made explicit, is not an entirely idle one. There is an evident suspicion--as discussed again below, in connection with the problem of consent--that "free" hospital abortions, especially second-trimester abortions, may in some cases be "traded" to indigent parents, in return for consent to participate in fetal experimentation. As before, the significant issue here is not whether this suspicion is well-founded, but the fact that it arises at all. For the reasons already indicated, therefore, I would myself hope that the proposed National Commission for the Protection of Human Subjects will accept responsibility for monitoring the social incidence of human experimentation in general, and particularly of fetal experimentation. A well-documented assurance that the burden of human experimentation was not being borne unduly by any one section of the population would both provide the public with legitimate peace of mind, and shield fetal research workers from any charge that their research was conducted in an inequitable or discriminatory manner.

#### Balancing Risks Against Benefits

Father McCormick has indicated that, in his view, the possibility of justifying nontherapeutic fetal experimentation depends on an appropriate balance of risks against benefits. He offers us two complementary criteria: (1) the risks involved must be low, and the prospective benefits high enough to outweigh them, and (2) there must be no alternative route to the same results. It states in quite general terms, these propositions might win support from a majority of panel members. (Even Paul Ramsey suggests at one point that his opposition to McCormick's position might weaken, if the criterion of "low risk" were applied stringently enough.) Furthermore, these criteria have the merit of covering quite generally all types of experimental procedure applicable to the complete fetus itself, whether in utero or ex utero before death. But there are some significant differences between the panelists when it comes to spelling out the rules governing their actual application in practical situations.

Thus, Sissela Bok recommends that the United States follow the British guidelines in laying down a specific term and/or weight as the index of "fetal viability," and in ruling that "the use of the whole previable fetus [in nontherapeutic experimentation] is permissible, provided that only fetuses weighing less than 300 grams are used." This recommendation appears to me too undiscriminating to meet McCormick's requirements. Let me set aside for the moment the question, whether "viability" -- which Bok admits to be a "fluid and shifting concept" -- is the relevant issue at this point. Quite aside from that, I would question whether it is morally appropriate to draw only a hard-and-fast line, dividing one class of fetuses which may not be used in nontherapeutic experiments at all from another class of fetuses which may (it seems) be used in any scientifically justifiable experiment. Surely, the question whether the use of a fetus in nontherapeutic experiments is permissible at all, is not the only question: we must ask also what kinds of experiments are permissible for a fetus with given characteristics. So, while there may be reasons for laying down some definite upper size-limit, above which aborted fetuses may not be made the subject of any experimentation, it will probably be necessary also to balance off "risks" and "benefits" further, by establishing guidelines governing what types of procedures may or may not be undertaken on fetuses at different stages of development below that upper limit. In the event that a restricted program on nontherapeutic fetal research is resumed, indeed, one may foresee that the actual practice of human experimentation committees in research hospitals will come to be based, not on any single, hard-and-fast "index of permissibility," but rather on a more discriminating body of "case law" and "precedents"; and it should be one responsibility of the National Commission for the Protection of Human Subjects to keep a watchful eye on the development of that "case law."

The problems that arise over the use of "the whole previable fetus" are less severe, however, than those that arise over the use of organs, tissues, etc., from aborted fetuses, in place of (say) animal organs, tissues, etc., in cancer research and similar fields of inquiry. Over this question we face serious practical difficulties, as well as difficulties of medical ethics, in determining a "cut-off" point beyond which such use is impermissible and in setting appropriate criteria of "fetal death." If the experimental use of fetuses below 300 grams in weight is approved, it is presumably also supposed

that a fetus must be clearly dead before organs or tissues may be removed for study. Yet what tests of "fetal death" are envisaged? As Bok points out, the proposed DHEW guidelines 46.307 (d) and (e) are substantially more restrictive in this respect than the British Peel Commission recommendations; in particular, paragraph (e) which lays down that "experimental procedures which would terminate the heartbeat or respiration of the abortus will not be employed." Bok herself would remove this latter restriction, and would permit researchers to perform experiments which might accelerate the death of the fetus. On this issue I personally favor 46.307 (e), and consider the further problems raised by suspending it too serious to set aside. It could be argued, no doubt, that a "previable" (and so presumably nonsentient) 250-gram abortus, which has no hope of surviving more than a short time anyway, has "nothing to lose" by meeting an accelerated death at the hands of an experimenter, so that dismemberment should not be regarded as involving an "injury" to such a fetus. while I share Bok's sense that the risk of causing pain to the fetus is the most weighty consideration, I still find it hard to go along with her acceptance of the Peel Commission's less restrictive recommendations. Even in the case of a 250-gram fetus, I myself still feel the force of the analogy with McCormick's argument that we cannot properly consent by proxy to a child's (e.g.) giving up a kidney for a transplant operation.

Rather, the questions at issue here appear to me strictly parallel to those which arise in obtaining suitable hearts, or other complete organs, for transplantation operations. On the one hand, the success of such operations depends on the availability of organs that are still (so to say) "fresh"; on the other hand, in the case of heart transplants particularly, this has on occasion meant removing the organ from a (euphemistically called) "donor" at a time when his actual death was still problematic. The question at just what point it should be permissible to remove organs from a dying patient, for transplantation to another patient, has been much argued over the last 10 years. (I would particularly refer to the 1968 Beecher report in which the loss of brain function in an irreversible coma is suggested as marking a significant point of transition on the passage from life to death.) Like Ramsey, Walters and Siegel, I believe that "the criteria for ascertaining death in the fetus should be consistent with the criteria applied to other organisms," and more specifically with the criteria relevant to human organ transplantation operations.

The difficulty of deciding under what circumstances the removal of fetal organs or tissues for study would be permissible is particularly acute, for a reason that may at first sight appear merely technical. The abortion procedures commonly used in the early months of pregnancy—at a stage when the fetus is clearly presentient and "previable"—are of kinds that gravely damage or destroy the fetus and its organs. It is only in cases of hysterotomy, or comparable procedures, that an entire live fetus is recovered from an abortion; and, by the stage in pregnancy at which these more drastic procedures are justifiable, we are approaching the point at which legitimate questions can be raised about "viability" and sentience. Evidently, if it were a simple matter to obtain experimental material from the detritus of a simple six—week miscarriage or an early D and C—in which case it would probably be inappropriate for the mother to claim any serious "psychological investment" in her issue—the difficulty would not arise with the same force. As matters stand, however, the point in

fetal development at which we have unambiguously crossed the line dividing the detritus of a D and C, on the one hand, from a sentient being on the other, is inconveniently close to that at which destructive procedures of abortion have to give way to nondestructive procedures, such as hysterotomy. (I shall argue later that this may not be a mere coincidence, but that it is relevant to the task of clearing up the ambiguities surrounding the concepts of "viability" and "personhood.") At any rate, it is only in the case of hysterotomies and the like that the question of experimental dismemberment becomes an active one, and the fetuses available for this purpose seem, all of them, to be within significant range of sentience and "viability."

#### The Problem of Consent

The other practical topic discussed at length by the panel is that of consent, and consent procedures. What parties can claim authentic legal or moral interests in the issue of an abortion, whether spontaneous or induced? And what sorts of consent procedures should be required, in order to respect those interests and give the various parties proper opportunities to exercise any corresponding "rights" in the disposal and handling of that issue? I will summarize the outcome of these discussions under three heads: Fetal Consent, Maternal Consent, and The Interests of Third Parties.

#### Fetal Consent

Evidently, the question of fetal consent is a purely theoretical one; but it is one over which (as we have already seen) a good deal turns, particularly, in respect to the mother's own standing in the matter. Granted that there is no question of obtaining consent to nontherapeutic experimentation from a fetus directly, as one can from an informed adult, two questions arise. Is it (1) necessary and (2) possible to obtain a satisfactory equivalent in the form of vicarious or proxy consent? Three main answers are represented in the papers before the Commission. In the first place, we can declare fetal consent to nontherapeutic experimentation both indispensible and unobtainable (as Paul Ramsey does); and so condemn all such experimentation as unethical. second place, we can declare fetal consent unnecessary, on the grounds that the fetus itself has no legal or moral standing and therefore no formal "interests" in the case (as Sissela Bok does); and we can then give the mother primary rights of consent directly, rather than vicarious or proxy rights, that are now unnecessary. Or, in the third place, we can accept fetal consent as necessary, but infer or presume it (as Richard McCormick does) on the basis of proxy decisions taken vicariously by the parents, regarded as having the interests of the fetus at heart. Given the borderline nature of the present case, all three positions seem to me to run into some difficulties on a theoretical level. For practical purposes, however, the differences between them become significant only when we turn to consider what other parties have authentic claims and how they should be exercised.

#### Maternal Consent

As to the mother's rights of consent or veto, we have one clear starting point. In the case of a full-term infant, there can be no doubt of the mother's right to approve or veto the use on her infant of any experimental procedure, particularly a nontherapeutic one. We may therefore take as our starting point the question under what circumstances, if any, a mother could forfeit that right to have a say in the treatment or disposal of her issue.

In the Senate sub-committee testimony and elsewhere, there has been eloquent advocacy of the view that a mother forfeits this right simply by choosing to have an abortion, so that she should not have any right of veto over the use of the resulting fetus for experimental purposes. By electing an abortion (it is argued) the woman "puts her own welfare before that of the fetus," and so destroys the presumption on which proxy consent depends: viz., that she "has the interests of the fetus at heart."

This view finds no serious support from the panel, but its weaknesses are worth spelling out here since they embody some influential confusions. Four different counter arguments can be offered against it, all of which tend to strengthen the presumption in favor of a maternal veto on nontherapeutic fetal experiments.

- 1. The argument for forfeiture rests on a false assumption. Very rarely can the decision to terminate a pregnancy be represented as being merely the mother's choice "to put her own welfare before that of the fetus." It is commonly an agonizing decision, in the course of which many considerations are weighed, including the fetus' own interests. (The argument, "it would not be right for me to bring this child into the world in my present circumstances," is not necessarily a self-deceiving one.) Whatever one may think about the mother's motives in one or another particular case, accordingly, the argument offered gives no grounds for an automatic forfeiture of rights by the very decision in favor of abortion.
- 2. All question of motives apart, the mother retains the normal psychological stake in her issue, which demands respect whether the pregnancy is terminated naturally or by surgical intervention. This psychological investment is, of course, not a mere matter of conventional sentiment. It is associated with physiological, particularly hormonal, changes which are disrupted at abortion with consequences that should not be lightly disregarded or dismissed as morally irrelevant. (LeRoy Walters cites an interesting side argument at this point: viz., that the right of parental consent for medical or surgical procedures on children is derived from the parents' continuing personal and financial stake in the child's future--the parents will have to go on taking responsibility for the child after the treatment, whatever its outcome, so they should have the chance of vetoing it -- in which case the right of consent would again lapse on abortion which spares the parents any need to take subsequent responsibility for the fetus. But here too we can reply that the parents' psychological stake in the child goes far beyond that created by future caretaking responsibilities, so forfeiture again does not follow.)

- 3. The analogy advanced by supporters of the forfeiture argument, viz., that a mother who chooses an abortion is like a parent who abandons a child, does not serve the required legal purpose. Although abandonment of the child no doubt calls in question a parent's fitness to retain custody of that child, few jurisdictions would treat it as entailing automatic, still less irreversible forfeiture of all parental rights. By abandoning a child one loses at most only some parental rights. Law and custom alike require us to take care to respect the wishes of parents or other next-of-kin, especially in respect of the disposal of the dead, whatever may have been the state of personal relations between the deceased and his survivors.
- 4. Most significantly in the context of the present discussion--even if a mother could forfeit or renounce her rights and responsibilities towards her offspring in any way, those rights and responsibilities would in no case fall automatically to the nearest medical research scientist, or even to the attendant physician. Rather, the offspring would merely become a ward of the State, which would have the responsibility of acting in loco parentis. So, the onus of obtaining consent to nontherapeutic experimentation would not be removed: its locus would merely shift from the mother to the competent authority of the State.

Accordingly, there appears to be no basis for the suggestion that hospitals should be free to assume full rights and responsibilities over the issue of abortions, in disregard of the mother's wishes. This conclusion is not affected by the Peel Commission's argument that it would cause "unnecessary suffering" to obtain consent for experimentation from the mother, under the circumstances of an abortion. (That is a comparatively straightforward matter of consent procedures, and I shall return to the question below.) While maternal consent may not by itself be sufficient to authorize the use of a fetus for experimental purposes, therefore, it should normally be a necessary requirement; while a maternal veto should in all cases by treated as final.

#### The Interests of Third Parties

Can any other parties, besides the mother, plausibly claim any interest in the disposal of an aborted fetus? In different ways, claims of five other parties need to be considered.

1. Where the abortion takes place within a marriage, the father can claim certain moral and even legal rights in respect of all his offspring--including aborted ones--and some of these moral rights, at least, might well be extended also to the presumed father, even where conception has taken place out of wed-lock. (In both cases, too, some degree of psychological investment can reasonably be argued.) On the other hand, in many out-of-wedlock pregnancies the father may be unidentifiable, unavailable or indifferent, so that his interest in the offspring may reasonably be regarded as having lapsed. As a general guideline to the subject of paternal consent, therefore, one could suggest the twofold rule: (a) where a father is either present or in effective touch with

the mother, he should also have the right of veto over nontherapeutic experimentation on his offspring, and (b) where the father is neither present nor in effective touch with the mother, no special effort need be made to obtain his consent.

2. We may consider the attendant physician at the delivery and also the research scientist who proposes to perform an experiment on the fetus. In both respects, the relevant moral issues seem to be well taken care of by the Peel Commission's recommendation, 4(iii):

"The responsibility for deciding that the fetus is in a category which may be used for this type of research rests with the medical attendants at its birth and never with the intending research worker."

In particular, the medical research scientist should not normally play any direct part in the decision either to abort or to approve the issue of an abortion as suitable for any particular class of research.

- 3. A specific public interest is involved, notably, in insuring that the "separation of powers" between the attendant physicians and the research scientist is respected and observed. Here again, we must not ignore the element of distrust or disquiet that has grown up recently—the suspicion that hospital physicians and research scientists are to some extent "in collusion"— even if we consider it without foundation. The more groundless this distrust may be, indeed, the easier it will be to accept a simple procedural provision that can set it at rest. For this purpose I would recommend that the proposed lay assessors on the human experimentation committees of research hospitals (referred to earlier) should have the further responsibility of satisfying themselves that decisions about abortion, and about making an aborted fetus available for experimentation, are in fact being taken in accordance with these general rules.
- 4. In addition to this general public interest, there is a specific State (or Federal) government interest in the disposal of aborted fetuses. The issues that arise in this connection involve somewhat technical problems of law, rather than ethical problems. But, evidently, the existing responsibilities of the Registrar of Births and Deaths, and of the Coroner, whether in respect of births, deaths, and/or stillbirths, together with the rules about the timing and legal implications of registration, must extend in certain respects, and on certain conditions, to aborted fetuses. In a situation where ambiguities in the law have already led to criminal prosecutions, indeed, the legal rules in question are in urgent need of clarification. This is particularly urgent if, as Sissela Bok proposes, the Commission follows the Peel recommendations, in permitting fetal experiments in which the death of a "previable" fetus is accelerated by the experimental procedure itself. Over this delicate point, a clearer set of rules and sympathetic cooperation between a research hospital and the local coroner's office could do as much to protect the legal standing of fetal experimentors as it does to insure that the State (or Federal) government's rules are being respected.

#### Consent Procedures

In general, the point at which the Peel Commission recommended code of practice appears, at this distance, to be vaguest and least satisfactory is over the procedures for obtaining and documenting parental consent to fetal experimentation. Three points need to be made:

- 1. I referred earlier to the Peel Commission argument that, in cases where "the separation of the fetus from the mother leads to the termination of its life," to seek parental consent for the use of a fetus in experimentation "could be an unnecessary source of distress to parents." This argument would carry weight (in my view) only if the consent were deferred until after the abortion. There is no evident reason, on the other hand, why consent for the experimental use of tissues or organs from the fetus should not be given or denied before the abortion, at the same time, and on the same document, as consent to the operation itself. (The Peel Commission in fact goes on to make a very similar proposal.) Apparently, the consent or denial would have a different legal standing in different situations: e.g., it might have binding legal force only in case the fetus were delivered alive. But one might hope that hospitals would not be too ready to disregard parental wishes, even where these were not legally binding.
- 2. There is an evident risk involved, nonetheless, in the use of such a combined form. The Peel Commission's requirement 3(iv), viz., that there is not monetary exchange for fetuses or fetal material must be understood as covering not merely open monetary exchanges, but also "barter deals"; and there is a need to guard against the possibility that indigent parents might come to regard consent to the experimental use of tissues as an implicit "price" for obtaining a free hospital abortion. It is both ethically and socially important that any such "payment in kind" be clearly brought under the scope of any recommendation against "monetary payment" for the use of fetuses or fetal material.
- Something much more specific needs to be laid down about the form of consent proposed and about the manner and circumstances in which maternal or parental consent is to be obtained. Consent or denial of consent must be directly documented on a form which, if need arose, would be available to a competent Court for review. Furthermore, it should wherever possible be given not just in the presence of the attendant, physician alone, but to the satisfaction of a third party representing the public interest. (A hospital social worker, acting on behalf of the lay representative or representatives on the human experimentation committee of the hospital, would be a suitable person.) One needs only a limited exposure to the problem of consent to understand that "informed consent" is an ideal rather than an easily attained result. In so delicate a situation as that of a mother consenting to the use of her aborted fetus for experimentation, however, it is certainly desirable that every reasonable step be taken to insure that her consent is as clearly and fully informed as is practicable: not least, because care taken at this stage may serve to alleviate, later on, the psychological shock and grief which are probably an inevitable consequence of the abortion and everything associated with it.

#### IV. APPENDIX

Two general subjects of a more theoretical kind need to be commented on in conclusion. These are (1) the dispute about "personhood," "viability" and related concepts; and (2) the psychological aspects of pregnancy and abortion and their moral relevance to the rights of the mother over her issue.

#### Personhood, Viability and Quickening

The public debate about abortion and fetal research has given great prominence to the question, "Is the fetus a person?"; while the papers before the Commission concentrate rather on the question, "In what circumstances is a fetus viable?" Both questions are evidently intended, in part, to give more precision to a widespread sense that the changes taking place in the course of pregnancy, both in the development of the fetus itself and in the mother/fetus relationship, justifies us in taking a very different attitude--both legally and morally--towards abortion and experimentation at different stages in the process. (In respect to the first couple of months, there may be much force in the argument that a newly implanted embryo or early fetus is analogous to, say, tonsils, or a benign tumor; whereas, in respect of the final trimester of pregnancy, this would certainly not be an acceptable analogy; yet, by what criteria are we to draw the line between these two phases in pregnancy?) Neither of these two ways of posing the question is, however, capable in my view of clearing up the existing difficulties. What is needed, if this issue is to be clarified, is a more careful analytical scrutiny of the distinctions and interrelations between no less than six different concepts, which are frequently run together at present under one or another of the two words, "personhood" or viability"; and such an account can be given in a fully acceptable form only a posteriori, i.e., in the light of detailed expert testimony about the actual changes involved in the successive months of pregnancy.

This is not the place to provide the fully detailed analysis required for this purpose. But it will be worth drawing some first distinctions here, and indicating how easily cross-purposes and confusions can arise if these distinctions are not clearly respected. At one extreme, then, we can recognize (1) the strictly legal use of the term, "person." To be a "person," in this sense, is to have a standing before the Courts, and so to be able to bring an action, either directly and in person, or through a legally qualified representative. In this sense, of course, a corporation can be a "person," and so is a newborn child--on whose behalf a parent can sue ex parte, as legal guardian--but it has now been definitely ruled that a fetus is not a "person" in this sense. For judicial purposes, that is to say, "personhood" begins only with a live birth, though nothing need follow from that fact about "personhood" as defined in other senses or for other purposes. In particular, the judicial withholding of legal rights from the fetus does not by itself settle the question under what conditions a fetus is entitled to primary moral rights. Rather than rest the discussion throughout on the ambiguities of the term "person," therefore, I have set out the issues raised in this paper explicitly in terms of the question, whether a fetus has moral rights and interests of its own, as contrasted with those of its mother.

At the other extreme, there is (2) the very broad term, "living." Nobody in this debate would presumably trouble to deny that a newly implanted zygote, or early embryo, is "living" or "alive," at least in the sense of being composed of living cellular tissue; and this fact alone differentiates it from (say) nailparings. Even so, there is a distinction to be drawn between recognizing an early fetus as "living" and acknowledging it to be a creature "capable of independent life"; for instance, not every piece of actively developing living tissue (e.g., a carcinoma) is independently "viable" in any sense of that term. somewhere between the two extremes there is (3) the Aristotelian notion of the embryo as "potentially human," or "potentially rational." It may well be helpful to apply this notion, as Richard McCormick does, as a basis of discussing the moral status of the fetus, in terms of the natural-law tradition; but it appears to me an insecure basis for attributing primary rights (or "personhood," in an extra-judicial sense of that term) to the embryo or zygote from the moment of the implantation, or even fusion.

For the purposes of the Commission's deliberations three further concepts are more directly relevant, but also more problematic. On the one hand (4) the term "viable" is defined (though not, by implication, used by the members of the present panel) in a sense that is strictly relative to the life-support techniques and equipment available at a given time and place. A fetus will, in this sense, be "viable," if and only if it is capable of being brought to the point of independent life, with the help of techniques and equipment available where and when it is delivered. Viability, in this sense, might be a legitimate term to apply in discussing the responsibilities of the medical attendants engaged in an abortion, but it is a most unsatisfactory criterion for laying down any kind of moral or ethical doctrines about the intrinsic state of the fetus itself, at one stage or another in pregnancy. For are we to put ourselves in a position where our ethical attitudes towards a fetus, and its possible moral status, are entirely dependent on the state of medical technology? (To go to the extreme: if methods of "zygote culturing" were brought to the point at which in vitro gestation became a real possibility, we might then be forced to say that every fresh zygote had, in principle, been thereby rendered "viable"! And we surely would not wish to say, on that account alone, that there was no longer any such class of things as "previable fetuses"?)

My own sense of the matter is that the term "viable" is, at this point, standing in for one or another of two further concepts, neither of which is made fully explicit in the papers before the Commission. One of these can be referred to by (5) the term "sentient," which I have used more than once in this survey. Sissela Bok's references to the risk of causing pain to the fetus clearly presuppose some such idea of "fetal sentience," though she does not discuss explicitly the question of how close the capacity to feel pain is connected, in her view, with "viability." On that subject, as I suggested in the body of this paper, expert testimony is needed; and I am not myself convinced that sufficient knowledge of the development and consolidation of the fetal brain and central nervous system, during the second trimester of pregnancy, is yet available to settle the matter adequately.

On the other hand, there is no doubt that certain very striking changes do occur in the fetus, in reasonably close proximity, during that second trimester.

In addition to--and in consequence of--the consolidation of the nervous system, the fetus becomes autonomously active, so that the mother herself begins to regard it less as a part of herself than as an independent creature, if not an actual "opponent"; while, at the same time, it begins to move towards that dominant position in the pregnancy, as a result of which it eventually appears to be capable even of initiating the onset of labor. Much of this is hinted at in (6) the use of the traditional terms, "quick" and "quickening." The history of these terms is examined in the Supreme Court's judgment in Roe v. Wade, 410US113 (1973). Quickening was commonly associated with the period around the sixteenth through the eighteenth weeks of pregnancy; and, before the New York statute of 1828, the abortion of a prequickened fetus was not regarded as a criminal offense. As Chief Justice Blackmun pointed out in the majority opinion (pp. 132-133):

"The absence of a common-law crime for pre-quickening abortion appears to have developed from a confluence of earlier philosophical, theological and civil and common-law concepts of when life begins."

It is around the same period that the fetus also acquires that recognizably "human" form which was canonically required for baptism of a premature child or fetus.

It is not my intention to revive the issues covered in Roe v. Wade. point is simply to suggest that the Peel Commission and others have tended to use the modern-looking but intrinsically confused term, "viable," not in the sense discussed above under (4), but rather as an approximate synonym for (6), i.e., the traditional term, "quick." No doubt, some real precision could be added to our understanding of that term if we were to bring all our new medical and scientific knowledge about pregnancy and fetal development to bear on its definition; and, once again, this raises issues about which expert testimony is required. But, as so often, a great deal of morally and legally relevant human experience was built into the common law over the centuries of its evolution; and this experience is directly relevant to our own problems here. As I myself read many of the contributions to the present discussion -- e.g., the Peel Commission's recommendation that "the use of the whole previable fetus is permissible . . . ", and Sissela Bok's commentary on this recommendation--it would clarify their sense if we were to drop entirely the terms "viable" and "previable," with their misleading allusions to the current state of medical technology, and substitute either the traditional terms, "quick" and "prequickened," or some up-to-date refinement of them which would refer directly to the new kinds of fetal activity, autonomy and sentience that apparently develop somewhere around the seventeenth week of pregnancy.

#### The Psychology of Pregnancy

In working through the material before the Commission, I was surprised to find how little was said about the psychological aspects of pregnancy and the relation to the parents'--especially the mother's--stake in the issue of that pregnancy. Fetal development and the mother/fetus relationship were discussed in predominantly physiological terms, as though the mother's sense of proprietorship, responsibility, attachment, and even identification towards the fetus were, from the ethical point of view, epiphenomenal, and so lacked serious ethical relevance.

With this in mind, I set on foot a literature search, assuming that a body of understanding did indeed exist on this subject, which had somehow been overlooked and disregarded by commentators on the fetal experimentation issue. The results were meager. Very little of any substance seems to have been written on the subject. The only general account that came to my attention was an interesting and perceptive, but somewhat impressionistic, survey from a psychoanalytic standpoint by Helene Deutsch; while the psychiatric research literature in the medical libraries of Chicago brought disappointingly little fresh material to light.

Deutsch at any rate has the merit of emphasizing that a woman has a strong and deep psychological investment in her fetus, even in the case of an unwanted pregnancy; and that this committment is in no way canceled out by the decision to terminate the pregnancy by abortion. (On the contrary, the abortion will normally be an occasion for feelings of grief, guilt, and even self-mutilation.) None of this should surely be any real surprise, even from the physiological standpoint, given the radical changes in a woman's hormonal regime associated with pregnancy. Quite aside from all discussions of the significance of regression and identification during pregnancy, therefore, we might have expected the psychological and psychiatric implications of hormonal and other physiological changes to have attracted more attention than they appear to have done.

On the level of common sense and common knowledge (or "old midwives' tales") there is, of course, a certain body of inherited folk-wisdom about these things. In maternity homes for unmarried mothers, for instance, great care is often taken to prevent the woman from seeing or hearing her baby during delivery, if it is already earmarked for adoption. It is explained that any sensory contact with the infant makes for a much more painful separation, and aggravates the psychological impact of the loss. (This belief ties in well with more recent suggestions, from the direction of ethology, that auditory and/or visual cues may "imprint" a mother on her infant at birth so that she thereafter, say, recognizes its cry at once, even against a background of other babies cries.) Yet, once again, these folk-traditions seem never to have been systematically brought together or related to any coherent account of maternal psychology during and after pregnancy.

Arguably, these psychological issues form a significant part of the back-ground against which any questions about the ethics of abortion and fetal research need to be considered. The whole notion of "risk to the mother" should be treated as embracing risk of psychological damage; discussions about the parents' state or investment in the health or survival of an infant, or in the handling and disposal of a stillbirth or an aborted fetus, should similiarly be taken as including their psychological stake or investment; and the nature of a mother's ethical "rights," "responsibilities" and "entitlements," in respect of her issue, cannot be considered inadequate depth without paying proper attention to the psychological factors involved.

To repeat, this is not just a matter of the casual or conventional sentiments that a woman may express about her condition and offspring. It is a matter that has to do with one of the two linked aspects of a sequence of changes that are at once physiological and psychological: one aspect of a process which could not achieve its natural function unless the anatomical, physiological.

and biochemical developments taking place in the mother and her offspring were associated with well-matched psychological changes. Considering the striking manner in which a woman is physiologically prepared to take up her maternal role--with all its deep emotional and behavioral concomitants--after delivery, it is clear that significant psychological changes are already in train much earlier in pregnancy. The Commission would be doing a real service, accordingly, if it gave its encouragement to a new program for research in this area. At the very least, it would be a great help to have some sort of a first map of the different psychological, physiological and hormonal changes characteristic of the different stages in pregnancy, and their consequences for the mother's sense of commitment and identification towards her offspring.

(This paper was prepared in collaboration with Donna Boyan and Marilyn Di Salvo, to whom my thanks are due).



# DETERMINING DEATH AND VIABILITY IN FETUSES AND ABORTUSES

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beneficial to his patient or be equally beneficial to his patient but lead to improved treatment for other sufferers of similar discretes. On the other hand, many experiments are not intended to benefit the subject (nontherapeutic experimentation), but are conducted solely in the pursuit of new knowledge. The subject might be a patient under a doctor's care for an unrelated ailment . . or he might be a healthy volunteer. Different standards should govern therapeutic and nontherapeutic experimentation. The therapeutic purpose itself serves to justify a doctor's exposing a terminal leukemia patient to substantial risk in an effort to prevent or postpone imminent death, while a stronger independent justification should be required for allowing a researcher to expose a healthy volunteer to a similar risk simply to gain new knowledge." <sup>57</sup>

From the above definitions it should be apparent that in considering fetal rights in research, it is important to distinguish between different types of research, different stages of gestation, different states of being (in utero or ex utero), and the different, countervailing interests present in each situation.

In launching this consideration, I return first to *Roe* v. *Wade*. The wisdom of the Court's opinion has been seriously criticized as an unjustifiable extension of the constitutionally protected right to privacy and as court-made legislation. Professor John Ely of Harvard Law School says: "... What is frightening about *Roe* is that this superprotected right [a woman's freedom to choose an abortion] is not inferable from the language of the Constitution, the framers' thinking respecting the specific problem in issue, any general rules derivable from the provisions they included, or the nation's governmental structure . . . "<sup>59</sup> He argues that the opinion is an unwarranted exercise of substantive due process, a twin to *Lochner* v. *New York* <sup>60</sup> but possible more pernicious because it employs a higher standard of judicial review. <sup>61</sup>

The results in *Roe*, but not its legal reasoning, has been defended by another Harvard Law School professor, Lawrence Tribe. 62 Professor Tribe argues that the question "when life begins" has become an essentially religious issue, 63 not resolvable by resort to the slippery slope of biological development, 64 and that if governmental decisions are based on the pervasive interference of religious groups in legislative considerations, the establishment clause must be invoked unless there are compelling, wholly secular reasons for the legislation.65 As in *Roe*, in his view the government may intervene only after viability, because only at that point in time is the fetus in the same status as an infant for the secular purpose of protecting it from infanticide.66

I agree with Professor Ely that a state may claim a compelling interest in protecting human life, and this interest could override the mother's constitutional right to privacy at any point in time during pregnancy. Moreover, the interest in protecting potential life should be as important a secular purpose as the state's interest in enacting Sunday closing laws. The Supreme Court has upheld such laws <sup>67</sup> for the less than compelling secular purpose of promoting the recreational pursuits of the general population despite the obvious sectarian influence that fostered these laws.

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# Determining Death and Viability in Fetuses and Abortuses

The purpose of this paper is to explore and clarify the notions of fetal "life," "death," and "viability," and to suggest general principles, standards, and operational criteria for determining (a) when a fetus (or abortus) is no longer alive, and (b) when a fetus (or abortus) is "viable." This is, therefore, an inquiry both biological and philosophical—not ethical. This paper will not address the thorny ethical issues of what may and should be done, or not done, with living or dead or viable fetuses, in utero or out, especially in biomedical experimentation. These ethical questions cannot be settled merely by determining whether the fetus is alive or dead, or whether the fetus is viable or nonviable.

Yet these determinations (of alive or dead, and of viable or nonviable), while not decisive for resolving the ethical questions, are always central to properly formulating them, sometimes decisively so. For example, if contrary to fact, it could be demonstrated that a nonviable fetus is in no way different from a dead one, then the ethical questions concerning experimentation on nonviable fetuses would be identical to those concerning experimentation on dead fetuses. Or if it could be shown, again contrary to fact, that the fetus becomes a distinct, living organism only after birth or only after reaching the stage of viability, then the ethical issues of experimenting with a previable fetus would be no different from those raised by experimenting on tissues or organs. Finally, even after the different classes are distinguished and defined, the proper "class" identification of each individual fetus will be necessary in order correctly to formulate the concrete ethical issues regarding its disposition and use. In short, discussion of the ethical issues, about classes or individuals, can only begin after the nature of the experimental subject is clarified, for only when the subject is known can one consider how it may morally be treated.

When the passions hold the reins of debate, as they often have in the debates about abortion or about research on living fetuses, words tend to lose their common meaning, as partisans on each side attempt by loose or loaded usage to hide certain facts or to distort others. But all responsible parties to the debate on the ethical issues of fetal research should insist on calling things by their right names and on precisely and carefully distinguishing in speech those things that are distinguished in fact—and also, on speaking equally frankly and precisely about those matters which are indistinguishable or even confused in fact.

#### I. PRELIMINARY CLARIFICATIONS

#### A. Preliminary Definitions

- 1. Fetus: The human embryo from conception to delivery, including what is normally called the embryonic state. (Here I follow the definition given by the Peel Commission Report.<sup>1</sup>)
- 2. Abortus: A whole fetus of whatever gestational age short of term, outside the uterus, whether expelled spontaneously or by a medical or surgical procedure. This definition excludes the placenta, fetal material macerated at the time of expulsion, and isolated fetal tissues or organs excised from a living or dead fetus or abortus. (I follow here, but only in part, the definition given in both the 1973 and 1974 policy guidelines proposed by the U.S. Department of Health, Education, and Welfare.<sup>2</sup> Two significant departures from that definition should be noted: (1) By my provisional definition, an abortus is not necessarily pre- or nonviable; (2) By my provisional definition, an abortus is not necessarily living. I have made these changes partly because I do not wish to beg the question that it is my task to explore, namely, that of determining which abortuses are and are not living, dead, and viable, partly because the necessary and sufficient distinguishing features of an abortus are that it is (a) a fetus, (b) whole or intact, and (c) outside the womb.)
- 3. "Fetus or Abortus": When this phrase is used below, fetus will mean "fetus in utero," and abortus (as always) "fetus outside," indicating by this juxtaposition that the statement in which this phrase occurs applies equally to both.

## B. How These Questions About the State of the Fetus are Related--and Unrelated--to Abortion

Whether the fetus or abortus is alive or not, or is viable or not--and also the issues raised regarding its possible use in experimentation--are questions at least to some extent independent of where it is situated and how it is obtained. A fetus may be dead in utero or alive on the table. A living fetus can be obtained by spontaneous or by induced abortion, by induced abortion that is legal or illegal (or moral or immoral), by induced abortion in which the mother desires the death of the fetus or by induced abortion (say, for the sake of health) in which the mother desires that the fetus could be kept alive.

The decision to have an abortion does not turn a living fetus into a dead fetus. The decision to abort, like the spontaneously occurring "threat" of a miscarriage, makes the fetus at most a "dying" or "condemned" fetus but not yet a dead one. The to-be-aborted fetus is still alive. It is abortion, not the decision, which is the lethal act.

Yet not all abortions are lethal. Not every abortion necessarily turns a living fetus into a dead abortus. For example, where abortion is produced by expulsion or by hysterotomy, some fetuses "survive" the procedure as living fetuses (sometimes even viable ones). The very term "abortion" is ambiguous: does abortion mean only womb-emptying, or does abortion also mean, necessarily, feticide? In most cases, womb-emptying and feticide go together, but obviously not in all. It is precisely in those cases where abortion means or effects only womb-emptying that the procedure issues in living abortuses that can be used for research. For this reason, "abortion" in this paper will mean only "womb-emptying."

#### C. The Fetus is an Organism

We are concerned here not with the life and death of fetal cells or tissues or organs, nor with the aliveness or so-called "viability" of the same cells, tissues, or organs if removed from the fetus for transplantation or laboratory culture. Such parts of an organism may in some cases survive when they are no longer parts of the organism-but their aliveness or death poses no moral question, and demands of us no clear definition of cellular life, death, etc. The questions of alive or dead and of viable or not viable that we must address concern only the fetus as a whole organism.

While it may be difficult to say, fully or precisely, what the wholeness of the fetus is, there can be little doubt that it is such a whole, i.e., that the fetus is an organism—even in utero. Though it is composed of tissue, it is not merely tissue, unlike muscle or skin or collagen. The assertion that the fetus is a part of the mother is simply false. It is a different organism, no matter how dependent it is on the mother. The fetus, in its varying stages, is a self-developing, self-changing whole, which assimilates and transforms food supplied by the mother, and grows and differentiates itself according to the plan encoded in its own DNA. It becomes, on its own and from within, progressively more organized—i.e., possessed of organs that contribute to the maintenance and functioning of the other organs and of the whole. It has a unique genotype, different from that of the mother and those "parts" of her which are truly herself and "her own." The fetus is a distinct organism right from its start.

To say that the fetus is an organism is not to say that it is a person. This is a question still to be argued about, but not in this paper. But whether or not the fetus is a person or a fully human, human being, it is, in any case, a living organism—until it dies or is killed. Further, the fetus (or abortus) is human at least in the sense that it is of human origin and is (or was) in the process of becoming a human being if nothing interferes. These facts—and I think they are indisputable—are presupposed when one asks for criteria for determining fetal "life," "death," and "viability," and when one raises questions about the status of a fetus as a fit subject for scientific investigation.<sup>3</sup>

#### D. Alive and Dead, Viable and Nonviable--How are These Terms Related?

The two pairs of contraries—alive and dead, viable and nonviable—are not synonymous. That this is so will finally be clear only after each of the terms has been explored and defined, but there is need for their provisional distinction. As seen in Figure 1, "viable" and "nonviable" refer to states of a living fetus or abortus on either side of some watershed (however wide, vague, or illdefined it may be, and however we determine its boundaries) that occurs during the otherwise continuous process of growth and development from zygote to infant (to adult), the viable fetus having matured "over" the watershed, the non- or previable fetus being less mature, i.e., not-(yet)-viable.

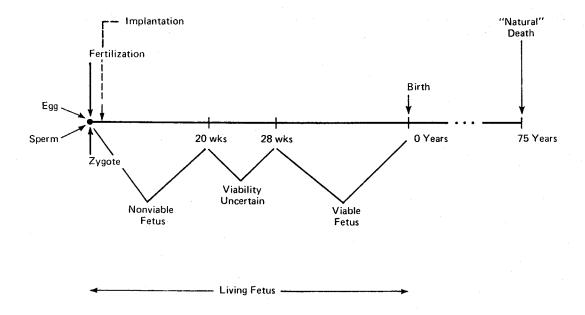


Figure 1. Nonviable and Viable Stages of Fetal Life

Whereas "viable" and "nonviable" refer to and name particular stages of development, "alive" and "dead" refer to two mutually exclusive conditions of the organism which are independent of stage of development. The fetus is alive from fertilization, but, therefore, it can die at any stage. Like any living organism, like any living child or living adult, a living fetus at whatever stage--nonviable or viable or full term--can die or be killed, i.e., can become a dead fetus (or dead newborn). The same must be true of the fetus outside the mother's body, i.e., of the abortus or premature infant (I repeat: How the fetus got outside the mother is irrelevant for deciding whether or not it is in fact alive or viable once it is outside). The nonviable and the viable abortuses are alive until they are dead, 5 and the terms nonviable and viable should be used exclusively to refer to species of the genus "living fetus" or "living abortus."

We have, then, determined one crucial matter: To say that a fetus or abortus is pre- or nonviable is not the same as saying that the fetus or abortus is dead. A dead fetus or abortus is no longer either previable or viable—it is simply dead. The nonviable abortus will soon be a dead abortus, and a viable abortus may in fact not survive (it may be killed or it may succumb to respiratory distress, just like a newborn or a premature infant), but in order for these terms to be properly applied to the fetus or abortus, it must then still be alive.

With these preliminaries behind me, I turn to the two main tasks, determining whether a fetus or abortus is dead, and determining whether a fetus or abortus is viable. (This choice of focus--on "dead" and "viable"--has been adopted because it is reasonable to say that after fertilization, a fetus is alive until proven dead, and also to say that a fetus is nonviable until proven viable.) In discussing both matters, I consider first, some general principles, then specific standards and operational criteria, both for the abortus and for the fetus in utero.

#### II. DEATH OF THE FETUS AND ABORTUS

#### A. General Principles

To begin with, I repeat that we are concerned with determining whether the organism as a whole is dead or alive. This task is at once difficult and easy. Difficult because biology and medicine are not able to give an adequate explanation for, or account of, the "livingness" of living things, or for that mysterious occurrence in which a living organism becomes a dead body. What "livingness" is, and what is responsible for it—these are long and complicated questions which admit no simple answer. Yet in almost all cases, we are easily able to distinguish the living from the dead, even if we cannot say in words what essentially or at bottom lies at the basis of the distinction. The living and the dead are distinguished by what they do not do.

A living organism, unlike a dead one, does or can do one or more of the following: digest and assimilate food, metabolize, grow, respire, circulate its blood, eliminate waste, move itself, receive and respond to outside stimuli, experience its aliveness. A dead organism can do none of these things, and has irretrievably lost the ability to perform all these vital activities and functions. Because of these fairly obvious differences between the organism alive and the organism dead, we can look for functional standards and criteria to determine that an organism has died, without first struggling to discern what death itself, or aliveness itself, are.

The first and major principle, then, for determining fetal death and fetal aliveness is this: since the fetus is an organism, one should try to evaluate its aliveness or deadness as one would any other mammalian organism, human or not, namely, by taking as the standards the presence or absence of certain most

vital organismic functionings. To the extent to which they are applicable, the same operational criteria should be used for determining these functionings in the fetus or abortus as in the newborn or the adult.

#### B. Standards and Criteria for Determining That a Fetus or Abortus Has Died

There has been a movement in recent years to revise the criteria for the determination of death in adults, occasioned by the advent of life-sustaining technologies that render questionable in some cases the value of certain vital signs as genuine signs of life-e.g., heartbeat. There has been a tendency-very much in error, in my opinion-to call these new criteria, "criteria of brain-death," even though they necessitate that functions of organs other than the brain be examined (e.g., spontaneous respiration), and even though they are intended to permit diagnosis of death not of a brain but of a whole human being. Yet, with one notable exception, the new criteria are very much like the old criteria. And this exception, concerning the heartbeat and other criteria of circulatory function, is an exception only in cases in which certain lifesustaining technologies are in use. In ordinary cases, the new and old standards and criteria are identical.

What are the standards of organismic life? The organism as a whole is alive as a whole, in some degree at least, if any of the body-wide systems are functioning on a body-wide basis, to perform the functions of circulation, respiration, digestion, excretion, regulation, awareness, responsiveness, motion, These various activities depend decisively on (1) circulatory and (2) respiratory and (3) central nervous system function, each of which is in turn dependent, at least in part, on the other. For example, the ability to breathe spontaneously requires a mature and functioning respiratory center in the brain stem, and the functioning of the brain stem in turn requires adequate circulation of oxygenated blood. Thus, spontaneous circulatory and respiratory functioning and spontaneous central nervous system activity are the standards for judging the presence of "life," and any sign of such functioning must be regarded as a sign of life. Thus, a fetus or abortus will be considered dead if, based on ordinary procedures of medical practice, it has experienced an irreversible cessation of spontaneous circulatory and respiratory functions and an irreversible cessation of spontaneous central nervous system functions.

Though medical progress and changes in ordinary medical practice may alter, in part, the specific operational criteria for evaluating these standard functions, some criteria can be set down which are unlikely to change. These include (1) spontaneous muscular movement—that is, movement "initiated by" the fetus or abortus, (2) response to external stimuli, such as touch, changes in temperature, and stimuli which generally produce pain, (3) presence of reflexes, (4) spontaneous respiration—that is, respiration initiated by the fetus or abortus, and (5) spontaneous heart function—that is, spontaneous cardiac contraction and movement of the blood. The presence of any one of the aforementioned is a sign that the organism is alive.

The first three criteria are self-explanatory. The last two require some further comment. Respiration is an ambiguous term; it is used variously to refer

to (1) the expansion of the chest, (2) the effective ventilation of the lungs, (3) the effective exchange of gases between lung alveoli and the blood, or (4) the effective exchange of gases in the various tissues of the body (which may be obtained by perfusion with oxygenated blood, in the absence of lung function). By spontaneous respiration I here mean only (3) the effective exchange of gases between the lungs and the blood. Thus, while the fetus in utero does make, and the nonviable abortus may make, so-called "respiratory movements," neither has spontaneous respiration, and hence both lack this sign of life. Nevertheless, these very same spontaneous movements, and the "effort" to expand the chest even when the lungs are not yet inflatable, are fetus- or abortus-initiated movements, and are on that ground signs that the fetus or abortus is still alive, even if it will soon be dead. The effort to "breathe," to expand the chest, is a vital sign even though it is not respiration. It reveals the presence of a functioning nervous system acting "at a distance" on a functioning part of the musculo-skeletal system.

Spontaneous heart function, in the absence of external assistance to induce or maintain respiration, must be regarded as a sign of life. By heart function, I mean more than the palpable beat of the heart and certainly more than electrical activity of the heart. I mean a functioning, beating heart causing blood to flow through the peripheral blood vessels, producing pulses in the arteries. The unassisted circulation of blood in the fetus or abortus is a sign of organismic and not merely cellular life. In the absence of spontaneous respiration, say in the case of a nonviable abortus (e.g., 16 weeks), this circulatory activity will soon cease, and with it or shortly thereafter, all other signs of organismic life. Spontaneous heart function may, therefore, serve as the last and least sign of organismic life in the organized and aborted fetus.

In children and adults, the usefulness of pulse and heartbeat as signs of life is reduced only in those cases in which cardiorespiratory function is artificially and mechanically sustained--e.g., in a case of a comatose, unresponsive, and areflexive patient on a respirator whose heart beats "spontaneously" but only because of the presence of artificial, externally driven respiration. There has been much discussion of whether or not such a patient is indeed already dead or whether, instead, he is not yet dead but becomes very quickly dead once the respirator is turned off. This question does not admit of easy resolution. An identical question may come up in determining the status of circulation as a sign of life in those intact abortuses whose aliveness is sustained (i.e., whose dying is prolonged) by external support (e.g., with perfusion). But this complication will not arise initially in determining whether the intact abortus, as delivered, is alive or not. Spontaneous circulation is a sign of life in the newly delivered or expelled abortus, even in one that is incapable of respiring on its own, and even, therefore, in one that cannot sustain this circulatory functioning on its own for very long.

Should the guidelines for fetal research permit the use of artificial devices to support the life of such a fetus (i.e., one with spontaneous circulation but no spontaneous respiration), say by providing gaseous exchange through a heart-lung-type machine, the circulation of blood in the fetus, and its pulses and its heartbeat, will no longer remain reliable signs of life, just as they are not reliable signs of life in a dying adult who is on a respirator or on a

heart-lung machine. The assisting machinery would have to be disconnected and the abortus examined to see if spontaneous circulatory function were still present. If it were, the fetus would still be regarded as living.

To sum up: For the fetus outside the uterus, life is present if there are any signs--i.e., if there is even only one sign--of spontaneous circulatory, respiratory, or central nervous system (brain and spinal cord) function. The satisfaction of any one of the five criteria mentioned above is a sign that the abortus is not dead. Fetologists and pediatricians, now and in the future, may wish to add to and enlarge this list of criteria, so that even in the absence of all five of the criteria, there may be deemed to be present organismic life. But any one of the above five would be sufficient for determining aliveness, and their complete absence is necessary--even if not finally sufficient--to declare an abortus dead.

#### C. The Fetus In Utero

The foregoing standards, readily applicable to the abortus, apply equally to the fetus *in utero*, although they may be harder to evaluate. The fetus *in utero* is, of course, not accessible to direct physical examination. Also, as long as it remains *in utero*, it will never reveal whether it is capable of spontaneous respiration. Before quickening or before the time when fetal heart tones may be heard (audible using the Doppler principle by about 12 weeks), the diagnosis of fetal death must be made indirectly, by means of various laboratory tests, and it is often difficult. Regardless of the stage of pregnancy, the diagnosis of fetal death *in utero* usually requires more than one examination.

The difficulty of diagnosing fetal death in utero is not a problem pertinent only to fetal research; it concerns obstetricians (and patients) generally in ordinary prenatal obstetrical practice. And while the standards of "aliveness" and "deadness" to be tested for will remain the same, it is likely that new techniques for making these diagnoses in utero will be forthcoming in the near future. Thus, the Commission ought not to rigidly specify the tests needed to diagnose fetal death in utero, but should leave it up to the evolving procedures of ordinary obstetrical practice to provide the most reliable indicators.

Common sense does dictate one clear presumption concerning the fetus in utero: Once the diagnosis of pregnancy has been made, the fetus in utero is presumed to be alive until proven dead. The burden of proof rests on showing that fetal death has occurred. This applies equally to the fetus about-to-be-aborted: such a fetus is to be considered alive at least as long as it remains within or connected to the mother, unless clear proof of fetal death can be obtained. (After separation, the abortus can be examined for signs of life.) These presumptions of aliveness will be correct in almost all cases (except, perhaps, in cases of threatening spontaneous abortion), and have the added advantage that no living fetus will be mistaken for a dead one. 11

#### D. The Fetus During Induced and Spontaneous Abortion

During spontaneous abortions or induced abortions likely to produce an intact abortus by expulsion, the fetus-becoming-abortus should be presumed alive until examination of the expelled abortus reveals it to be dead.

If abortion is done by hysterotomy, the finite transition between the fetus inside and the fetus outside will be directly observable. Under these circumstances, the diagnosis of fetal aliveness should be easy, a pulsating umbilical cord being a clear sign of spontaneous fetal circulation. In such cases, I suggest that the fetus is to be considered alive until (a) it is killed in situ by the surgeon, 12 or (b) the cord is cut and the separated abortus is examined and found to lack all five of the above criteria of "aliveness."

#### E. The Fetus at Very Early Stages

The foregoing standards will make it possible to decide the status of most if not all fetuses and abortuses that may now be considered as possible subjects for research. Regarding research on the intrauterine fetus, all fetuses in utero are presumed alive until proven dead or killed during abortion. Research on the intact abortus usually contemplates an organized fetus, usually age 13 weeks or more—since first trimester abortions, done by dilatation and curettage or by suction, do not yield abortuses fit for whole—abortus research. Thus, the criteria for "life" and death" proposed in this paper are adequate to the main task, based as they are on those signs of organismic life which are present in an organized fetus—minimally, in a fetus with an intact circulatory system. These criteria would, however, be difficult to apply to an abortus "delivered" in the very early stages of fetal life, especially prior to the differentiation of the great organ systems. Clearly, a blastocyst or two-week-old embryo is alive, but not by any of the aforementioned criteria.

There is no point at present in going ahead to try to elaborate criteria for organismic aliveness and deadness for these early stages. However, it is worth noting that the criteria here given may need to be supplemented or altered in the future, especially when and if (1) new methods of early abortion (e.g., prostaglandin expulsion) appear which yield intact and obviously living embryos which by the above criteria will not be identified as alive, or (2) in vitro fertilization and laboratory growth of early human embryos is perfected, able to produce partially differentiated and growing organisms in laboratory culture.

### III. VIABILITY OF THE FETUS AND ABORTUS 13

#### A. Viable--An Ambiguous Term

Before considering standards and criteria for distinguishing the viable from the nonviable fetuses and abortuses, we need to clarify certain confusing

and misleading ambiguities in the term "viability." The term "viable" can refer to a present state and its capacities or can denote a prediction of the future. Someone might say that a healthy newborn baby, if abandoned by its parents, is not viable, and the same might be said of the child who falls unnoticed off the ocean liner and who cannot swim, or of the man who contracted bulbar polio in the days before the iron lung. In all these cases, the use of "not-viable" is meant as a prediction; one means to say that the now living being will not continue to live, i.e., is certain to die and soon. 15

These predictions about the future are of course related to the current state of the organism and its current environmental circumstances. The discovery of the abandoned baby by loving foster parents, the unexpected and prompt arrival of a rescue party, and the invention of the iron lung could keep the above three people alive, i.e., render them again viable, "likely to live."

These examples reveal something fundamental about this meaning of "viability." Viability, in this sense, is determined by the relation of the individual organism and its environment. Whereas the aliveness or deadness of the organism can be discerned by examining the organism alone, viability can be discerned only by considering both the organism and its environment. Changes in environment, and for our purposes, especially changes in technology, may render a nonviable organism viable, and vice versa. Both the man with polio and the 16-week-old abortus are unable to breathe on their own. The development of the iron lung made the first man viable; a comparable future technological development, say an artificial placenta able to sustain the fetus to 28 weeks, could enable today's nonviable fetus to become viable.

Yet there is a second meaning of "viability" that is not relational. There is a noticeable difference between the man needing an iron lung and the 16-week-old abortus. The former has lost the ability to function on his own as a self-sustaining whole, whereas the latter has never reached that state, and moreover, cannot at present be brought to that stage. There is a developmental immaturity in the 16-week old abortus which makes it intrinsically nonviable, and, it is also incapable of bringing itself or of being brought to the maturational stage of viability with presently available technology.

This more technical sense of "viable," referring to an achieved stage of maturity, is of prime importance for our present purpose. Though we must remember that future technologies may enable a nonviable abortus to be brought alive to this stage of viability entirely artificially—paralleling the way in which the fetus in utero normally attains viability on its own, with the "aid" of maternal nourishment and protection—this stage of viability can be defined, at least formally, in an unambiguous and nonrelative way, as the stage at which (and after which) the fetus (or abortus) is able to function as a self-sustaining whole outside of the mother's body (and outside of an artificial womb). In practice, it may be rather difficult to say which fetus has reached this stage and which has not, especially during the twilight period between 20-28 weeks—and I shall discuss this problem shortly—but what it is we are seeking when we seek signs of viability should now be clear: the intrinsic ability to function as a self-sustaining whole outside the womb. 16

#### B. The Nonviable Fetus and Abortus: Two Distinct Classes

If a fetus with this ability is a viable fetus, what is a nonviable fetus? Are nonviable and previable the same thing? The terms are often used interchangeably—and there is at present no good reason for not doing so—in refering to the abortus, although the term "nonviable" invites some to think "dead" rather than living-but-previable. But there is need for further clarification.

The Peel Commission Report defines a previable fetus as follows: "one which, although it may show some but not all signs of life, has not yet reached the stage at which it is able, and is incapable of being made able, to function as a self-sustaining whole independently of any connection with the mother." This definition mentions two inabilities: an inability to function independently, and an incapacity to be made able to function independently. These two deficiencies are, at least in principle, separable. There may be two classes of fetuses or abortuses below the stage of viability: those that are not-yet-viable but are able to become or to be made viable (e.g., by some to-be-developed artificial placenta), and those that are both not yet viable and not able to become or to be made viable (by anything).

I thus distinguish three classes, as follows:

- 1. <u>Viable</u> (fetus or abortus): Able to function as a self-sustaining whole outside the womb. A viable abortus is thus nothing other than a premature infant.
- 2. Previable: Not yet able, but able to become or to be made able, to function as a self-sustaining whole outside the womb; in other words, the potentially viable.
- 3. Not-at-all-viable: Not yet able, and not able to become or to be made able, to function as a self-sustaining whole outside the womb. This state and only this state carries the prediction of certain and imminent death.

If one considers only the extrauterine abortus, today's technology is such as to render the "previable" a null class. The abortus is either viable or not-at-all-viable (not withstanding the difficulties we may have in determining which it is, in some cases). But when we consider all fetuses—both inside and out-we see that we have, even now, all three classes before us. For, so long as the fetus is alive in the uterus, connected to the maternal circulation, it is capable of being brought to the stage of viability, no matter what its age; it is hence "previable" in the sense defined above. These distinctions are made clear in the following table.

Table 1. Condition of Fetus at Varying Ages as a Function of Place

Location

# Age of Fetus In Utero If Taken Out 12 Weeks Previable Not-at-all Viable 24 Weeks Previable [Uncertain] 30 Weeks Viable Viable

In utero, all living fetuses are at least previable, because they can "be brought to viability" if there is no abortion. Whether, for purposes of formulating the ethical questions of experimentation on fetuses, these previable fetuses are to be considered more like the viable or more like the not-at-all-viable is a matter to be considered. Still the previable intrauterine fetus becomes not-at-all-viable only upon removal—and not until removal, even when removal is planned. I hold no particular brief for my terms "not-at-all-viable" and "previable," though I do think they point to a factually significant, and probably morally significant, difference between two classes of not-yet-viable fetuses. Moreover, development of new life-sustaining technologies for extrauterine fetuses—e.g., some kind of artificial placentas—may render previable some, and eventually, perhaps, even many, abortuses that are, at present, not-at-all-viable.<sup>17</sup>

The distinction of the two kinds of nonviability enables us to discern clearly the difference between the broader and narrower meanings of "viable." The class of fetuses that are "viable" in the broad sense of "savable" or "salvageable" or "likely to live" comprise (a) the viable in the technical sense and (b) previable, i.e., those able to become or to be made viable. Only the notat-all-viable are not savable. I thus suggest the following precise classification:

Table 2. Precise Classification of Fetuses

#### The Salvageable Fetus or Abortus

The Not-Salvageable Fetus or Abortus

The Viable

The Not-at-all Viable

The Previable

It would seem that the relevant distinction for moral purposes is between the salvageable and the not-salvageable, not between the viable and the nonviable. Indeed, in considering the ethics of experimentation, I would treat all intrauterine fetuses as members of the same class, the salvageable, including those for whom abortion is planned. That is, I would urge that the guidelines formulated for research using the previable fetus be governed by the same principles that govern the guidelines for research using the viable fetus, or in yet other words, that all intrauterine fetuses are to be considered as equals for the purposes of experimentation.

Still, the question can be raised, "When a decision to abort is made by the mother, does not the previable fetus immediately become a not-at-all-viable fetus, by virtue of that decision?" I think not. Because any decision for abortion can be reversed up until the procedure is begun, because the woman may miss the scheduled date for the D & C or her doctor may become ill or die, even en route to the operating room, I would urge that the previable fetus in utero be regarded always as previable, and hence as potentially viable, even after the decision has been made for abortion. Only when the abortion procedure itself has begun, and there is no turning back, can we regard the intrauterine previable fetus as a not-at-all-viable fetus (though it is then still alive until it in fact dies).

#### C. Standards and Criteria for Viability

A viable fetus is one which manifests spontaneous circulatory, respiratory, and central nervous system functioning. Whereas the diagnosis of "aliveness" entails the presence of any one of the five criteria listed above, the diagnosis of viability requires the presence of all of these criteria: spontaneous movement, responsiveness, reflexes, spontaneous circulation, and spontaneous respiration. As the ability to inflate the lungs and to engage in effective exchange of gases between lungs and blood is the last of these abilities to be acquired in normal development, it can serve as the best single guide. And since there is at present no means to inflate and make even partially functional the uninflatable lungs of a not-yet-viable fetus, the presence or absence of spontaneous respiration is a clear, unambiguous, and decisive criterion. This applies, of course, only to the extrauterine fetus, i.e., abortus. In utero, it is not possible to prove whether the fetus would or would not be capable of spontaneous respiration if brought outside. Still, in the abortus, spontaneous respiration is a significant sign of viability, and, along with the others mentioned, constitute the suggested operational criteria.

Some comment should be made about other criteria now used to determine viability: gestational age, body weight, and crown-rump length. Though these criteria may be useful, they offer no assurance, and in some cases, can be misleading. Gestational age is notoriously difficult to determine precisely. The length of the average menstrual cycle of women varies greatly, and the use of the date of last menstrual period to calculate fetal age, even in women with regular cycles, may produce a range of uncertainty of up to 3 weeks. (Menstrual cycle ranges from 21-42 days, ovulation occurring 14 days before menses, and hence from 7 to 28 days after the date of the last menstrual period.) Moreover, 20 percent of women will have bleeding episodes during the first 20 weeks of pregnancy which some may mistake for a menstrual period and thus underestimate how long pregnant they are. Conversely, a missed period may occur prior to the period in which conception occurs, thus leading to an inflated estimate of gestational age.

Weight, though obviously much easier to measure accurately, is not always a good indicator of real gestational age or maturity. Some babies are small for gestational age, others large. Black babies are, on the average, smaller than white babies of comparable age; other things being equal, small black babies do better than small white babies because they are more mature (i.e., older). Finally, it is not clear how weight should be used as a criterion of viability. Should one take the weight at which the average fetus can function outside the womb, or the weight of the smallest fetus ever to have done so? One fetus born at 395 grams has survived. By retrospective definition, it was viable at that weight, though no other fetus at that weight has been.

#### D. Determining Viability of a Fetus In Utero

This is admittedly difficult to do. Estimates of gestational age of less than 20 weeks, by history and size of uterus, should clearly permit the diagnosis of a previable fetus with little or no likelihood of error. The diagnosis of viability can be made, presumptively, again with little likelihood of error, if

by calculating gestational age and uterine size, the fetus appears to be 28 weeks or older. In between 20 and 28 weeks, there is uncertainty and the likelihood of error.

In view of this uncertainty, I have no suggestions to make for how one may accurately diagnose viability or its lack in a fetus in utero, between 20 and 28 weeks gestation. All one can do is to try to develop reasonable criteria for a presumption of viability. Various courses could be followed, to be determined in part by a prior decision about on which side to err. For example, in any case in which abortion is to be performed by hysterotomy or by prostaglandin expulsion in a woman pregnant 20 weeks or more, one could argue for presuming the fetus to be viable, because it just might come out viable. And for the purpose of setting guidelines for research involving intrauterine fetuses, I would certainly think the wise and prudent course is to err on the side of never mistaking a viable fetus for a nonviable fetus. On this principle, I offer the following criterion of presumptive viability: A heartbeat audible with the fetoscope, which appears at about 20 weeks of gestational age. This is a clear and, in the hands of a competent observer, unmistakable sign of fetal life and approximate fetal age. My suggestion is this: treat every fetus with a stethoscope audible heartbeat as if it is viable. Some will not be, but none that are will be mistaken for not. (This criterion, though more reliable than estimates of gestational age, will have approximately the same consequences as the criteria suggested by the Peel Commission: 20 weeks gestation, corresponding to a weight of approximately 400-500 grams.)

The Peel Commission suggested drawing a further line, on the immature side of viability--namely at 300 grams--which roughly marks the stage before which "those parts of the brain on which consciousness depends are, as yet, very poorly developed structurally and show no signs of electrical activity." <sup>18</sup> If these facts are correct, this line may indeed recommend itself to those who wish to consider not viability or salvageability, but possible awareness and feeling, and who want to rule out all possibility that the fetus used in experimentation may "feelingly" suffer in any way as a result. A consideration of accuracy of the claim and of the merit of this moral concern are beyond the scope of this paper. Still, as I have more than once suggested, it is not clear which of the lines that can be drawn should be given decisive weight in arguing the moral issues, and I therefore mention the line of "as-yet-no-brain-function" as one more possible morally significant "boundary" in this undeniably continuous process of growth and development.

#### IV. RECOMMENDED CRITERIA FOR DETERMINING FETAL DEATH AND VIABILITY

#### A. Criteria for Determining Death

A fetus or abortus will be considered dead, if, based on ordinary procedures of medical practice, it has experienced an irreversible cessation of spontaneous circulatory and respiratory functions and an irreversible cessation of spontaneous central nervous system functions.

- To be declared dead, a fetus or abortus must show an absence of

   (1) spontaneous muscular movement, (2) response to external stimuli,
   (3) elicitable reflexes, (4) spontaneous respiration, and (5) spontaneous heart function—heartbeat and pulse.
- 3. The presence of any one of the above criteria is a sign that the fetus or abortus is alive.
- 4. Electroencephalographic examination is not necessary to make the diagnosis.
- 5. Once the diagnosis of pregnancy has been made, the fetus *in utero* is presumed to be alive until proved dead.
- 6. During abortions likely to produce an intact abortus, the fetusbecoming-abortus should be presumed alive until examination of the expelled or removed abortus reveals it to be dead.

#### B. Criteria for Determining Viability

- 1. An aborted fetus is to be considered viable if it manifests all five of the vital signs listed in A-2 above. Spontaneous respiratory activity is a sine qua non of the diagnosis of viability. Weight and estimated gestational age are insufficient criteria and should not substitute for clinical examination of the abortus.
- 2. An intrauterine living fetus should be considered previable (i.e., potentially viable) before the age of 20 weeks and viable after the age of 28 weeks.
- 3. Accurate diagnosis of viability is not possible for the fetus *in utero* between 20 and 28 weeks. The presence of a stethoscope-audible heartbeat should be taken as a sign of presumptive viability.
- 4. The to-be-aborted fetus, before the heartbeat is audible, should be regarded as previable, and hence as salvageable, until the abortion procedure is in progress and cannot be reversed. Only then can the fetus be regarded as not-at-all viable.
- 5. Following expulsion or removal of a fetus, adequate time to assess the presence of life and viability must be allowed before experimentation can be considered. The diagnosis of viability, where there is likely to be doubt, should be made by the delivering obstetrician, and then only if he is not himself likely to be engaged in subsequent experimentation on the abortus.

#### REFERENCES

- 1. "The Use of Fetuses and Fetal Material for Research: Report of the Advisory Group," London: Her Majesty's Stationery Office, 1972, p. 2.
- 2. "Protection of Human Subjects: Proposed Policy," Federal Register 39 (No. 165): 30648-30657, at 30653, August 23, 1974; and "Protection of Human Subjects: Policies and Procedures," Federal Register 38 (No. 221): 31738-31749, at 31747, November 16, 1973. These two publications will be referred to as the 1974 and the 1973 DHEW guidelines, respectively.
- 3. The general use of the terms "experiment" and "experimentation" is often confused and confusing, thanks to the ambiguity of the terms. At least two meanings are intended and these are often interchanged. One meaning refers to the purpose of a procedure or activity, the other to its likelihood of success. In its first meaning, "experimental"—usually in the sense of "scientific" or "investigational," i.e., for the purpose of gaining new knowledge—is opposed to "therapeutic," This distinction is ethically important because it points to the problem of who will benefit from the procedure, of whose purposes are served. In its second meaning, "experimental"—in the sense of "new and untested" or "uncertain"—is opposed to "usual and tested" or "proven" or "certain." This distinction (usually applied to procedures having a therapeutic purpose) is ethically important because it points to the problems of risk and uncertainty, and thus of weighing risks and of calculating benefits and harms. Throughout this paper, "experimentation" will be taken in the first sense only.
- 4. Later in this paper the class "nonviable" will be shown to contain two distinct subgroups, which I call the "previable" and the "not-at-all-viable."
- 5. To say "dead nonviable" fetus or "dead viable" fetus seems strange, and points up a source of the confusion. To speak precisely, we should say that the former is a dead fetus or abortus that died before it had reached the maturational stage of viability, the latter a dead fetus or abortus that died after it reached that stage. But the dead nonviable or dead viable fetuses are not any longer nonviable or viable; they are simply dead—a proof: it would make no sense to reverse the adjectives and speak of a "viable dead" fetus. This is why I urge that the terms "nonviable" and "viable" be reserved for living fetuses only.

To be sure, in some cases, it may be difficult to find out whether or not the fetus has reached the stage of viability, and one may never know, even retrospectively, about a 20-28-week-old abortus that fails to survive, since the death of the abortus need not have been due to its failure to attain the viable stage. I return below to this problem of uncertainty in my discussion of "viability."

#### REFERENCES (Continued)

- 14. We have already dealt with the confusion caused by assuming that "viable" is a synonym for "alive." All viable fetuses are living, but not all live fetuses are viable.
- 15. Without this qualification of "and soon," the term "nonviable," in this meaning, would apply to all of us, all of the time.
- 16. My definition is the same as that used in the Peel Commission Report. It differs slightly from that used in the DHEW guidelines. The latter, in both the 1973 and 1974 versions, add the phrase "given the benefit of available therapy," and imply that viability is in part a function of available technology (a broader sense of "viability" than mine). Also, both versions of the DHEW guidelines speak about procedures that would terminate the respiration of an abortus (by their definition, nonviable), yet one would have been led to believe that a nonviable fetus or abortus has no respiration. The DHEW guidelines are thus confusing on the matter of viability.
- 17. I am not suggesting that the presence of new technologies permitting doctors to prolong the life of nonviable fetuses and abortuses to the point of viability would make the use of such technologies obligatory on all or even any nonviable abortus. But the availability of such life-saving technologies would undercut one ground some people use to justify research on previable fetuses, namely, that they are necessarily going to die anyhow, that there is no way to avoid their death. Other possible justifications, those not dependent on the inevitable and imminent death of the fetus, would, of course, not be so undermined. I do not here argue which, of any, of such proposed justifications are now adequate, and for what kinds of research.
- 18. The Peel Commission Report.
- 19. Quotations from or other uses of this paper require permission of the author.

#### APPENDIX

#### IV. What Can and Should Be Legislated?

Arguments both for and against the desirability of legislation "defining" death often fail to distinguish among the several different subjects that might be touched on by such legislation. As a result, a mistaken impression may exist that a single statutory model is, and must be, the object of debate. An appreciation of the multiple meanings of a "definition of death" may help to refine the deliberations.

Death, in the sense the term is of interest here, can be defined purely formally as the transition, however abrupt or gradual, between the state of being alive and the state of being dead.<sup>57</sup> There are at least four levels of "definitions" that would give substance to this formal notion; in principle, each could be the subject of legislation: (1) the basic concept or idea; (2) general physiological standards; (3) operational criteria; and (4) specific tests or procedures.<sup>58</sup>

The basic concept of death is fundamentally a philosophical matter. Examples of possible "definitions" of death at this level include "permanent cessation of the integrated functioning of the organism as a whole," "departure of the animating or vital principle," or "irreversible loss of personhood." These abstract definitions offer little concrete help in the practical task of determining whether a person has died but they may very well influence how one goes about devising standards and criteria.

In setting forth the general physiological standard(s) for recognizing death, the definition moves to a level which is more medicotechnical, but not wholly so. Philosophical issues persist in the choice to define death in terms of organ systems, physiological functions, or recognizable human activities, capacities, and conditions. Examples of possible general standards include "irreversible cessation of spontaneous respiratory and/or circulatory functions," "irreversible loss of spontaneous brain functions," "irreversible loss of the ability to respond or communicate," or some combination of these.

Operational criteria further define what is meant by the general physiological standards. The absence of cardiac contraction and lack of movement of the blood are examples of traditional criteria for "cessation of spontaneous circulatory functions," whereas deep coma, the absence of reflexes, and the lack of spontaneous muscular movements and spontaneous respiration are among criteria proposed for "cessation of spontaneous brain functions" by the Harvard Committee.

Fourth, there are the *specific tests and procedures* to see if the criteria are fulfilled. Pulse, heart beat, blood pressure, electrocardiogram, and examination of blood flow in the retinal vessels are among the specific tests of cardiac contraction and movement of the blood. Reaction to painful stimuli, appearance of the pupils and their responsiveness to light, and observation of

movement and breathing over a specified time period are among specific tests of the "brain function" criteria enumerated above.

There appears to be general agreement that legislation should not seek to "define death" at either the most general or the most specific levels (the first and fourth). In the case of the former, differences of opinion would seem hard to resolve, and agreement, if it were possible, would provide little guidance for practice. In the case of the latter, the specific tests and procedures must be kept open to changes in medical knowledge and technology. Thus, arguments concerning the advisability and desirability of a statutory definition of death are usually confined to the two levels we have called "standards" and "criteria," yet often without any apparent awareness of the distinction between them. The need for flexibility in the face of medical advance would appear to be a persuasive argument for not legislating any specific operational criteria. Moreover, these are almost exclusively technical matters, best left to the judgment of physicians. Thus, the kind of "definition" suitable for legislation would be a definition of the general physiological standard or standards. Such a definition, while not immutable, could be expected to be useful for a long period of time and would therefore not require frequent amendment.

University of Pennsylvania Law Review 121: 102-103, 1972.

<sup>57.</sup> For a debate on the underlying issues see Morison, Death: Process or Event?, 173 SCIENCE 694 (1970); Kass, Death as an Event: A Commentary on Robert Morison, 173 SCIENCE 698 (1971).

<sup>58.</sup> To our knowledge, this delineation of four levels has not been made elsewhere in the existing literature on this subject. Therefore, the terms "concept," "standard," "criteria," and "tests and procedures" as used here bear no necessary connection to the ways in which others may use these same terms, and in fact we recognize that in some areas of discourse, the term "standards" is more, rather than less, operational and concrete than "criteria"—just the reverse of our ordering. Our terminology was selected so that the category we call "criteria" would correspond to the level of specificity at which the Ad Hoc Committee framed its proposals, which it called and which are widely referred to as the "new criteria" for determining death. We have attempted to be consistent in our use of these terms throughout this Article. Nevertheless, our major purpose here is not to achieve public acceptance of our terms, but to promote awareness of the four different levels of a "definition" of death to which the terms refer.



# REPORT ON VIABILITY AND NONVIABILITY OF THE FETUS

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### Contents

	INT	RODUCTION	12-1		
1.	DEFINITIONS				
2.	CHANGES IN SURVIVAL RATES				
	A.	Sources	12-2		
	в.	Limitations	12-2		
	c.	Weight and Gestational Age Classifications and Survival	12-3		
	D.	Survival Trends for Premature Infants by Weight Groups	12-3		
	E.	Special Problem of the Discrepancy Between Prenatal Prediction of Fetal Age and Weight and the Postnatally Measured Weight of a Premature Infant	12-8		
	F.	Summary of Case Reports of Survivals at Less Than 601 Gram Weight or at Gestational Age of 24 Weeks or Less	12-9		
	G.	Quality of Survival	12-11		
3.	CHANGES IN MEDICAL TECHNOLOGY AND CARE OF THE PAST DECADE				
	Α.	Introduction	12-13		
	В.	Sources	12-13		
	c.	Limitations	12-13		
	D.	Overview	12-14		
	E.	Major Changes in the Technology and Care of Premature Infants	12-15		
	F.	Potential Areas for Medical Advances Directly Related to the Care of Premature Infants Which May be Dependent in Part on Investigation of the Human Fetus and Premature			
		Infant During the Next Decade	12-24		
4.	FORMULATION OF GUIDELINES FOR PHYSICIANS				
	Α.	Viability and Nonviability	12-25		
	в.	Fetal and Premature Infant Death	12-27		
	c.	Options and Their Implications for Premature Infants	12-27		
	BIBLIOGRAPHY				
	APPENDIX A				
	APPENDIX B				
	ADDENDTY C		12-10		

# Report on Viability and Nonviability of the Fetus

#### INTRODUCTION

This report is organized into four sections:

- 1. Definitions
- The changes that have occurred over the past ten years in survival rates, particularly weight specific survival rates
- 3. The changes in medical technology and care during this period, including an assessment of the present state of technology and medical care relevant to improving survival for premature infants
- 4. Based on 2, 3, and present medical understanding, a formulation of possible guidelines for use by physicians in determining whether a fetus, delivered spontaneously or as a result of an induced abortion is viable, nonviable or dead. Some of the implications for newborn infant care of various interpretations of the biologic data will also be indicated.

#### 1. DEFINITIONS

- The Fetus: the human embryo from conception to delivery. (As in the "Peel Report" and the preliminary Mahoney report to the Commission, no distinction is made between embryonic and fetal periods of intra-uterine development.)
- The Premature Infant: The human fetus after delivery that weighs less than 2500 grams (5-1/2 lbs.) is not born dead, and is judged by a physician in attendance to have a chance of surviving despite low weight and/or gestational age. Thus, a stillborn or deadborn infant and a 100-gram prematurely delivered infant are not counted in determining the incidence of prematurity or premature survival rates.
- Fetal Death: (1) The death of a product of conception prior to complete expulsion or extraction from the uterus, or (2) the death of a product of conception expelled from the uterus, judged to have no chance of survival at delivery because of low weight or gestational age. Thus,

a stillborn or deadborn infant and a premature infant judged not to have any chance of survival because of its low weight and/or gestational age may be included as a fetal death for official recording purposes. In some instances stillborn infants are recorded separately.

- <u>Inborn Infant</u>: An infant delivered in the hospital where the infant is receiving neonatal care.
- Outborn Infant: An infant delivered in a hospital other than that where the infant is receiving neonatal care.
- Neonatal Infant: An infant of less than 28 days of life for most recording purposes. However, commonly used to include infants up to six weeks of life who may, if sick, be cared for in Neonatal Intensive Care Centers.

#### 2. CHANGES IN SURVIVAL RATES

- A. <u>Sources</u>. A survey was made of the English literature, vital statistics for the United States and the Canadian province of Quebec, selected vital statistics of individual states and unpublished or partially published data from 27 major centers with obstetrical services and special intensive care units for premature units.
- B. Limitations. The United Nations and the U.S. Census Bureau estimate the world population at approximately 3,860,000,000. Using the estimate of 32 births per 1,000 population of 1972, there are approximately 123.5 million births per year in the world. There are approximately 3 million births in the United States which represent less than 3 percent of the total world's births. The weight specific survival data and related information are obtained from a relatively small subset of the births in the United States and Canada selected on the basis of availability and the time constraints of the Commission's report. This does not represent a statistical sampling of the total world births, U.S. births or Canadian births over the ten-year period. Each of the medical centers whose data are presented accepts premature infants referred for care after delivery elsewhere (outborn) as well as infants delivered at the center itself (inborn). Data were not available in the U.S. on the total number of deliveries in each area from which the hospitalized infants are drawn and the fraction of this total number which the delivery of these infants represents. Such data were available for Quebec and one center in Montreal. Since a true estimate of probability of survival depends on this information, only crude estimates of weight specific survival probabilities were possible.

Most of the world, national and state information on births that is collected makes no attempt to record data on premature infants by small weight increments; rather, all infants less than 2500 grams and/or less than 1000 grams are grouped together. There is also an uncertain area where premature deaths and fetal deaths tend to merge for recording purposes. Depending on local custom and laws, this area is usually about 500 grams, but may on occasion range between 500 and 1000 grams.

The most reliable quality data for weight specific survival were obtained from the province of Quebec in Canada and from a number of individual neonatal intensive care centers and obstetrical services in the United States. It is in these medical centers that the most advanced technology and care have been applied during the past decade. It is potentially possible in these centers to evaluate the effect of changes on survival of premature infants that cannot be detected for city, state or national populations. Using regional and state data it is difficult to evaluate the beneficial or adverse effects of changes in care because of the inclusion of large numbers of low-risk premature infants of birth weights of 1500-2500 grams.

Data from selected neonatal intensive care centers are provided in Appendix B. These data are limited because not all centers had information available for a ten-year period. Most had to review and organize their data especially for the Commission, giving priority to providing data at small increments for low birth-weight groups.

- Weight and Gestational Age Classifications and Survival. Up to the present almost all of the information available relating weight to gestational age during fetal life has been based on correlating the weights of the products of conception after they have been delivered (e.g., premature infant, deadborn or those products of conception not judged to have any chance of surviving) with estimates of postconception age calculated from menstrual histories (from the first day of the last menstrual period [LMP]). Estimates of gestational age based on LMP cannot be determined in 15-30 percent of pregnancies. The variation in estimated gestational ages at different weights is presented in Table 1 (see Appendix B). Conversely, on the basis of observations in animals, in human twin pregnancies, in small groups of women carefully monitored for date of conception and menstrual history, and from ultrasound studies of fetal length and head circumference, it also has been established that a substantial variation in weight may occur at specific gestational ages. The variation in weight at different gestational ages in centers surveyed in this report is illustrated in Table 2. The available data relating percent survival to different weight groups or to different gestational ages should be considered with these variations in mind. The use of both weight and gestational age together at birth is of clinical importance in predicting which groups of infants are at increased risk of death or illness before clinical symptoms or signs develop. However, this use is different than relying upon a prenatal estimate of a "nonviable" gestation age to predict the likelihood that an infant will, in fact, be born at a "nonviable" weight (see page 12-7).
- D. Survival Trends for Premature Infants by Weight Groups. There are no national or international data available that provide rates of survival by 250-gram weight groupings for the past decade. However, such data are available for New York City and are generally considered to be of high quality by authorities in the field of public health and epidemiology. Data are collected in a uniform manner by the Department of Health from all hospitals in the City. From 1962 to 1971 there was a 4.5 percent increase in the survival rate for all premature infants (infants under 2500 grams) which is equivalent to a 26 percent reduction in mortality (Table 3). The improvement in survival of the nonwhite group was 6.9 percent, a 36 percent decrease in the mortality rate. This improvement was

#### REFERENCES (Continued)

- 6. The distinction between "standards" and "criteria," and between these and the more general "concept" of death on the one hand, and the more specific "tests" and "procedures" on the other hand, have been elaborated in an article by Alexander M. Capron and Leon R. Kass, entitled, "A Statutory Definition of the Standards for Determining Human Death: An Appraisal and a Proposal," University of Pennsylvania Law Review 121: 87-118, 1972), the relevant pages of which are reproduced in an appendix to this paper.
- 7. See, for example, "A Definition of Irreversible Coma: Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death," Journal of the American Medical Association 206: 337-340, 1968; and "Refinements in Criteria for the Determination of Death: An Appraisal," (A Report by the Task Force on Death and Dying of the Institute of Society, Ethics, and the Life Sciences), Journal of the American Medical Association 221: 48-53, 1972. This is perhaps a good place to emphasize that the determination of death is a matter absolutely distinct from a second important question with which it has often been confused, namely, "When is it permissible to allow a patient, still alive, to die?" Here the question is, "When is the (ex)patient dead?"
- 8. This commits the fallacy of confusing the whole with its albeit superior part. See Capron and Kass, op. cit., p. 112.
- 9. See description in "A Definition of Irreversible Coma," cited in reference 7.
- 10. See section below on death in the fetus at very early stages.
- 11. That some dead or dying fetuses may be mistaken for living fetuses does not pose any grave ethical questions, but does raise significant problems for the interpretation and significance of any scientific research that might be done using these fetuses and abortuses. Indeed, on purely scientific grounds, one might question the value of at least some kinds of experiments that have been done on fetuses prior to and during abortion procedures, because the experimental subjects may have already been dying and in very unphysiological states, thus rendering doubtful any inference that might be drawn from the data about normal fetal physiology or metabolism.
- 12. By my understanding of the opinion of the Supreme Court in Roe v. Wade, such an action would not be legally culpable as manslaughter or murder, since the Court held that the fetus in utero is not legally a person.
- 13. The reader is reminded that the definition of "abortus" in this paper differs from the more usual definition given by obstetricians or by the DHEW guidelines. Here, abortus means any extra-uterine fetus expelled by spontaneous or induced abortion, nonviable and viable. Usually, abortus means only an expelled nonviable fetus.

primarily in infants weighing less than 2000 grams with increases of 68 percent, 20 percent and 6 percent in the survival rates of infants in the under 1000 gram, 1001-1500 gram, and 1501-2000 gram weight groupings; respectively. When the data available from the thirteen New York City Premature Centers were separately analyzed (Tables 4-13), a further improvement in survival of inborn white infants in these same weight groupings was apparent from 1971 to 1973 for inborn premature infants, especially for white infants of 751-1500 grams (a 49 percent increase in survival rate) and nonwhite 751-1000 grams (a 127 percent increase in survival rate) (Tables 11-13). Further analysis of the trends in these Centers suggests that there may have been increases in survival in the outborn white premature infants in 1964 (1001-1250 gram weight group) and 1967 (in the three weight groups between 751-1250 grams), in all outborn infants in 1967 and 1968 and in inborn nonwhite infants in 1968 and 1969 (in the three weight groups between 751-1250 grams). For purposes of general comparison over this same period of time the neonatal mortality in the United States was reduced 24 percent. In Oregon the neonatal mortality decreased 30 percent and the survival of premature infants of 1001-2500 grams was increased 4.9 percent (a 38 percent decrease in the mortality rate) (see Table 14).

(1) Probability for Survival of Infants Weighing Less Than 1001 Grams. Any estimation of the chance of survival based upon the overall experience in the United States would need to be calculated from the documented survivors recorded in case reports and Premature Center statistics compared to the total number of births per year. On the experience of the past decade this would mean that there is about one chance in 5-6 million total births of an infant weighing less than 601 grams surviving in the United States. Although based on a large number of deliveries from census data, the uncertainty that all cases were reported and the lack of information about the numbers of infants born by weight subgroupings made us reject this approach in developing a probability table.

Alternatively, if we used the Quebec data to calculate a probability of survival based on the number of survivors in each 50-gram weight grouping compared to the total births in each weight grouping, this would lead us to estimate that there would be no survivors of 551-600 grams. However, this inference would be based on only 190 births which we consider too small a number of births for calculating a clinically valid probability (Table 15). Therefore, the probability of survival in each weight group was calculated by a comparison with the total births in the Province of Quebec during the period studied (276,531).

For the entire province of Quebec from 1970 to 1972 there were 272,445 livebirths. None of those weighing less than 601 grams survived (Table 15). As the risk of fetal death is lowered, the number of infants born alive will correspondingly increase. Thus, the chance of survival is best expressed in terms of the number of premature infants surviving per total births (stillborn or deadborn plus liveborn). The lowest fetal death rate (percent stillbirths) for all weights is probably that obtained at the University of California in Los Angeles where there has been the most extensive experience with ultrasonic monitoring of the fetal heart rate. This rate was 15 fetal deaths per 1,000 livebirths in 1970 to 1972. Adding these calculated fetal deaths to the Quebec livebirths during this

period, there were no survivors less than 60l grams out of 276,53l total births in Quebec. The chances of survival at birth weights above 600 grams were:

Probability of Survival	Probability of Survival Per Million Total Births
11000011101 01 11111	
1 in 276,531	3.6
1 in 92,177	10.8
1 in 92,177	10.8
l in 69,132	14.4
1 in 34,566	28.8
1 in 27,653	36.0
1 in 14,554	98.4
1 in 14,554	98.4
	1 in 92,177 1 in 92,177 1 in 69,132 1 in 34,566 1 in 27,653 1 in 14,554

Unfortunately, data are not available in the United States to permit analysis of the weight specific survival rates in terms of the total number of deliveries that occurred in the population served by any one of the major premature referral centers. However, this has been done for the premature center at the Montreal Children's Hospital. Table 16 shows that no infant weighing less than 700 grams survived from 1970-1974 from a total of 85,200 consecutive livebirths in the referring hospitals. The one survivor in the 701-750 weight group represents a probability of survival rate of 11.5 per million total deliveries (when corrected for the fetal death rate) at a neonatal intensive care center. This is in comparison with the prediction of 10.8 estimated for the entire province of Quebec, which includes many hospitals without intensive care units.

The appropriateness of applying this kind of interpolation to the United States can be evaluated by looking at the data from Stanford University Medical Center from 1964-1974 (Table 17), University of Colorado Medical Center, 1963-1973 (Table 18), Boston Hospital for Women from 1963-1973 (Table 19), University of Minnesota, 1970-1974 (Table 20), and Cincinnati General Hospital, 1973-74 (Table 21). Of the total number of fetuses and premature infants (inborn and outborn) in the weight groups below 601 grams cared for in these institutions there were no survivors. At stanford there was one survivor who weighed 551-600 grams, but since 1971 there have been no survivors of less than 901 grams. At Cincinnati General Hospital there was one survivor of 501-550 grams and there have been no survivors of less than 851 grams since 1973. In Boston there have been no survivors for the entire period (1963-1973) weighing less than 601 grams. Similarly, there were no survivors below this weight (Table 22) and few survivors below 750 grams at the University of California in San Francisco (one survivor at 601-650 grams), University of Minnesota (one survivor at 751 grams), University of Colorado (one survivor at 851-900 grams), Tucson Medical Center (one survivor at 651-750 grams), or University of Arizona Hospital (one survivor at 651-750 grams) (Table 23). Figures 1-3 summarize this information (see Appendix A). Figure 1 shows the total number of survivors in each weight group. Figure 2 represents this total number of survivors as a fraction of the total livebirths. Figure 3 illustrates the improvement in survival that has occurred in each weight group from 1963-1969 to 1970-1974. The increased number of infants in each weight category in the more recent period reflects, in part, an increase in prompt regionalized referrals to these Centers. Many of these infants previously did not survive long enough to get to these Centers.

Because of the small numbers of premature infants born weighing less than 1000 grams who are cared for each year in an individual premature center, survival trends over the past decade may be poorly appreciated when looking at data reported by a particular center. The survival data for the whole of New York City for the years 1962-1971 is, however, useful to delineate these trends (Table 3). It represents experience with over three times as many infants in this weight grouping as the experience in Quebec. There was a 68 percent improvement in survival rate of infants weighing less than 1000 grams during this period but there were no survivors out of 989 births under 500 grams cared for in the thirteen premature centers of the City of New York. These centers care for infants from the entire New York metropolitan area including Westchester, New Jersey and Long Island. Unfortunately, only 250 gram weight groups are used so it is only possible to determine the weight distribution of survivors in two groups: 501-750 and 751-1000 grams.

Age. Four centers had gestational age estimations grouped at two-week intervals available for analysis: University of California at San Francisco, 1965-1974 (Table 22), University of Colorado, 1963-1973 (Table 18), University of Minnesota, 1970-1974 (Table 20) and the Royal Victoria Hospital, 1966-1974 (Table 24). In no instance did an infant of 24 weeks or less gestational age survive (Table 25). The surviving infants of 25 weeks gestation weighed more than 750 grams. Menstrual histories were generally used to estimate gestational age, although some ages may have been adjusted to make them compatible with gestational age estimated by physical examination (see page 12-15).

Figures 4 and 5 indicate the number and percent of livebirths surviving at each gestational age. These results are combined in Figure 6.

The results from these centers do not permit a numerical estimate of the probability of survival for those infants of 25 weeks or greater gestational age since the total population of births, of which these infants are a small part, is unknown. By interpolation from Table 2, Table 15 and the total births of the province of Quebec, an infant of 25 weeks probably has a chance of surviving no better than 3.6 parts in 1 million.

(3) Changes in Survival at Selected Neonatal Intensive Care Centers. Changes in survival of premature infants during the past decade also can be evaluated in terms of the experience prior to the creation of neonatal intensive care centers and trends in these individual centers over a number of years. Table 26 suggests a marked improvement in survival of infants of 751-1000 grams since 1920 and when two more recent time periods were compared at the Royal Victoria Hospital, Montreal. A comparison of results at this premature center with those of the province of Quebec is provided in Figure 7 and Table 27. These results demonstrate improved survival at the borderline of viability but no survival at less than 25 weeks.

The changes resulting from intensive obstetrical care have been well demonstrated at the Los Angeles County-USC Medical Center. Here, continuous intrauterine fetal heart rate monitoring with ultrasound was initiated on high-risk

obstetrical patients in 1970 before it was generally accepted in obstetrical practice. The unmonitored patients were low-risk patients. As the number of patients monitored increased, the fetal death rate decreased (Table 28). The intrapartum death rate of infants weighing more than 1500 grams decreased 64 percent from 1970 to 1973. A controlled study was not undertaken, but Table 29 shows that the fetal death rate was lower in those monitored high-risk women, who should have had the highest fetal death rate than it was in the unmonitored low-risk pregnant women. It was also lower than at the Parkland Hospital (Table 30) of the University of Texas Southwestern Medical School where special clinical observation but no electrical monitoring was employed for similar patients. The neonatal death rate at Los Angeles County-University of Southern California was also decreased in comparison to Parkland (compare Tables 28 and 30). The survival of all monitored premature infants at Los Angeles County-University of Southern California was improved compared to unmonitored premature infants at the same institution (Table 31).

Comparable results to those on the West Coast have been obtained at the Columbia-Presbyterian Medical Center in New York City. Figure 8 summarizes birth rate and mortality data over the last 20 years at this Center, divided into five periods. The first period is prior to monitoring. Fetal acid-base monitoring was begun on a very limited scale in 1963. Fetal heart rate monitoring was added in 1968. Both techniques were not used extensively until the last period. The annual birth rate has fallen considerably from over 4,000 per year to 3,000, particularly since the introduction of legalized abortion. The stillbirth rate has not shown any particular trend, but the neonatal death rate in liveborn infants of 1000 grams or more has fallen from a high of 12.9 per thousand to a low of 6.8 per thousand, representing a 47 percent improvement. Although the birth rate has fallen, the incidence of prematurity has remained approximately the same at about 9 percent. The greatest change in mortality coincided with the largest increase in the use of monitoring. Perinatal mortality also showed a decrease over the same period. It is of particular importance to note that 90 percent of the monitoring is done on ward or service (nonprivate) patients who are primarily indigent black and Hispanic. A very large proportion of these pregnancies are classified as being at high fetal and neonatal risk compared to the unmonitored private patients. However, the monitored high-risk nonprivate patients has 10 percent less neonatal deaths, 14 percent less perinatal deaths (fetal and neonatal) and 37 percent less intrapartum fetal deaths.

The major trends in survival of premature infants must also be viewed from the perspective of individual neonatal intensive care centers where there is the greatest concentration of expertise and technology. The general trend of decreasing neonatal mortality apparent in the neonatal intensive care units at Los Angeles County-USC Medical Center and University of Oregon Hospital are typical for this country (Table 32). When examined by weight groups, consistent improvement in premature survival in such centers is documented by representative data obtained from neonatal intensive care units at Denver Children's Hospital and the University of California at San Francisco (Tables 33 and 34).

A decreased incidence in the birth of premature infants of 751-1250 grams in weight may have occurred since the frequency of legal abortions increased (Table 35). Data from the center of the University of California at San Francisco

are particularly illustrative. Both the percent of premature infants surviving and the intelligence quotient of the survivors have improved over the past decade (Figure 9). A difference in survival is demonstrated by comparing the neonatal mortality at this center with that of the City of San Francisco and the United States (Figure 10).

E. Special Problem of the Discrepancy Between Prenatal Prediction of Fetal Age and Weight and the Postnatally Measured Weight of a Premature Infant. The only presently used clinical means of estimating fetal weight is based on the obstetrician's experience in manual abdominal palpation of the uterus. It is as accurate as any other method that has been proposed which involves ancillary measurements and calculations. The error of the experienced obstetrician in estimating fetal weight in this manner increases with decreasing weight from the end of the first trimester through the beginning of the second trimester and may be greater than 100 percent. Thus, the physician's estimate of the weight of a 600 gram fetus in utero may be consistent with delivery of a 1000-1200 gram premature infant.

Fetal gestational age may be estimated from the height of the uterine fundus; the time of maternal perception of fetal movement (quickening); first detection of fetal heart tones; roentgenographic evaluation of fetal size, ossification centers and dispersion of lipid soluble dyes; amniotic fluid analysis for creatinine phospholipids, bilirubin, osmolarity, electrolytes and cytology; and measurement of fetal head dimensions with echoes of sound frequencies above audible levels (ultrasonic cephalometry). These methods should not be confused with the estimation of the gestational age of an infant by physical examination after birth (see page 12-15).

Ultrasonic cephalometry has been used in clinical human fetal experiments to determine the relationship of gestational age estimated by last menstrual period in a number of normal pregnancies (selected for the reliability of menstrual histories) to the linear head dimensions of the fetus determined by ultrasound in these pregnancies. This information is now used to monitor changing head dimensions during pregnancy as an index of normal fetal growth. This can help to identify certain abnormalities in the developing fetus for purposes of initiating prompt treatment after delivery in an appropriate hospital facility or for purposes of abortion of grossly malformed infants. It is the most accurate method presently available, but at best most experienced clinical investigators believe it has an error of ±1 week (±2 standard deviations) from 22 to 26 weeks gestational age (Figure 11). Several authorities believe this error to be ±2 weeks. The combined use of several of these methods to estimate gestational age has not demonstrably decreased this error.

The ultrasound technique can also be used as an indirect way of determining chances of fetal survival: the head dimension of a fetus of unknown or estimated gestational age (by menstrual history) is measured by ultrasound and this measurement is equated with a specific gestational age from the aforementioned series of normal pregnant women whose menstrual histories were considered to be very reliable. There is, of course, no information relating this gestational age or the ultrasonic head measurement to the fetal weight at the time of measurement since all the information is obtained from normal pregnancies that deliver months after the ultrasonic measurement is made.

One must then relate this estimate of gestational age to a prediction of survival (page 12-6) or to a weight, which is itself related to a prediction of survival (page 12-5). If one relates gestational age to weight, it is seen from Table 2 that at 24 weeks gestational age the one-week error implicit in the gestational age estimation by ultrasound before birth is consistent with the birth of a product of conception weighing 500 grams or 1000 grams. There is no chance of survival if the weight is 500 grams, but a 1000-gram premature infant has 98 chances in 1 million of surviving and would unquestionably be considered "viable" in current medical practice.

If a legal abortion had been undertaken at the estimated gestational age of 24 weeks (by ultrasound), in the above example there would be a definite, although small, possibility that the woman could be delivered of a 25-week gestation, viable 1000-gram premature infant. If the gestational age before birth is estimated at 23 weeks, it is extremely unlikely, but possible, that the product of conception would be of a weight and gestational age associated with survival. Thus, there are two problems presented here: (1) the problem of the potential discrepancy between expected weight (and survival) based on the best available prenatal estimate of gestational age and (2) the actual weight of the product of conception after birth based on an actually measured weight. In both instances despite the legality of the abortion and the best prenatal medical judgment, the outcome of medical management may be contrary to the intention of the pregnant woman and the physician. In regard to human investigation initiated after delivery, the subjects can be precisely selected for no probability of survival by accurate determination of weight after birth. When initiating human investigation before birth, the same precision in subject selection is not possible over the entire gestational time period when abortion is legal. At 24 weeks gestation it is not always possible to predict before delivery that the abortus will be delivered at a weight incompatible with survival because the abortus may, in fact, be 25 weeks gestational age.

at Gestational Age of 24 Weeks or Less (see Appendix C for greater detail). In each of the following cases either weight was inappropriately small for the gestational age or some serious question can be raised about the validity of the weight or gestational age. In no instance did a reported infant survive who was both less than 601 grams and of a gestational age of 24 weeks or less. The Apgar score referred to in the following cases is a clinical system for evaluating the degree of depression at birth at 1 and 5 minutes. A low 5-minute score (6 or less on scale of 10) has been established by a national collaborative project to correlate with a later increased incidence of handicaps, motor and mental abnormalities.

#### Case No. 1

A 580-gram black female infant was born by breech extraction at the University of Cincinnati Medical Center with Appar scores of 5 and 8 at 1 and 5 minutes, respectively. *In utero* estimation of gestational age was 25-27 weeks. Physical examination revealed an infant with an estimated gestational age of 24-26 weeks. During hospitalization she developed severe respiratory distress, diagnosed as hyaline membrane disease, apnea, bradycardia, sepsis and anemia. Following

appropriate therapy she was discharged at three months of age at a weight of 2270 grams. On follow-up at 17 months her size was small, physical and neuro-logical examinations were within normal levels, but developmental milestones were retarded.

#### Case No. 2

A 539-gram black female was born at the University of Maryland Hospital by normal spontaneous vaginal delivery with Apgar scores of 0 and 4 at 1 and 5 minutes, respectively. Physical examination showed a premature normal female with an estimated gestational age of 28 weeks. During hospitalization she developed respiratory distress, persistent metabolic acidosis, apnea and sepsis. She responded to therapy and was discharged at three months of age at a weight of 2693 grams. On follow-up she has done well, and at two years of age she was thought to be normal neurologically and developmentally.

#### Case No. 3

A 580-gram infant was transferred to Colorado General Hospital on day of birth. The estimated gestation by menstrual history was 29 weeks, and estimated gestational age on physical examination was 30-34 weeks. The pregnancy was complicated by edema, proteinuria and hypertension. The infant's Apgar scores were 3 and 8 at 1 and 5 minutes, respectively. Infant required endotracheal tube positive pressure resuscitation. Subsequent feeding activity and neurologic examinations indicated a mature infant. The child was discharged at 1940 grams and considered normal at two months of age.

#### Case No. 4

A 624-gram female infant was born at the University of Arizona at Tucson by normal spontaneous vaginal delivery. Apgar scores were good. Physical examination indicated the infant was of approximately 24 weeks gestation. During hospitalization she developed apnea and congestive heart failure due to a patent ductus arteriosus which necessitated surgical correction. She also developed necrotizing enterocolitis. Her weight fell. She is still hospitalized and now weighs 600 grams.

#### Case No. 5

A 397-gram female infant was born in Canada at 32 weeks gestation by menstrual history. The weight was obtained on a grocery store scale on second day of life and subsequently was verbally reported to the physician. On follow-up at one year the child was reported to be healthy and normal physically and mentally. She was small for her age.

#### Case No. 6

An 879-gram, 21 week gestation.

#### Case No. 7

A 999-gram, 22 week gestation.

These two cases were included as survivors in a report by Alden et al., <code>Pediatrics 50:40, 1972</code>. When the gestational ages of these infants were reevaluated, it was noted that the gestational ages listed were taken from the obstetrical records of the referring hospital and were probably inaccurate. The birth weights do not correlate with the aforementioned gestational ages. According to intrauterine growth charts these infants were about 26 weeks and 26-1/2 to 27 weeks, respectively (using the 50th percentiles).

#### Case No. 8

A 450-gram infant was born in a rural hospital in Poland at 25 weeks gestation (by last menstrual period) after threatened first trimester miscarriage. Length: 27 cm. Grandmother and granduncle were reported to have been 900 and 1300 gram prematures, respectively. There is no indication of how these weights were obtained in 1900-1920. History of three sets of paternal twins. Physical examination was consistent with last menstrual period gestational age. Child was normal at three months. The report proposed that genetic factors in this family might be responsible for increased incidence of very small surviving premature infants. However, the reported weight, length and gestational age are so incompatible as to raise some question as to the accuracy of the facts.

G. Quality of Survival. The impact of the advances in care of premature infants over the past decade also have been reflected in an improvement in prognosis of very low birth-weight infants. The outlook for these infants born in the 1950s and 1960s revealed a uniformly poor prognosis for survivors who weighed less than 1500 grams at birth with handicap rates ranging from 33 percent to 60 percent. In general, the smaller the infant, the worse the outlook. recent study by Stewart and Reynolds (see reference 189) evaluating infants weighing 1500 grams or less at birth and cared for in their intensive care unit from 1966 to 1970 is representative of the improved prognosis and survival that have occurred. Of these children, 90.5 percent had no detectable handicap, while 4.2 percent (4) had mental handicaps and 5.3 percent motor handicaps. An analysis of the individual children revealed "a clear relationship between the presence of a handicap and the occurrence of neonatal illness, particularly those presumed to have caused severe hypoxia." Many of the changes in care in Stewart and Reynolds' premature unit were directed primarily at decreasing the incidence of hypoxia. The constellation of these advances which were associated with this improved prognosis included the use of maternal hormone assays (estriol) and ultrasonic biparietal diameter measurements to determine a more optimal time for delivery; continuous electronic fetal heart rate monitoring and fetal acid-base monitoring to decrease the incidence and severity of intrauterine asphyxia; improved resuscitation at birth, oxygen therapy closely adjusted to blood measurements; electronic monitoring of respiratory rate in the management of apneic infants; improvements in artificial and assisted ventilation.

Several examples of specific advances taken from other centers are illustrative of the nature of the kind of improvements that have occurred for certain subsets of patients that result in improved prognosis. At Babies Hospital, Columbia-Presbyterian Medical Center, long-term follow-up of the low birth-weight premature infants with Apgar scores of 3 or less at 5 minutes, in association with intrauterine asphyxia, revealed an incidence of handicap approaching 80 percent.

Figure 12 depicts a changing morbidity rate as assessed by the Apgar score at 1 and 5 minutes over three time periods at Babies Hospital. The first is prior to continuous intrauterine monitoring of fetal heart rate and intermittent fetal blood acid-base monitoring. The second is during 13 percent acid-base and 25 percent heart-rate monitoring. The third is during 25 percent acid-base and 52 percent heart-rate monitoring. The number of patients included in the first period is small. They were the only infants at that time who were scored at 1 and 5 minutes and were part of a large group of 37,000 patients from 12 centers in a collaborative project. Nearly 25 percent of these infants had a 1-minute Apgar score of 6 or less. This particular incidence of depressed infants at 1 minute was similar for the 37,000 infants of the combined data obtained from the national collaborative project and appeared for many years to be an irreducible number, considered a standard figure both in the United States and Great Britain. With the increasing use of intrauterine monitoring of high-risk patients and those that showed evidence of fetal difficulty during labor in period two, the number of depressed infants at 1 minute fell to 13.1 percent and at 5 minutes to 3.3 percent. This decrease in morbidity in 1972 was associated with 13 percent acid-base monitoring and 25 percent heart-rate monitoring. This lower number of depressed infants persisted into the third period when acid-base monitoring increased to 25 percent and heart rate monitoring to 52 percent. For the number of patients considered, the reduction in the number of depressed infants at 1 and 5 minutes both from the first to the second and from the first to the third period is substantial.

When morbidity is measured in terms of duration of hospitalization, a similar improvement is documented. Figure 13 indicates the duration of stay in the newborn intensive care unit for 398 infants; 213 were monitored during labor, while 181 were not. Although the number of monitored patients admitted to the unit was greater than those who were not monitored, the proportion of monitored infants requiring extended recovery periods was markedly less than for unmonitored infants for all admissions of 1000 grams or more. When only those infants weighing 2500 grams or more were considered, the difference became even more striking. Figure 14 illustrates that the mean duration for the monitored infants was six days and for the unmonitored infants ten days. Only 20 percent of the monitored patients required nine days or more of hospitalization as compared to 40 percent in the unmonitored group.

Another specific example of decreased morbidity relates to infants with respiratory distress syndrome or hyaline membrane disease. When the changes in mortality and morbidity are analyzed in terms of the major cause of neonatal and premature infant death, respiratory disease, the central importance of advances in respiratory care designed to improve oxygenation is recognized, e.g., improved mechanical ventilation and technology to increase end expiratory pressure during breathing. Despite a constant incidence of respiratory distress syndrome (Figure 15), survival has markedly increased (Figures 15 and 16), as has the intelligence quotients of survivors at the University of California at San Francisco.

The possibility that measures taken to increase survival of infants of very low birth weight would result in increased number of handicapped children entering the community where they would become a burden on their families and society has not, in fact, occurred. Rather, these measures taken to increase survival rates

of premature infants have improved the outlook for such surviving infants entering the community without handicaps. The number of very low birth-weight infants surviving with handicaps has markedly decreased compared to the period prior to the institution of the clusters of medical advances that characterize present neonatal intensive care centers. This is of even greater importance since the data from the New York City Premature Centers indicate a marked increase in survival of the 750-1000 gram nonwhite inborn infants in 1973 (Tables 11 and 13).

### 3. CHANGES IN MEDICAL TECHNOLOGY AND CARE OF THE PAST DECADE

- A. Introduction. Advances in clinical care of human fetuses and premature infants, as in many other areas of medicine, have not evolved smoothly in a logical progression of closely related studies with the results promptly accepted and uniformly applied. In contrast, advances have developed haltingly by a combination of serendipity, empiricism and investigation of a broad spectrum of interrelated but tangential questions. In no instance has it been possible to directly translate the results of a fetal animal experiment to human therapy. Rather, animal studies have occasionally contributed to the background of understanding upon which human investigation is, in part, based. Alternatively, only a few major changes in medical treatment of the premature infant have been the direct result of carefully controlled human experiments designed to test specific innovations prospectively. Many have resulted from a combination of suggestive evidence from basic and clinical experiments, scattered uncontrolled observations on patients, and inferences from improved understanding of normal physiologic mechanisms. Continuous fetal heart rate and uterine pressure monitoring to detect fetal distress and the advances in the diagnosis and treatment of fetal erythroblastosis resulted from a variety of empiric clinical observations and poorly or partially controlled studies in normal and affected human subjects. Animal studies did not contribute to the advances in these instances. The evolution and acceptance of these new modes of treatment were dependent on amassing cumulative experience and observations over a number of years. In contrast, defining the optimal temperature for premature infants that would increase survival resulted in large measure from a combination of carefully controlled rigorous animal and human experiments. Thus, advances seem eventually to emerge from a highly diversified matrix of thought and activity of widely scattered individual scientists and physicians.
- B. <u>Sources</u>. These data were obtained from a survey of the English literature and from the recorded experience and recollections of the consultants and their associates (physicians, nurses and administrators) involved in providing medical care in their respective neonatal intensive care centers (NICC).
- C. <u>Limitations</u>. Regular diaries are rarely kept in NICC's to record the dates when new procedures and therapies are introduced and existing treatments discontinued. This can be documented by retrospective analysis of patient charts, but such a study was not undertaken because of time constraints. However, in selected instances patient charts were checked to evaluate the time periods.

Each consultant was mailed a form on which he or she was asked to indicate the year when the particular innovations listed were introduced in the center (see Appendix C). No attempt was made to survey innovations which were discarded before or during this period because new knowledge and experience from human investigation indicated that they were not beneficial or harmful. The consultants filled out the questionnaires individually often after consultation with other associates in their center. A meeting was then held to clarify questions about the form and the replies and to determine whether a consensus existed concerning when the innovations were introduced and when they became disseminated on a regional or national basis. The consultants also identified critical or index advances that in their judgment, based on patient care experience, were most important. These are given special emphasis in this analysis.

The foregoing activity was carried out independently of the analysis of survival trends presented in this report. Each consultant, however, brought to these discussions his own perceptions of local and national survival trends. No attempt was made as a group to relate these discussions to survival data. This correlation was done later by the authors of this report after the survival data were obtained from diverse sources and analyzed.

D. Overview. Figure 17 describes in semiquantitative terms the trend in the numbers of major advances in obstetric and pediatric care of the fetus and premature infant introduced during each of the past ten years. Particular innovations or constellations are far more important in themselves than is the cumulative frequency of the number of innovations when trying to assess the impact on mortality and morbidity. Further, in general it takes one to three years from the introduction of an innovation at one or several centers to its acceptance in most centers around the country and Canada, and in some instances, in community hospitals. Further, many advances are of such a technical or specialized nature that they are only appropriately used in neonatal intensive care centers where risks can be kept at an acceptable level relative to benefits and where, generally, there is continuous, critical, open and objective evaluation of patient mortality and morbidity.

The improvements in overall survival rates of prematures noted on page 12-4 in 1967-1969 may be related to the advances in 1964-1966. These advances consisted of a constellation of changes that included reorganization of premature nurseries into intensive care centers with extensive monitoring of blood gases, and chemistries; continuous physiologic monitoring of vital signs; emphasis on hand ventilation with ambu bags; regulation of the thermal environment; a greater density of nursing personnel; and a more aggressive approach to correction of abnormal laboratory values, e.g., hypoxia, hypoglycemia. In 1962-1966 there was also a major obstetrical advance with the *in utero* diagnosis with amniocentesis of severely affected fetuses with erythroblastosis and the introduction of intrauterine fetal peritoneal transfusion.

In England a similar conclusion to that from the United States data was drawn from the mortality trends at University College Hospital and Medical School, London. Only 45 to 50 percent of infants weighing 1001 to 1500 grams survived in the 1950s and early 1960s. In contrast the survival rate for inborn and outborn averaged 69 percent and 70 percent respectively, during 1966-1970 when the

aforementioned cluster of neonatal intensive care advances was introduced in their premature unit. The lag between introduction of these changes and improvement in morbidity is greater than the lag between introduction and survival because the children need to reach preschool and school age before adequate assessment can be obtained. It is now becoming apparent that there has been an improvement in morbidity probably related to these innovations in the mid-1960s (see page 12-14).

The increases in survival in 1971-1973 may reasonably be correlated with a different constellation of advances in 1968-1970: extensive monitoring of the amniotic fluid for chemical abnormalities, inborn errors of metabolism and the diagnosis of fetal lung immaturity; increased use of maternal estriol determination in managing high-risk pregnancies; the introduction of continuous fetal heart rate and uterine pressure monitoring with ultrasound to detect and aggressively manage fetal asphyxia during labor; the use of neonatal transport systems and improvement in physiologic support during referral; major advances in the design and use of infant respirators and the management of respiratory distress syndrome with various techniques to provide increased end expiratory pressure; the use of total intravenous alimentation in premature infants; and the extensive use of phototherapy for jaundice.

- E. Major Changes in the Technology and Care of Premature Infants.

  Appendix C contains a detailed listing of the innovations in care of premature infants that have been assimilated into the routine practice of premature intensive care. Several of these have been selected for further discussion in order to assist in clarifying the meaning of some of the medical terminology and "jargon" which have been used to describe the advances of the past decade.
- The gestational age of the newborn infant at birth is important in predicting the mortality rate and the best way of handling infants of certain weights and ages. During the past decade it has been increasingly appreciated that different clinical problems develop in newborns of the same weight but different gestational ages and, therefore, they require different plans of therapy. Studies of these variations in expected weight for gestational age have been increasingly used to improve care. For example, preterm infants who are small for gestational age have a lower mortality rate than preterm newborns of appropriate gestational age, while term infants of low birth weight have a higher mortality rate than term infants of normal birth weights.

There are several ways of determining the gestational age of the newborn infant. These include: (1) physical examination; (2) neurological examination; (3) nerve conduction time; and (4) electroencephalogram. The most accurate estimate of gestational age is obtained by using a combination of several of the above methods. In order to evaluate gestational age by physical examination, the extent of sole creases, breast nodule diameter, quality of scalp hair, cartilage of the ear lobes, descent of testes, and rugation of the scrotum are evaluated (see Figure 18). The neurological evaluation is usually done at 48 hours of life. This is a difficult examination, especially in the small premature infant. Also, one has to be careful of its interpretation in a sick newborn infant. Figure 19 illustrates the neurological findings that are used to

diagnose the neurological maturation and thereby the gestational age of the infant. A third method, which is the most accurate  $(\pm 2 \text{ weeks})$  method used, to determine gestational age is the motor nerve conduction velocity which is dependent on the degree of myelination of the peripheral nerve fibers. This increases with age during the gestational period. For example, low birth weight and small-for-dates infants have higher nerve-conduction velocities than preterm infants who are of the same weight but are of appropriate gestational age. The conduction velocities are measured by stimulating the ulnar nerve at the elbow and the wrist with rectangular supramaximal stimuli at two different points and recording the evoked muscle action potential (Shulte). The electroencephalogram (EEG) is another method of measuring gestational age. The EEG reflects the degree of maturation of synaptic structures in the central nervous system. By analyzing the pattern of the EEG one can also estimate the gestational age of the infant within  $\pm 2-3$  weeks. It is only practical to carry out the general clinical and neurological estimation of gestational age in the delivery room.

(2) Resuscitation. Resuscitation in the delivery room has been performed with increasing effectiveness and innovation in recent years. Resuscitation refers to a group of techniques and procedures, the cornerstones of which are artificial ventilation with mask, or endotracheal or nasotracheal tube, and external cardiac massage. In addition to evaluating and supporting the newborn's cardiac and respiratory systems, it is important to maintain body temperature in premature and asphyxiated infants who are very sensitive to cooling. Newborn beds in the delivery room may have radiant heaters for this purpose, with servocontrols to automatically adjust the heat provided to the heat lost from the skin.

For any infant who has passed meconium during labor or has meconium-stained amniotic fluid, the posterior pharynx and larynx are examined. If any mecomiun is seen in this area, it is suctioned under direct vision and the larynx is intubated and suctioned by mouth to tube suction until watery mucus is obtained. This is done to prevent meconium aspiration, which results in a high morbidity and mortality in the newborn. Meconium is passed per rectum by the fetus following an asphyxial (poor oxygenation of the fetus) episode in utero. If this asphyxia is severe enough, it may be accompanied by prolonged gasping. At this time, the fetus may aspirate meconium into his lungs.

Another technique that may be used in the delivery room is measurement of the acid-base status of the newborn. This is important in determining his respiratory and metabolic state at birth. This can be done easily by double-clamping the umbilical cord and obtaining blood from the umbilical vein and artery for acid-base analysis. This is especially important in low birth-weight and asphyxiated infants.

An additional development over the past decade has been the administration of buffers like sodium bicarbonate through the umbilical vein or a peripheral vein to correct acidosis (low pH) due to in utero asphyxial episodes which require resuscitation. During prolonged asphyxia there is depression of the central nervous and cardiovascular systems and biochemical changes which result in acidosis in the fetus. Acidosis further potentiates this depression. Asphyxia may be associated with maternal factors like hypotension, toxemia of pregnancy,

inferior vena cava obstruction by a large uterus; and fetal factors such as umbilical cord occlusion. Infusion of buffers (correcting the acidosis) and glucose during artificial ventilation of these infants may speed their responses to resuscitation.

(3) Catheterization of Umbilical Vessels in the Newborn Infant. The umbilical artery and vein are located in the umbilical cord and, in utero, carry blood between the fetus and placenta. Under appropriate circumstances (outlined below) either vessel may be cannulated with an inert, soft, radiopaque plastic catheter after birth.

For umbilical artery procedures the catheter is passed through the artery to a location about 1 cm above the diaphragm or between the iliac bifurcation and the renal arteries. Catheter location is verified by X-ray. The catheter is kept open with a slow infusion. This procedure is indicated for the newborn or premature infant who requires oxygen therapy either unassisted or with a respirator. Arterial blood samples are drawn from the catheter as indicated clinically to determine the degree of oxygenation of the blood (which in turn reflects the respiratory status of the patient). The importance of doing this is to prevent retrolental fibroplasia and other forms of oxygen toxicity. The arterial catheter also can be used to measure the intra-arterial blood pressure via a transducer. This is continually projected on an oscilloscope monitor and, if needed, is connected to an alarm system.

Umbilical vein catheterization may be done (1) as an emergency procedure in the delivery room to administer fluids like glucose water or buffers such as sodium bicarbonate to correct early acidosis (see Resuscitation), (2) for intravenous feeding of very small prematures when it is impossible to maintain a peripheral intravenous line, and (3) for exchange transfusions for hyperbilirubinemia (jaundice).

(4) Electronic Monitoring of the Neonatal Infant. The development of several kinds of monitors in recent years has improved the care of the high-risk and sick infant.

Apnea monitors are of two kinds. The first type runs on the principle of impedance plethysmography utilizing electrodes which are applied to the child's chest and/or arms. The monitor is set at a certain regulatory rate and time (15-20 seconds). When the infant has an apneic episode (stops breathing for longer than 20 seconds), an alarm goes off to alert the personnel. Another type is an air-filled mattress with a temperature sensing device that detects movement of air coincidental with respiration. When apneic episodes occur, an alarm sounds.

Cardiac monitors record the heart rate of the newborn using electrodes strategically placed on the infant's chest and extremities. The heart rate is recorded either on an established scale or displayed on an oscilloscope as the electrocardiographic figure. The monitor is set at a certain rate and when the heart rate falls below this, an alarm goes off.

Blood pressure is measured in the neonate by several methods, but the most accurate and most commonly used in the neonatal intensive care units are the intra-arterial and Doppler methods. Intra-arterial blood pressure is measured via the umbilical arterial catheter, as described previously, via a transducer and is projected on an oscilloscope as the number or wave form. The transcutaneous Doppler method is a noninvasive method and detects very weak impulses which a regular sphygnomanometer would not detect. Studies have established a good correlation between the Doppler and arterial blood pressure.

Temperature. Appropriate temperature control is of utmost importance to the premature low birth-weight infant. The survival of prematures can be improved by proper heat control. If the artificial environment is too warm, the newborn becomes febrile and tachypneic. If it is too cool, the energy and oxygen requirements will increase to generate more heat, decreasing the energy stores which are already low in prematures, causing metabolic acidosis and hypoglycemia. Cold may interfere with surfactant production in the lung (increasing likelihood of respiratory distress syndrome). Thus, it is important to keep the infant, especially the low birth-weight infant, in a neutral thermal environment (temperature of 34.5-36.5°C). In most isolettes used today in the intensive care units the heat is controlled by using a fan to circulate warm air and the temperature of the isolette is controlled by the infant's skin temperature via a cutaneous sensory thermistor connected to the abdomen. New "open beds" with radiant heat units above the bed are used in some intensive care units and delivery room as treatment beds instead of isolettes. These are also controlled by thermistor probes taped to the infant's abdomen.

Microchemistry. The development of rapid microchemistry techniques for analyzing the chemical abnormalities in the newborn has greatly helped the care of these high-risk sick infants. Because of the small amount of blood needed, it is now possible to monitor many chemical parameters as, for example, blood glucose, calcium, electrolytes, bilirubin, liver chemistries, Mg, P, etc. Chemical aberrations can be corrected much sooner and injury prevented. New microtechniques have also been developed for hematological tests (blood typing and counts, G6PD, vitamin E levels, etc.).

Blood gas analyzers that only require a very small amount of blood and are easy to operate have greatly improved the respiratory care of newborn infants. This machine is often located within the intensive care area and operated by the physicians involved in the infant's care. This provides immediate results on the respiratory status of the infant so appropriate changes in therapy can be made.

(5) Oxygen. Oxygen can be delivered into the isolette when small increases in the environmental oxygen are needed or into a plastic head box within the isolette when higher concentrations of oxygen are needed. Using the head box, more accurate concentrations of oxygen can be delivered and fluctuations in oxygen concentration can be prevented. The oxygen delivered must be warmed and humidified. If the oxygen is not warmed, it may be a cold stress to the sick premature and if it is not humidified, it will dry the respiratory mucus, increasing the viscosity of the pulmonary secretions, worsening the newborn's respiratory distress. Monitors are now available for continual oxygen monitoring in the isolette or headbox. A

monitor is set at the desired oxygen concentration and, if the environmental oxygen is at a too high or too low point, an alarm goes off. The setting is, of course, determined by the infant's respiratory condition (arterial and capillary blood gases).

(6) Mechanical Ventilation. The criteria for mechanical ventilation (respirator therapy) vary from one intensive care unit to another. Each intensive care unit has its own criteria for when to place an infant in respiratory distress on the respirator, but one common indicator is apnea (no breathing). At present, either an orotracheal or nasotracheal tube is used for artificial ventilation. Tracheostomies are occasionally used for long-term ventilation. There are many types of positive and negative pressure respirators available. Positive pressure respirators are either pressure or volume controlled. The method of ventilation depends on the individual unit. Regardless of the type of respirator, the infant must be followed with repeated blood gases to determine its efficiency and infant's progress.

Recently, continuous positive (CPAP) and negative airway pressure and positive end expiratory pressure (PEEP) have been introduced for the treatment of respiratory distress syndrome. The principle of this is to not allow the diseased lungs to collapse at the end of expiration but to keep the alveoli open by a continuous distending pressure and thereby improve the diffusion of gases (oxygen and carbon dioxide). Infants who have RDS often grunt. The grunt is produced by exhaling against a partially closed glottis which increases the transpulmonary pressure. This probably prevents and decreases the extent of collapse of the alveoli (air sacs of lungs). In respiratory distress syndrome a large percent of the alveoli are collapsed at the end of expiration due to the lack of surface active material (surfactant) which is necessary to prevent their collapse. The use of constant distending pressure functioning in principle like a grunt has decreased the mortality rate of respiratory distress syndrome. CPAP can be delivered via a head box, mask, nasal prongs or endotracheal tube. If mechanical ventilation is necessary, the positive pressure (PEEP) is delivered via the endotracheal tube at end of expiration. All of the above methods require an expert staff of dedicated and skilled physicians, nurses and respiratory technicians.

(7) Nutrition. Feeding practices have changed in the last decade. In the 1950s and early 1960s full-term infants were not fed for the first 12-24 hours and premature infants were not fed before 24-36 hours of life. It is now known that early feeding of infants is important in decreasing morbidity and mortality. As soon as an infant can tolerate feedings, they are started, usually between 4-6 hours of age and earlier in small-for-dates infants or infants of diabetic mothers. This may decrease the incidence of hypoglycemia, hyperkalemia (high potassium), hyperbilirubinemia and azotemia. Very low birth-weight infants are still a special problem because of their inability to suck, small stomach capacity and danger of aspiration. These infants are usually fed by gavage (tube passed into the stomach at feeding times--every 2-3 hours) and supplemented with glucose water intravenously for adequate fluid intake and supplemental calories.

An alternative method is nasojejunal feedings in which a tube is passed into the jejunum (small intestine). This method decreases the chance of aspiration, provides greater volume of formula than is tolerated by the stomach, and can be used in sick term and premature infants.

Another recent development is total intravenous alimentation. It may be used when enteral nutrition is not possible for prolonged periods in infants of very low birth weight and after radical gastrointestinal surgery. This provides continuous infusion of fluid, calories, electrolytes and vitamins. The solution consists of amino acids, hypertonic glucose, electrolytes, and vitamins. It can be infused either via a peripheral vein as a supplement to oral feedings or via the internal or external jugular vein for a prolonged time as a total source of nutrition. There are serious risks associated with this treatment. It should only be used with very experienced personnel and in the presence of an adequate microchemistry laboratory.

- (8) The Neonatal Intensive Care Unit. This unit admits any infant under six weeks of age who requires intensive care, including premature infants. This includes any sick infant with infection or respiratory distress, any infant requiring major surgery or special nursing care (e.g., infants needing hyperalimentation or tracheostomies and infants of birth weight less than 1500 grams). The nursing personnel undergo special training and orientation in order to work in these units and are provided ongoing education covering new techniques and instruments used in the intensive care unit. There is usually a 1:2 nurse to patient ratio and 1:1 ratio for the sickest infants. The physicians include a full-time doctor trained in neonatology, full-time pediatric housestaff, including neonatal fellows, a full-time anesthesiologist and consultants in a variety of specialties. It is in such units that most of the medical advances relevant to newborn infants have been initiated over the past decade.
- (9) Transportation and Regionalization of Care. In recent years premature transport systems, using ambulance and/or helicopter, have been established in many rural and urban areas in the United States. The purpose of such a system is to bring high-risk infants from hospitals not equipped to care for such newborns to units where they will obtain proper care. Specially trained personnel are necessary for this transport. Some transport ambulances are equipped as small intensive care units, and carry respirators and laboratory equipment in order to provide immediate care for the critically ill newborn before starting the transfer to a special care unit. Thus, the constellation of advances that make up intensive care have been applied outside of the hospital.

Regionalization of care includes the transport of sick newborns to a special care unit from several participating hospitals in the area which are not capable of providing intensive care. Regionalization also includes the education of physicians, nurses and ancillary staff in recognizing the sick newborn and being able to care for some of the less ill neonates.

(10) <u>Transitional Care Nurseries</u>. The transitional nursery is usually located close to the labor-delivery suite. Infants born to high-risk mothers (toxemia, diabetes, drug addiction, fever, Caesarian section, Rh sensitization,

cardiovascular disease, etc.), infants of low birth weight (either preterm or small-for-date) and distressed infants (respiratory, shock, asphyxia) are admitted to this unit for stabilization and observation for no longer than 6-8 hours before transfer to the regular nursery or the intensive care unit. The transitional nursery is supplied with the necessary equipment to sustain the sick newborn, including monitors for heart rate, respiratory rate, temperature and other emergency equipment. The staff includes a specially trained pediatrician, registered nurses and aides. Laboratory and x-ray facilities are also available for this unit.

- (11) Phototherapy. Phototherapy is a new mode of therapy used to treat hyperbilirubinemia. It is especially applicable to sick or premature neonatal infants who are much more susceptible to bilirubin encephalopathy at lower levels of bilirubin than healthy full-term infants. In addition, hypoxia, acidosis and cold stress may increase this susceptibility as well as immaturity of the liver in metabolizing bilirubin. Phototherapy is also used in ABO incompatibility and postexchange for Rh incompatibility and appears to have decreased the number of exchange transfusions that may be required to lower serum bilirubin levels. The exposure to light of high intensity decreases the level of serum bilirubin. It is thought that the bilirubin is decreased by photooxidation which takes place mainly in the peripheral tissues. It may also promote hepatic excretion of unconjugated bilirubin. A decline of 1-4 mg percent of serum bilirubin can be expected in nonhemolytic jaundice after 8-12 hours of exposure. However, the potential long-term effects of exposing a substantial segment of our newborn population to this new mode of treatment has not been evaluated.
- (12) Fetal Electronic Monitoring. Fetal heart rate monitoring, including the analysis of beat-to-beat variation and its relationship to uterine contraction has become a very significant means of decreasing perinatal morbidity and mortality. It provides predictive information about the condition of the fetus during labor and influences the obstetrical management. The fetal monitor receives an electrical signal from the fetal heart by several different methods: from a microphone strapped to the maternal abdomen, from abdominal electrocardiographic electrodes, from an electrode applied transcervically to the presenting part, or from transabdominal ultrasound sensor. The fetal heart rate pattern is correlated with the uterine contractions recorded either directly by intraamniotic catheter or indirectly by an abdominal tocodynamometer. The following are evaluated: (1) Beat-to-beat variability in heart rate. The normal fetal heart rate shows variability or irregularity that reflects central nervous system control. A decrease in variability may reflect the effect of a drug as, for example, atropine, barbiturates, tranquilizers, or narcotics which were given to the mother in labor. (2) The heart rate. There are three types of decelerations (decrease in heart rate) that may occur during labor: (a) early deceleration begins with the uterine contraction and returns to the baseline heart rate at the end of contraction. This is interpreted to be due to fetal head compression. head compression results in a cardiac slowing which is probably mediated via the vagus nerve. It is not associated with an increase in fetal morbidity or mortality. (b) Late deceleration occurs after the beginning of contraction and ends after the contraction. This is thought to be due to utero-placental insufficiency resulting

in anoxia of the fetus. These patterns are often associated with changes in the acid-base status of the fetus and may result in neonatal depression. (c) Variable deceleration is slowing of the heart rate with no relationship to the onset of contractions. It is highly irregular and may be abrupt. This type of deceleration is thought to be due to intermittent compression of the umbilical cord between fetal parts and the contracting uterus. It may be mediated by the vagus nerve. If the deceleration is prolonged or associated with a decrease in beatto-beat variability, it can lead to anoxia. This is usually of short duration, benign and is often eliminated by change in the maternal position.

Another tool for examining the well-being of the fetus is the determination of the pre-ejection period of the cardiac cycle which represents the time from the onset of QRS complex to onset of ejection from the left ventricle. This can be measured from the ECG and Doppler ultrasound. It is related to the myocardial contractility and therefore is helpful in assessing the state of oxygenation of the fetal myocardium.

A new experimental method in fetal monitoring is the measuring of fetal respiration by recording fetal chest movements by ultrasound. Fetal chest movements occur at a frequency of 40-70/minute and are normally present for about 70 percent of the time during the last half of the gestation. Hypoxia and hypoglycemia are associated with a decrease in respiratory movements in the fetus and therefore this may be another sensitive method to detect fetal distress in utero.

- (13) Fetal Stress Tests. Contraction stress test or oxytocin challenge test is a measure of the fetal welfare and placental reserve before the onset of labor. It is done by monitoring the fetal heart rate changes by external monitors, either microphone or ultrasound transducers, for 30 minutes under simulated labor, either induced by pitocin stimulation or spontaneous contractions. A negative test shows a stable heart rate and, if indicated, may be repeated every seven days in high-risk pregnancies. A positive test shows repeated late decelerations and is associated with poor fetal well-being and tolerance of labor.
- (14) Erythroblastosis Fetalis or Rh Incompatibility. The prognosis of erythroblastosis fetalis has changed greatly in the last ten years as a result of the introduction of amniocentesis and evaluation of the bilirubinoid pigment in amniotic fluid by spectrophotometry, intrauterine transfusions, early induction of labor, exchange transfusions and aggressive intensive care of the newborn (mainly respiratory) and most recently the development of a method to prevent the disease. About 20 percent of fetuses were stillborn and 30 percent died in the neonatal period or were brain damaged. Now the perinatal mortality in those infants in whom the disease is not prevented has been reduced to about 5-10 percent.

An antibody titer is performed on each Rh negative mother during pregnancy (serially in the first sensitizing pregnancy) and if the titer is greater than 1:16, an amniocentesis (removal of fluid from the "bag of waters" surrounding the fetus) is done to analyze for bilirubin pigment in the amniotic fluid. This

bilirubin pigment has been identified as unconjugated bilirubin bound to albumin by spectral analysis. The spectral absorption of amniotic fluid is plotted on a semilogarithmic scale. In a normal pregnancy it was determined to be a straight line. If bilirubin is present there is a deviation at a specific wavelength (450 mu). The concentration of bilirubin is derived from the difference between the normal spectral curve and the spectral curve of the patient's amniotic fluid at this wavelength ( $\Delta$  OD 450). On the basis of several hundred pregnancies, values have been derived that correlate with the extent of sensitization. The initial amniocentesis in a first pregnancy is usually done at about 28-29 weeks gestation. In previously severely sensitized pregnancies it is done at 22-23 weeks gestation and repeated at 1-3 weekly intervals. Based on these results patients may be delivered spontaneously (where the risks of prematurity are less than the risks of the disease or other treatments) or patients may receive intrauterine transfusions. Intrauterine transfusions are performed by slowly injecting packed red cells compatible with the mother's blood into the fetal peritoneal cavity from where they are absorbed via the diaphragmatic lymphatics. Prior to the procedure, radio-opaque water soluble dye may be injected into the amniotic cavity to identify a hydropic fetus and to localize the placenta and the gastrointestinal tract on X-ray and fluoroscopy as a guide for proper needle placement. Intrauterine transfusion may be repeated every ten days until delivery. In recent years a method has been devised to prevent the disease in a fetus by preventing formation of the maternal antibody. This is done by destroying fetal cells which sensitize a mother to produce antibodies when they cross into her circulation.

- (15) Assessment of Fetal Lung Maturity. The lecithin/sphingomyelin ratio (L/S) is a measure of the relative proportion of two phospholipids manufactured in the lung of the fetus which may be detected in the amniotic fluid. Maturity of the fetal lung occurs at about 35-36 weeks gestational age and is demonstrated by a sudden increase in the lecithin fraction. When evaluation of lung maturity is desired in order to decide when to do Caesarian section or when to deliver an infant early for Rh incompatibility or maternal diabetes, an amniocentesis is done. The fluid is analyzed for the lecithin/sphingomyelin ratio by thin-layer chromatography. The concentration of lecithin is low and less than sphingomyelin until about 30-32 weeks of gestation when they become equal. Subsequently the lecithin concentration increases and sphingomyelin decreases. A mature L/S ratio is about 2 (depending on the laboratory). Lecithin is part of the surface active material necessary to lower the surface tension of the alveoli in the lung and prevent their collapse. The L/S ratio and lecithin and its precursors can be measured postnatally in tracheal fluid. If L/S ratio or lecithin or its precursors remain low when measured serially, the prognosis is very poor for the newborn regarding recovery from respiratory distress syndrome.
- (16) <u>Urinary Estriol</u>. Maternal urinary estriol is a measure used to evaluate the well-being of the fetus. This reflects the intactness of the fetoplacental unit. For this purpose the metabolism of estriol cannot be adequately studied in any animal. The human fetal adrenal gland synthesizes dehydroepiandrosterone (DHA). This is then hydroxylated by the fetal liver and then converted into estriol by the placenta and fetal liver. Most of the

estriol measured in the maternal urine (90 percent) is derived from the fetal DHA. The daily estriol excretion rises as normal gestation progresses and at term reaches values of 10-40 mg/24 hours in maternal urine. The measurements of estriol have to be done serially in the management of high-risk pregnancies. If consistently falling values are found (down to 2 mg/24 hours of maternal urine), this may indicate impending fetal death. There are other reasons for low estriol levels as for example small-for-gestational-age fetus, fetal hypo-adrenalism, ampicillin, phenobarbital. These do not require immediate intervention. Thus, in evaluating the fetus and deciding upon the management of pregnancy, estriol alone is not relied upon.

- (17) Betamethasone. Betamethasone, a glucocorticoid, if given to mothers in premature labor at gestational age of 28-32 weeks, may prevent the neonatal respiratory distress syndrome or hyaline membrane disease. It has been suggested that the betamethasone, given 24 hours prior to delivery, causes premature liberation of surfactant which is necessary to keep the alveoli of the lungs from collapsing. Betamethasone is thought to do this by inducing the enzyme concerned with synthesis and release of stored surfactant. In Dr. Liggin's uncontrolled series of pregnant women there was a drop from 25.8 percent to 9 percent in the development of respiratory distress syndrome in their infants and there were no deaths in this group of infants from respiratory distress syndrome. There may, however, be untoward effects in infants born to women who have toxemia. As stated, the betamethasone has to be given in two doses 24 hours prior to delivery in order to affect lung function. Because it is necessary to delay labor in these women for the desired effect, drugs such as alcohol (10 percent solution) and magnesium sulfate (1-2 gm/hour) have been used intravenously with success in a limited number of patients in order to allow time for the betamethasone to work. These drugs require further study in the fetus. More recently, adrenergic agonists such as orciprenaline and ritodrine have been used to inhibit uterine contractions experimentally in this country. These drugs seem to be more effective in stopping labor and may have very minimal effects on the fetus (slight increase in fetal heart rate).
- F. Potential Areas for Medical Advances Directly Related to the Care of Premature Infants Which May be Dependent in Part on Investigation of the Human Fetus and Premature Infant During the Next Decade. Attempts to predict future investigative needs are hazardous because of the nature of the way medical advances evolve (see page 12-13). No projections will be attempted in regard to the increasing number of suggested relationships between adult diseases and early development. However, there are at least four areas where research should be encouraged now because of the improvement that is likely to result in survival rates of premature infants and in the health and biologic potential of those infants who survive. Research on previable fetuses and premature human infants might play an important role in progress in these areas.
- (1) Prevention of Prematurity. This is dependent on research into the mechanisms that control the maintenance of pregnancy, its termination and labor. Five lines of investigation are involved: (1) the effects of normal and abnormal placental hormonal secretion during pregnancy; (2) the regulation of

the onset and progress of labor by new drugs; (3) the use of drugs to accelerate fetal maturity; (4) the development of new methods to estimate fetal maturity and weight; and (5) the application of technology to monitor the health of the fetus before birth more closely and accurately.

- (2) Prevention and Treatment of Birth Defects (Inborn Errors of Metabolism, Genetic Effects and Organ Malformations). At least two lines of investigation are emerging: (1) development of new and improved methods of early diagnosis; (2) research into regulation of early cell differentiation and the control of organ development during very early fetal life.
- Disease. Three lines of research are apparent: (1) investigation directed at improving the technology of artificial mechanical ventilation and aids to spontaneous respiration (increasing efficacy and decreasing risks); (2) the development of an artificial blood oxygenating system which can be used for prolonged periods (over weeks) in place of mechanical ventilation with respirators; (3) the investigation of measures to more closely and continuously monitor tissue oxygenation.
- (4) Evaluation of the Efficacy and Risks of Drugs in the Fetus and Premature Infant. This involves the study of drugs administered to pregnant women for appropriate medical indications, drugs approved for adults but not for fetuses or children that might be of benefit to the fetus or newborn infant; the evaluation of new pharmacologic agents developed for diseases peculiar to the fetus and newborn or of high incidence in this period of life; and studies of agents that may accelerate maturity of the respiratory system.

## 4. FORMULATION OF GUIDELINES FOR PHYSICIANS

A. <u>Viability and Nonviability</u>. A fetus or prematurely delivered infant is biologically viable when a minimal number of independently sustained, basic, integrative physiologic functions are present. In order for the fetus or infant to be viable the sum of these functions, considered together, must support the inference that the fetus or premature infant is able to increase in tissue mass (growth) and increase the number, complexity and coordination of basic physiologic functions (development) as a self-sustaining whole organism. This must be independent of any connection with the mother and when receiving only generally accepted medical treatments. If, in sum, these coordinated functions are not present, the fetus or prematurely born infant is biologically nonviable since it is incapable of being made able to exist as a self-sustaining whole organism independently of any connection with the mother. This may be the case even though some signs of life are apparent.

At this time (March 1975) the following functions taken together constitute the minimal number of basic integrative physiologic functions:

- The perfusion of tissues with adequate oxygen and the prevention of the increasing accumulation of carbon dioxide and/or lactic and other organic acids. This function consists of these components:
  - Inflation of the lungs with oxygen
  - Transfer of oxygen across the alveolar membranes into the circulation and the elimination of carbon dioxide from the circulation into the expired gas
  - Cardiac contractions of sufficient strength and regularity to distribute oxygenated blood to tissues and organs throughout the body and to eliminate organic acids from those tissues and organs.
- Neurologic regulation of the components of the cardiorespiratory perfusion function, of the capacity to ingest nutrients, and of spontaneous and reflex muscle movements.

The foregoing minimal basic integrative physiologic functions cannot at present be separately assessed in the fetus or prematurely delivered infant in a consistent, reliable and exact manner. The absence of the sum of these minimal functions, however, can be assessed indirectly in a reasonable and reliable manner by measurement of weight and/or an estimation of gestational age, since specific weights and gestational ages correlate with a lack of potential for subsequent sustained extrauterine growth and development (survival). In this biologic sense, fetuses or prematurely delivered infants of less than 601 grams and/or of 24 weeks or less gestational age, may be considered nonviable. At these weights and gestational ages signs of life such as a beating heart, spontaneous respiratory movement, pulsation of the umbilical cord and spontaneous movement of voluntary muscles are not adequate in themselves to be used to determine the existence of these minimal basic integrative functions, e.g., the heart may continue to beat for as long as 30 minutes after removal from the body.

In addition, regardless of weight and gestational age, the minimal number of basic integrative physiologic functions to sustain subsequent extrauterine growth and development (survival) are not present in fetuses or prematurely delivered infants with:

- Severe malformations of the central nervous system, such as anencephaly
- 2. Severe grotesque multiple system malformations, such as cyclops
- Severe fetal asphyxia or anoxia when there has been no response to manual resuscitation according to the existing medical practice.

In contrast, a weight of 601 grams or more and gestational age of 25 weeks or more may indicate that the minimal number of basic integrative physiologic

functions necessary for independent growth and development is present. Such a fetus or prematurely delivered infant may be considered biologically viable. At these weights and gestational ages a sign of life such as a beating heart, spontaneous respiratory movement, pulsations of the umbilical cord or spontaneous movement of voluntary muscles should be present to confirm that the minimal number of basic integrative physiologic functions necessary for survival exist.

- B. Fetal and Premature Infant Death. Fetal death or the death of a prematurely delivered infant, who has been determined to be viable, is judged to have occurred when there is a cessation of the minimal basic, independent integrative physiologic functions which, considered together, may result in sustained extrauterine growth and development or survival. The absence of all of the following indicates the cessation of these minimal basic independent integrative physiologic functions:
  - 1. A heart beat
  - 2. Spontaneous respiratory movements
  - 3. Spontaneous movement of voluntary muscles
  - 4. Pulsation of the umbilical cord.

When a prematurely delivered infant is being artificially ventilated, the absence of all of the above physical signs may no longer be reliable as an index of the cessation of the minimal basic integrative physiologic functions. these circumstances, the presence of two flat electroencephalograms obtained 24 hours apart when the infant is not receiving central nervous system depressants should also be used to indicate a cessation of the minimal number of basic integrative physiologic functions necessary for independent growth and development which characterize biologic life for the fetus and prematurely delivered infant. The technique of obtaining an electroencephalogram is difficult to apply to premature infants because of the low voltages generated and other technical problems, the limited sensitivity of the instruments, the nature of the electrical patterns from the immature cortex and the very small number of premature infants that have been tested. There are few adequate published reports and these do not provide precise details about weights and gestational ages in relation to EEG patterns. Nevertheless, the above EEG test for determining death of an infant on a ventilator is, in the judgment of all of the consultants, the best that can presently be formulated. The special problems of recording from the fetus in utero and the almost total lack of experience with preterm fetuses preclude the use of the electroencephalogram to determine the death of a fetus in utero.

C. Options and Their Implications for Premature Infants. Three general approaches to this problem can be delineated. First, the fetus could be defined as a person from the moment of conception and the fetal interests or individual rights allowed to override the interests of all other individuals and society. Since the fetus would not be physically capable of consenting, there could be no human fetal research. Second, the fetus could be defined as part of the mother's body until the moment of birth and the mother's interests or individual rights allowed to override all other individual rights or interests of the society as

long as she consented. Fetal research at any stage, thus, would present few moral problems. Biologic facts could be marshalled for and against both propositions but could not prove either extreme position. However, to accept either extreme or some minor variation of one of these positions involves some risks for society. DeTocqueville has cautioned that "Human institutions are so imperfect by nature that in order to destroy them, it is almost always enough to extend their underlying ideas to the extreme."

The third approach is to use the idea of viability as a mechanism for achieving an optimum balance between the interests of the several involved individuals and society. Such a solution should be based on a reasonable interpretation of biologic facts and should minimize the conflicts between the more important social interests and activities which are at stake.

For the viable fetus or premature infant, as for the adult, human investigation is presently considered unethical by the medical profession unless: (1) the potential therapeutic benefit for the individual is reasonably judged to outweigh the risks or if there is no potential therapeutic benefit, then the potential benefit for society is large and the likely risks to the individual judged to be small or inconsequential, and (2) the individual or a valid surrogate consent after receiving adequate information and explanation. A competent adult may take considerable personal risks even for no therapeutic benefit in the name of a greater social good. In the case of an incompetent adult or a child for whom a surrogate is designated to make the judgment, a de facto fiduciary relationship exists. When there is a potential therapeutic benefit for the individual, even though remote, the surrogate, usually a relative, may make decisions (including decisions which objectively are poor decisions) which can have untoward consequences for the patient, their family and society. In our opinion, if a surrogate is permitted to make a decision when there is no potential therapeutic benefit, the risks should be very small or inconsequential and the potential benefit to the class, of which the subject is a member, potentially very large.

There are three major additional interrelated issues involved when considering the nonviable fetus:

- The delineation of a weight and/or gestational age below which the probability of survival is so small as to be judged to be essentially nonexistant (when weight is used as an index of the presence of adequate independent coordinated functions for a whole organism to survive)
- 2. Provision for the situation where the improbable occurs and an unintended viable weight premature infant is born either because of the errors implicit in estimating probability of survival from gestational age determined before birth, or because of advances in the care of premature infants that improve chances of survival at lower weights
- 3. The potential consequences of these decisions for the health of other infants and children of future generations.

In general, the lower the prenatal gestational age cutoff for viability before birth and the higher the weight cutoff for viability after birth, the less likely is the chance of a discrepancy between prenatal prediction and postnatal reality. For example, if nontherapeutic research is only permitted on a fetus or premature of 23 weeks or less gestational age estimated by ultrasound head measurements, and an eleven chance in a million of survival is judged to be the equivalent of no survival (a weight of less than 751 grams), there is little risk of a fetus judged to be nonviable by gestational age turning out to be viable weight after birth. However, there is still the possibility of such an infant surviving and two years from now the probability of survival of a 751-gram premature infant might be as good as the chances of survival of a 1001-gram infant today. If this were to happen, the postnatal level of viability of a 751-gram infant would clearly be set too low and would need to be readjusted.

Alternatively, if research is only permitted on a fetus of 22 weeks or less gestational age estimated prenatally by ultrasound, and zero chance of survival in 1 million (less than 60l grams) is defined as the weight level of viability, there is very little, if any, risk of a fetus judged to be nonviable before birth turning out to be of a viable weight after birth. The need to readjust the weight level of viability within two years is much less likely. However, progress in clinical measures directed at improving survival and the quality of survival in heavier premature infants (those above 600 grams) might be impeded by not having the potential benefit of these measures being tried out first on abortuses who could not have survived. It is likely that the first application of some potential advance for human infants first will have to be tested on some sick infants who have a real chance of survival without the innovations. This means a certain number of premature infants are likely to be harmed or not survive who might have survived or not been injured if the new treatment had been studied on a fetus of 22-24 weeks gestation or an infant of less than 60l grams.

Finally, whatever the gestational age and weight cutoffs for viability, there is always a chance in the future that a viable infant by weight will be born after a prediction of nonviability by gestational age. When this occurs, the premature infant clearly must be cared for in accord with accepted medical care practice. For example, a mother who wants and is legally entitled to an abortion at 24 weeks gestation should be informed of the possibility of fetal survival before the abortion and either she must accept the responsibility for a liveborn viable infant or make arrangements for placement or adoption. Further, the physician should be protected from civil liability to the pregnant woman on whom the abortion is performed for unintentially delivering her of a liveborn viable premature infant.

In summary, the following might be considered as a reasonable way of proceeding in terms of the biologic facts and should be taken into consideration in formulating public policy.

1. Before birth, permit research on a fetus of estimated gestational age of 23 weeks or less.

- 2. After birth, permit research on a product of conception of less than 601 grams and 24 weeks or less gestational age by physical examination.
- 3. Set up an administrative mechanism to review No. 1 and No. 2 at regular yearly intervals.
- 4. State that a physician performing an abortion at 24 weeks should inform the pregnant woman that there is a chance of a survival of the abortus and that, if it is born at a viable weight and gestational age, it will be resuscitated. In this instance, protect the physician from a civil cause of action by the pregnant woman for delivery of a viable infant she did not want.

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APPENDIX A

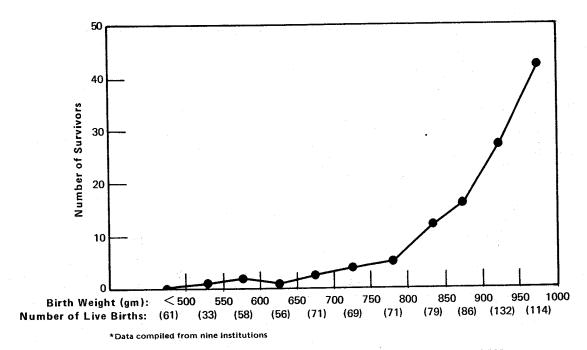
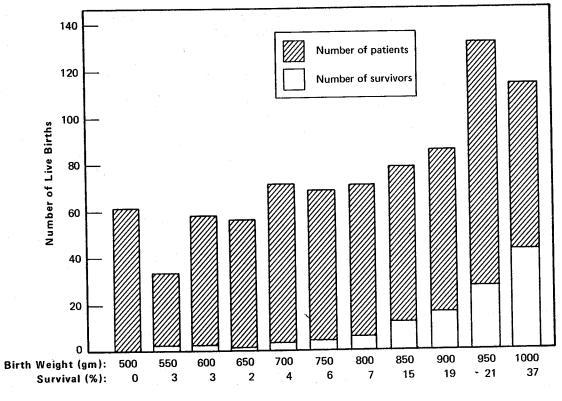
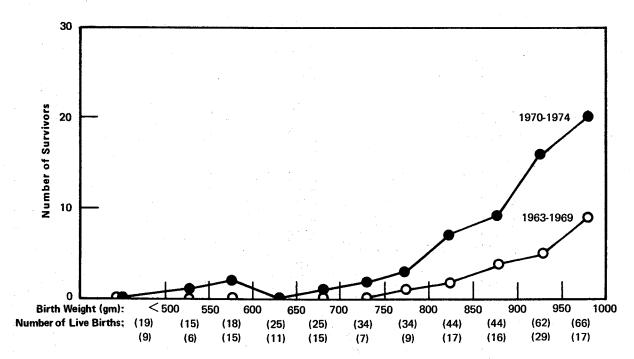


Figure 1. Number of Neonatal Survivors by Birth Weight during Years 1963-1974\*



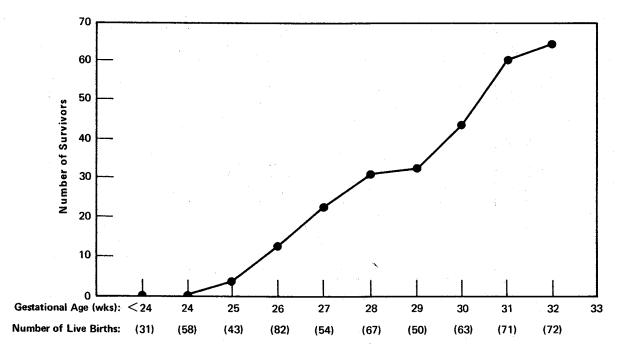
\*Data compiled from nine institutions

Figure 2. Total Number of Survivors by Birth Weight as a Fraction of the Total Number of Live Births\*



<sup>\*</sup>Data compiled from several institutions.

Figure 3. Comparison of Number of Survivors by Birth Weight during Years 1963-1969 and 1970-1971\*



\*Royal Victoria Hospital, University of Colorado, University of California at San Francisco

Figure 4. Neonatal Survival Rate by Gestational Age, 1964-1974\*

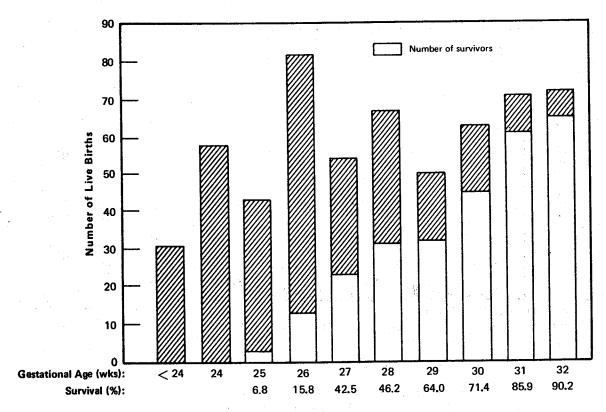
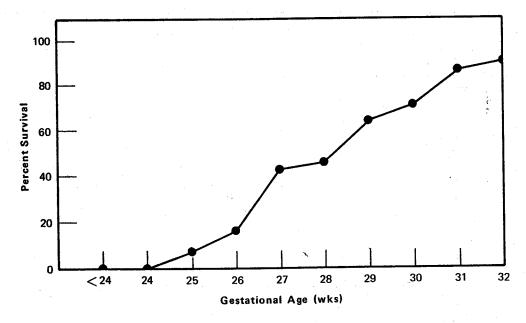
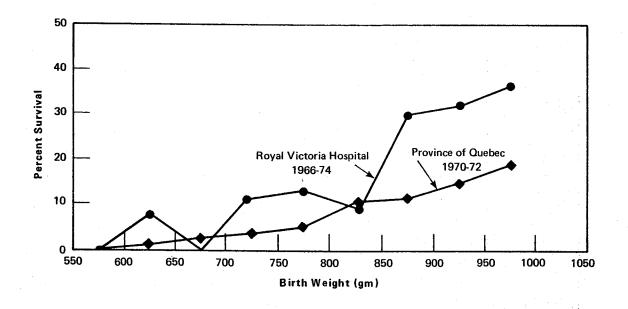


Figure 5. Neonatal Survival Rate by Gestational Age, 1964-1974



<sup>\*</sup>Royal Victoria Hospital, Montreal University of Colorado, Denver University of California, San Francisco

Figure 6. Neonatal Survival Rate by Gestational Age, 1964-1974\*



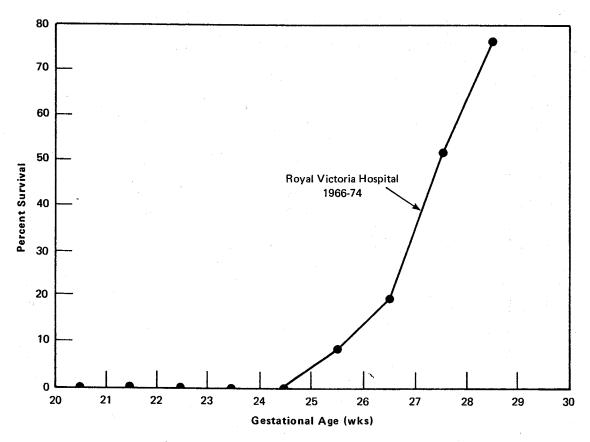


Figure 7. Survival Rates at the Borderline of Viability

	1954-1962	1963-1967	1968-1971	1972	1973
Total Deliveries*	33,736	22,260	16,057	3,339	3,089
Average Deliveries/Yr.*	4,217	4,442	4,014	3,339	3,089
Still Births*	10.5/M	11.6/M	10.8/M	10.2/M	12.6/M
Neonatal Deaths*	12.9/M	10.7/M	10.7/M	9.3/M	6.8/M
Perinatal Mortality*	23.3/M	22.3/M	21.5/M	19.5/M	19.4/M
	Acid-Base 0%	Acid-Base 5%	Acid-Base 10%	Acid-Base 10%	Acid-Base 25%
Monitoring	Heart Rate 0%	Heart Rate 0%	Heart Rate 5%	Heart Rate 10%	Heart Rate 52%

<sup>\*</sup>Over 1000 gms.

Figure 8. General Statistics — Presbyterian Hospital

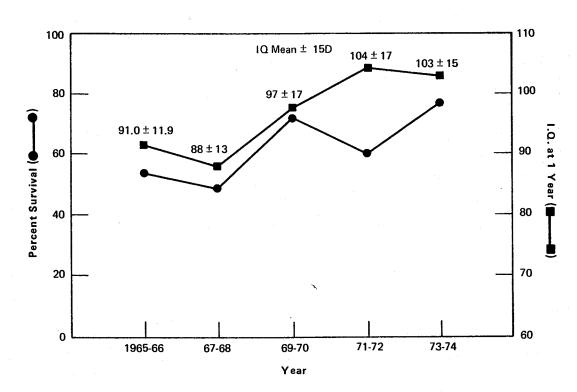


Figure 9. Infants Born at the University of California at San Francisco 1965-1974
Birth Weight 750-1500 Grams

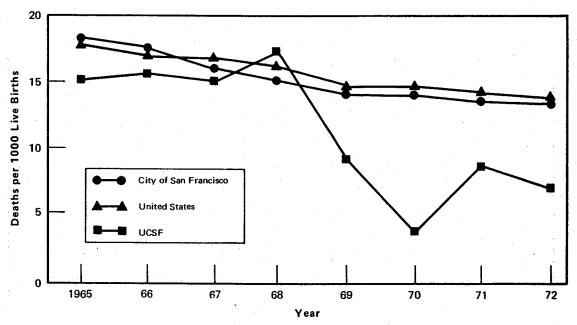
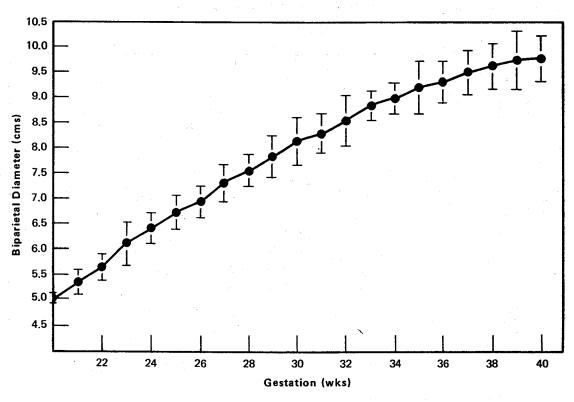


Figure 10. Neonatal Mortality for University of California at San Francisco, City of San Francisco, and the United States



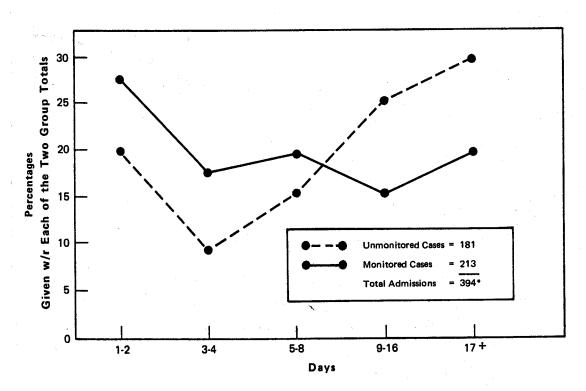
From Campbell, J. Obstet. Gynaec. Brit. Cwith. 76:603, 1969.

Figure 11. Mean fetal biparietal diameter values + or - 2 standard deviations for each week of gestation during the second half of normal pregnancy in 186 patients whose gestation was known (471 individual measurements)

	Period 1* 1960	Period 2 September-December 1972	Period 3 1973
Number of Deliveries	566	1135	3092
1 Minute Apgar <b>≤</b> 6	24.6%	13.1%	12.3%
5 Minute Apgar ≤6	4.5%	3.3%	3.4%
Monitoring	Acid-Base 0% Heart Rate 0%	Acid-Base 13% Heart Rate 25%	Acid-Base 35% Heart Rate 52%

<sup>\*</sup>Data from the Collaborative Project — Presbyterian Hospital Patients only -- Similar incidence found in combined data from 12 Centers and 37,000 Patients.

Figure 12. Apgar Scores at 1 & 5 Minutes



<sup>\*</sup>All admissions with Birth Weight  $\geq$  1000 gms included.

Figure 13. Distribution of Length of Stay in Intensive Care Unit Presbyterian Hospital September 1972-December 1973

Monitored Ele	ctronically	Unmonitored				
Duration o	of Stay	Duration	of Stay			
8 Days or less	9 Days or more 8 Days or less		9 Days or more			
80%	20%	60%	40%			
Mean Duratio	n of Stay	Mean Duration of Stay				
6 Days	5	10 Days				

Figure 14. Intensive Care Unit Recovery Time Requirements

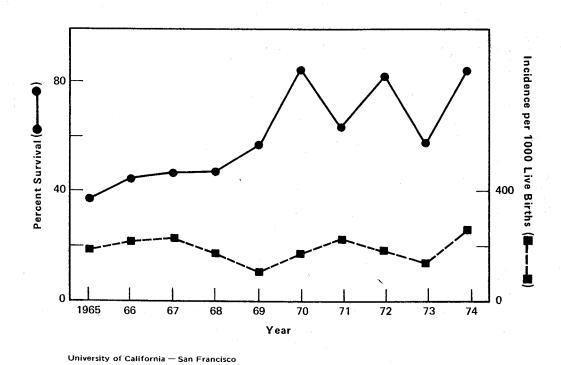


Figure 15. Incidence of Respiratory Distress Syndrome per 1000 Live Births With Birth Weight 750-2500 Grams, and Percent Survival Rate

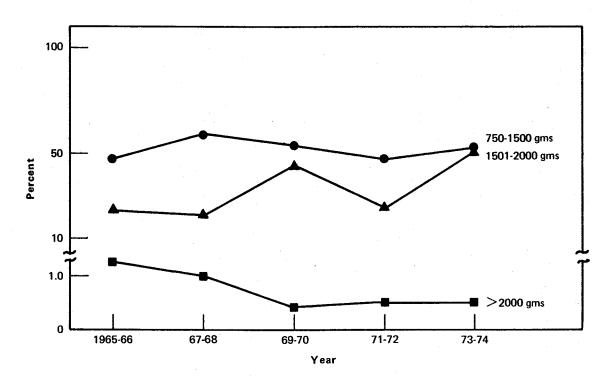


Figure 16. Respiratory Distress Syndrome, Progressive Neonatal Atelectasis Incidence
University of California at San Francisco

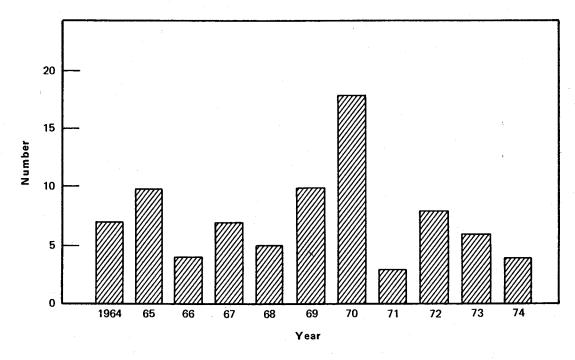


Figure 17. Approximate Number of Improvements in Medical Technology

	Evaluation									
	Evaluation	24	28	30	32	34	36	38	40	
	circumference cm ± 2 SD		23-28.3	25-30.4	23.8- 32.4	28.6-34	30.5- 35.5	32-36.5	33-37	Based on 300 single live births -all Caucasian
	Sole creases		Anterior transverse crease only						Sole covered with creases	
-1	Breast nodule diameter		Not palpable—absent				2 mm	4 mm	7 mm	If small may represent fetal mainutrition
CLINICAL	Scalp hair		Fine and fuzzy  Hard to distinguish individual				trands	Coarse and silky  Appear as individual strands		
S	Ear lobe		Pliableno cartilage				Some cartilage Stiffened by thick cartilage			
!	Testes and scrotum		Testes in lower canal Scrotum small — few rugae				Intermediat		dulous, scrotum ive rugae	

From Behrman, R. E., Fisher, D., Paton, J. B., and Keller, J.: In utero disease and the newborn infant. In Schulman, I., editor: Advances in pediatrics, vol. 17, Chicago. Copyright © 1970 by Year Book Medical Publishers. Used by permission. (Adapted from Amiel-Tison, Brett, Koenigsbergh, and Usher.)

Figure 18. Estimation of Gestational Age

AGE IN WEEK	S 24	28	32	34	36	40	
Traction			flexio	n of arms	always present		
Grasp	<del></del>	finger grasp	fully developed reflex	stronger	onger can be lifted off be		
Posture	frog-like p	osition					
	limbs extended	limbs	flexion of legs	stronger	flexion of all	limbs	
'	and rolls	extended		flexion of			
	onto side			legs			
Neck righting				trunk follows	rotation of h	ead	
Tone: Recoil	hypotonic	hypotonic	slow recoil	good recoil	slow recoil	good recoil	
			in legs	in arms	in arms	in arms	
Head		pendular	some attempt	still lags	initial lag	good tone	
Lag		head	to flex head	but less	then sudden		
_					flex	righting	
Ventral	floppy	floppy	some flexion	increased flexic	on of legs &	good flexior	
Susp.				arms	of legs &		
			_			arms	
Moro	<u></u>	complete	complete				
		but easily					
		exhausted					
Pupil React.			present at				
			29 weeks				
Glabella Tap			blink				
Suck	present but weak	·	]	synchronized			
present but weak			au only	with swallowing			
Head turning					•		
to light			present				
Walking		feeble	slow on toes	easier	easier	easy on hee	

Figure 19. Neurologic Development Related to Gestational Age



Table 1. Variation in Gestational Ages at Different Weights\*

Birth Weight in Grams	Estimated Weeks of Gestation
Under 500	22-28
501-750	22-30
751-1000	23-32
1001-1250	26–34
1251-1500	26-35
1501-1750	28-36
1751-2000	28-37
2001-2250	29-37
2251-2500	30-40
2501-2750	32-
2751-3000	33-
3001-3250	34-
3251-3500	

<sup>\*</sup>Based on data from University of California (San Francisco), University of Colorado, and The Johns Hopkins University

Table 2. Variation in Weight at Different Gestational Ages\*

Estimated Weeks of Gestation	Recorded Birth Weights in Grams
22	460-600
23	550-950
24	500-850
25	600-1000
26	400-925
27	630-1050
28	680-1000

<sup>\*</sup>Based on data from University of California (San Francisco), and University of Colorado

Table 3. Neonatal Survival Rate in New York City by Weight at Birth and Race — 1962-1971

1970	1971
20.0	21.0
18.7	12.7
21.2	28.2
66.6	66.2
61.6	57.2
71.5	75.2
90.0	90.8
86.9	87.1
93.7	94.2
97.7	97.5
97.3	96.8
98.3	98.4
88.5	89.1
88.5	88.2
88.4	90.2
	18.7 21.2 66.6 61.6 71.5 90.0 86.9 93.7 97.7 97.3 98.3 88.5 88.5

Table 4. City of New York Permature Center Statistics Survival Percentages (by Weight) 1963
Total All Centers

			White								
Weight Group	Born In	No. Survived	% Survival	Born Out	No. Survived	% Survival					
Under 500 gms.	30	0	0	1	0	0					
501-750 gms.	44	5	11.4	19	1	5.3					
751-1000 gms.	82	22	26.8	43	20	46.5					
1001-1250 gms.	81	42	51.8	90	49	54.4					
1251-1500 gms.	123	80	65	158	125	79.1					
1501-1750 gms.	173	139	80.3	193	174	91.1					
1751-2000 gms.	284	256	90.1	236	222	94.1					
2001-2500 gms.	1479	1443	97.5	96	85	88.5					
TOTALS	2296	1986	86.5	836	676	80.9					
,	Nonwhite										
Under 500 gms.	98	0	0	3	0	0					
501-750 gms.	98	3	3.1	20	1	5					
751-1000 gms.	127	29	22.8	38	22	57.9					
1001-1250 gms.	142	75	52.8	80	54	67.5					
1251-1500 gms.	174	140	80.5	116	96	82.8					
1501-1750 gms.	283	253	89.4	153	139	90.8					
1751-2000 gms.	441	423	95.9	200	192	96					
2001-2500 gms.	1795	1339	99.1	97	93	95.9					
TOTALS	3158	2702	85.6	707	<u>===</u> 597	84.4					
TOTALS	3158	2/02	85.0	707	097	04.4					
		Whit	e and Nonwhite	)							
Under 500 gms.	128	0	0	5	0	0					
501-750 gms.	142	8	5.6	38	2	5.3					
751-1000 gms.	209	51	24.4	81	42	51.8					
1001-1250 gms.	223	117	52.5	170	103	60.6					
1251-1500 gms.	297	220	74.1	274	221	80.6					
1501-1750 gms.	456	392	86	346	313	90.5					
1751-2000 gms.	725	679	93.6	436	414	95					
2001-2500 gms.	3274	3222	98.4	193	178	92.2					
TOTALS	5454	4689	86	1543	1273	82.5					

	White						Nonwhite					
Hospital	Dawn In	Sur	rvival	Danie Out	Sur	vival	B 1-	Survival		Born Out	Survival	
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	1	0	0	_	_		1	0	0	_	-	_
Bellevue	_	-		_	-	_	2	0	0	_	-	_
Bronx	7	0	0	_	_	_	3	0	0	_	-	
Elmhurst	1	0	0	_	_	_	8	0	0		-	_
Flushing	_	_	_	_	_	_		_		-	-	-
Harlem	1	0	0	_	_		15	0	0	–	-	_
Jewish Brooklyn	_	_	_	_	_	_		_	_	. —	-	
Kings County	4	0	0	1	0	0	54	0	0	2	0	0
Lincoln	4	0	0	_	1 –		4	0	0	1	0	0
L. I. Jewish	1	0	0		1 - 1		_	-	_		-	_
Mt. Sinai	5	0	0	1 –	_	_	1	0	0		-	_
New York	2	0	0	_			2	0	0	<b>–</b>	-	. <b>–</b>
Queens Gen.	l –	_	<b> </b>	_	_		6	0	0	_	-	-
St. Vincent's (NY)	1	0	0	l. –	l .— i	-	_	_	_		-	
St. Vincent's (SI)	3	O	Ŏ	_	<u> </u>	_	2	0	0	_	-	<b>—</b> .
TOTALS	30	0	0	=	0	0	98	0	0	3	<u> </u>	0

Table 4 (Continued)
Survival Rate (501-750 grams)

•			w	hite	***			-	Nor	white		
Hospital		Sur	vival		Sur	vival		Sur	vival	D 0 4	Sur	vival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	5	0	0	2	1	50	5	0	0	_	_	-
Bellevue	4	0	0	2	0	0	1	0	0	_	-	_
Bronx	4	0	0	_	_	_	. 5	1	20		-	
Elmhurst	4	0	0	1	0	0	6	0	0	_	-	-
Flushing		_	_	. 1	0	0	_			1	0	0
Harlem	2	0	.0	_	_	-	17	1	5.9		-	η-
Jewish Brooklyn	_		_	3	0	0	2	0	0	3	0	0
Kings County	2	0	0	2	0	0	47	0	Ö	7	0	0
Lincoln	7	5	70.3	_			6	1	16.7	_	-	_
L. I. Jewish	- 1	0	0	2	0	0	_	_	<b>—</b> 1	_	-	_
Mt. Sinai	7	0	0	4	0	0	2	. 0	0	4	0	0
New York	3	0	0	2	0	0	. 1	0	0	2	1	50
Queens Gen.	1	0	0	_	_	_	4	0	0	2	0	- 0
St. Vincent's (NY)	_	_	_	_	-	_		_	_	_	-	_
St. Vincent's (SI)	4	0	0	=	=		2	<u> </u>	0	1 ==		0
TOTALS	44	5	11.4	19	1	5.3	98	3	3.1	20	1	5

			W	hite					Non	white		
Hospital		Sur	vival		Sur	vival	D (	Sur	vival	Born Out	Sur	vival
	Born In	No.	%	Born Out	No.	· %	Born In	No.	%	Born Out	No.	%
Babies	11	. 1	9.1	10	2	20	7	0	0	4	2	50
Bellevue	7	1	14.3	4	1	25	. 5	1	20	2	1	50
Bronx	7	4	57.1	1	1	100	9	2	22.2	2	1	50
Elmhurst	5	0	0	3	1	33.3	5	0	0	3	2	66.7
Flushing	10	2	20	2	0	0	_	_	_	2	0	0
Harlem		_		_	-		26	3	11.5	2	1	50
Jewish Brooklyn	.4	1	25	5	2	40	5	2	40	5	2	40
Kings County	5	1	20	1	0	0	40	8	20	_	-	-
Lincoln	9	8	88.9	3	3	10Q	9	5	56.6	1	0	0
L. I. Jewish	2	0	0	5	1	20	-	_	-	1	1	-
Mt. Sinai	2	0	-0	6	5	83.3	2	1	50	2	1	50
New York	8	1	12.5	2	2	100	1	1	100	4	4	100
Queens Gen.	2	1	50		_	_	16	6	37.5	1 .	1	100
St. Vincent's (NY)	9	2	22.2	1	0	0	. 1	0	0	6	4	66.7
St. Vincent's (SI)	1	0	0	_	_	_	1	0	0	3	2	66.7
	=	==		=	=		=	=	===		=	
TOTALS	82	18	26.8	43	20	46.5	127	29	22.8	38	22	57.8

Table 4 (Continued)
Survival Rate (1001-1250 grams)

			W	hite					Nor	white		
Hospital	D	Sur	vival	D 0 .	Sur	vival		Sur	vival	D O .4	Sur	vival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	10	6	60	8	5	62.5	8	6	75	11	5	45.5
Bellevue	7	4	57.1	5	3	60	2	2	100	3	2	66.7
Bronx	2	0	0	-3	1	33.3	6	3	50	4	4	100
Elmhurst	2	1	50	9	4	44.4	4	0	0	8	6	75
Flushing	_ :	_	_	4	0	0	1	1	100		_	_
Harlem	1	0	0	_	-		35	19	54.3	_	_	
Jewish Brooklyn	4	3	75	5	1	20	7	5	71.4	7	4	57.1
Kings County	4	2	50	12	8	66.7	44	23	52.3	7	- 4	57.1
Lincoln	15	7	46.7	4	0	0	19	10	52.6	-	_	
L. I. Jewish	4	2	50	14	10	71.4	-	_	_	10	7	70
Mt. Sinai	8	6	75	9	3	33.3	1	0	0	5	5	100
New York	10	6	60	6	5	83.3	2	1	50	6	4	66.7
Queens Gen.	3	1	33.3	_	_	_	13	5	38.5	4	3	75
St. Vincent's (NY)	8	2	25	8	6	75	_	-	-	5	3	60
St. Vincent's (SI)	3	2	66.7	3	3	100	_	-	-	10	7	70
	==	=	===	_			=	=	===	<b>=</b>	=	
TOTALS	81	42	51.8	90	49	54.4	142	75	52.8	80	54	67.5

			W	hite					Nor	white		
Hospital	D 1	Sur	vival	D. O.	Sur	vival		Sur	vival	D O4	Sui	vival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	7	3	42.9	11	7	63.6	8	7	87.5	9	8	88.9
Bellevue	1.0	3	30	8	6	75	6	5	83.3	6	6	100
Bronx	11	8	72.7	9	8	88.9	2	2	100	4	3	75
Elmhurst	9	7	77.8	10	8	80	3	1	33.3	5	4	80
Flushing	9	.6	66.7	16	13	81.2	2	2	100	4	3	75
Harlem	_	_	_	5	5	100	24	21	87.5	2	2	100
Jewish Brooklyn	6	4	66.7	19	17	89.5	8	7	87.5	19	18	94.7
Kings County	5	3	60	3	2	66.7	62	46	74.2	6	3	50
Lincoln	17	15	88.2	1	1	100	28	26	92.8	2	2	100
L. I. Jewish	5	3	60	24	19	79.2	_ :	_	_	8	7	87.9
Mt. Sinai	20	12	60	15	12	80	4	3	75	9	8	88.9
New York	12	8	66.7	7	4	57.1	7	5	71.4	7	- 7	100
Queens Gen.	2	2	100	6	5	83.3	19	14	73.7	5	4	80
St. Vincent's (NY)	7	5	71.4	16	11	68.7	_	_	_	17	11	64.
St. Vincent's (SI)	3	1	33.1	8	7	87.5	1	1	100	13	10	76.9
		=	===	<b>=</b>	=	===	==	=		===		==
TOTALS	123	80	65.0	158	125	79.1	174	140	80.5	116	96	82.

Table 5. City of New York Premature Center Statistics Survival Percentages (by Weight) 1964
Total All Centers

			White			
Weight Group	Born In	No. Survived	% Survival	Born Out	No. Survived	% Survival
Under 500 gms. 501-750 gms. 751-1000 gms. 1001-1250 gms. 1251-1500 gms. 1501-1750 gms. 1751-2000 gms. 2001-2500 gms.	35 56 73 89 121 189 317 1325	0 9 14 39 87 157 287 1281	0 16.1 19.2 43.8 71.9 83.1 90.5 96.7	2 8 43 82 144 227 245 68	0 1 16 58 116 200 221 63	0 12.5 37.2 70.7 80.6 88.1 90.2 92.6 82.4
TOTALS	2205	1874	Nonwhite			
Under 500 gms. 501-750 gms. 751-1000 gms. 1001-1250 gms. 1251-1500 gms. 1501-1750 gms. 1751-2000 gms. 2001-2500 gms.	144 118 129 131 224 286 433 1721 3186	0 8 37 71 170 248 409 1701	0 6.8 28.7 54.2 75.9 86.7 94.5 98.8	5 22 37 79 124 175 166 104	0 3 16 56 114 166 162 97	0 3.6 43.2 70.9 91.9 94.9 97.6 93.3 86.2
		Whit	te and Nonwhite	9		<del></del>
Under 500 gms. 501-750 gms. 751-1000 gms. 1001-1250 gms. 1251-1500 gms. 1501-1750 gms. 1751-2000 gms. 2001-2500 gms.	179 174 202 220 345 475 750 3046 5391	0 17 51 110 257 405 696 2982	0 9.8 25.2 50 74.5 85.3 92.8 97.9 83.8	7 29 80 161 268 402 411 172 1530	0 3 32 114 230 366 383 160	0 10.3 40 70.8 85.8 91 93.2 93 84.2

			W	hite					Non	white		
Hospital		Sur	vival		Sur	vival		Sur	vival	Born Out	Sur	vival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	BOIN Out	No.	%
Babies	2	0	0		_	_	1	0	0	_	-	_
Bellevue	4	o	Ō	_	_	_	1	0	0	-	-	· . —
Bronx	6	ō	Ö	_	_		12	0	0	_	-	. —
Elmhurst	4	ŏ	Ō	_	_	_	3	0	0	_	-	. –
Flushing		_	_	_	_		_	-	-	-	-	_
Harlem	_	_	_	_	-	_	26	0	0	_	-	_
Jewish Brooklyn	_	_	_	_	-		<b>\</b> -	-	_	-	_	_
Kings County	2	0	0	_	_	<u> </u>	78	0	0	4	0	0
Lincoln	12	0	0	_	-	_	14	0	0	-	-	_
L. I. Jewish	-	_		_	-	_	_	-		_	-	-
Mt. Sinai	_	_	_	_		-	1	0	0	-	-	-
New York	1	0	0	_	I –	_	1	0	0	_	0	0
Queens Gen.	1	0	0	_	-	-	5	0	0	T	U	U
St. Vincent's (NY)	3	0	0	1	0	0		-	_	_	-	
St. Vincent's (SI)	-			1	0	0	2	0	0			
TOTALS	35	0	0	2	0	0	144	0	0	5	0	0

Table 5 (Continued)
Survival Rate (501-750 grams)

			W	hite					Non	white		
Hospital		Sur	vival		Sui	vival	_	Sur	vival	_	Sur	vival
,	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	. 1	0	0	1	0	0	7	- 1	14.3	2	0	0
Bellevue	5	0	0	1	1	100	4	0	0	3	0	0
Bronx	7	0	0	_	_	- '	6	0	0	_	_	
Elmhurst	1	0	0	_ `	_		1	0	0	1 1	0	0
Flushing	3	0	0	_	_		_	-	_	_	_	. —
Harlem		_	-	_	-		25	0	0	-		_
Jewish Brooklyn	4	1	25	2	0	0	3	0	0	2	0	0
Kings County	2	0	0	_	_	<b> </b>	47	0	0	2	0	0
Lincoln	17	8	47.1	_	-	-	11	6	54.5	2	1	50
L. I. Jewish	2	0	0		_	-	_	_	-	2	0	0
Mt. Sinai	1	0	0	1	0	0	1	0	0	_	_	_
New York	8	0	0	2	0	0	- 3	0	0	2	0	0
Queens Gen.	2	0	0			-	.9	1	11.1	4	0	0
St. Vincent's (NY)	1	0	0	1	0	0	-	-	_	1.	1	100
St. Vincent's (SI)	2	0	0	-	-	-	1 .	0	0	_	-	-
	=	=		==	=	===	=	=	===		=	=
TOTALS	56	9	16.1	. 8	1	12.5	118	8	6.8	21	2	9

			W	hite					Non	white		
Hospital		Sur	vival		Sur	vival		Sur	vival		Sur	vival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	9	1	11.1	6	3	50	6	1	16.7	3	1	33.3
Bellevue	9	3	33.4	3	0	0	2	0	0	1	0	0
Bronx	9	0	0		_	-	12	3	25	1	0	0
Elmhurst	4	0	0	3	0	0	6	0	0	5	2	40
Flushing	5	1	20	5	3	60	1	1	100	1	0	0
Harlem	_	-	_	_	_	_	24	7	29.2	4	3	75
Jewish Brooklyn	4	1	25	4	4	100	6	4	66.7	2	1	50
Kings County	_	_	-		-		38	8	21.1	3	1	33.3
Lincoln	8	4	50	_	_	<u>-</u>	10	7	70	2	2	100
L. I. Jewish	_	_	-	7	1	14.3	-	_	-	3	2	66.7
Mt. Sinai	13	2	15.4	2	1	50	4	2	50	2	1	50
New York	4	2	50	5	0	0	2	0	0	1	0	0
Queens Gen.	1	0	0	1	0	0	-12	2	16.7	2	0	0
St. Vincent's (NY)	3	0	0	6	4	67	4	2	50	4	1	25
St. Vincent's (SI)	4	0	0	1	0	0	2	0	0	3	2	66.
	_	=	=		==		==	=	==	==	=	
TOTALS	73	14	19.2	43	16	37.2	129	37	28.7	37	16	43.

Table 5 (Continued)
Survival Rate (1001-1250 grams)

· ·			W	hite					Non	white		
Hospital		Sur	vival		Sur	vival		Sur	vival	B O4	Sur	vival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	11	3	27.3	11	8	72.7	5	2	40	6	5	83.3
Bellevue	12	5	41.7	1	0	.0	4	- 2	50	1	1	100
Bronx	7	5	71.4	1	1	100	10	2	20	1	0	0
Elmhurst	8	3	37.5	7	6	85.7	7	3	42.9	3 2	2	66.7
Flushing	3	0	0	3	1.	33.3	_	-	-	2	2	100
Harlem	_	_	_	1	1	100	28	17	60.7	6	5	83.3
Jewish Brooklyn	3	2	66.7	9	5	56.6	10	9	90	8	6	75
Kings County	3	2	66.7	1	.0	0	37	18	48.6	8	2	25
Lincoln	10	7	70	-	-	-	13	10	77	3	3	100
L. I. Jewish	3	2	66.7	16	9	56.2	-	-	-	11	9	81.8
Mt. Sinai	7	4	57.1	2	1	50	2	1	50	8	5	62.5
New York	11	2	18.2	9	8	88.9	3	3	100	4	2	50
Queens Gen.	3	1	33.3	8	6	75	10	4	40	3	2	66.7
St. Vincent's (NY)	3	1	33.3	6	6	100	1	0	0	5	5	100
St. Vincent's (SI)	5	2	40	7	6	85.7	1 :	0	0	10	7	70
			===	=	=		=	=		=	=	==
TOTALS	89	39	43.8	82	58	70.7	131	71	54.2	79	56	70.9

			W	hite					Non	white		
Hospital	D 1	Sur	vival	D O	Sur	vival	Born In	Sur	vival	Born Out	Sur	vival
	Born In	No.	%	Born Out	No.	%	BOTH III	No.	%	Boin Out	No.	%
Babies	5	1	20	11	8	72.7	8	5	62.5	8	8	100
Bellevue <sup>.</sup>	17	10	58.8	6	4	66.7	8	5.	62.5	4	3	75
Bronx	11	8	72.7	4	4	100	18	15	83.3	_	-	_
Elmhurst	12	10	83.3	4	3	75	11	8	72.7	8	8	100
Flushing	11	8	72.7	14	11	78.6	2	2	100	. 7	7	100
Harlem		_	_	3	3	100	42	29	69	3	3	100
Jewish Brooklyn	8	8	100	23	16	69.6	15	10	66.7	15	14	93.
Kings County	2	2	100	_	_	-	66	50	75.8	2	1	50
Lincoln	8	7	87.5	2	2	100	16	14	87.5	6	6	100
L. I. Jewish	6	3	50	18	15	83.3	_	_	_	13	9	69.:
Mt. Sinai	13	10	77	12	9	75	5	3	60	13	12	92.
New York	. 9	5	55.6	12	9	75	4	4	100	11	11	100
Queens Gen.	4	- 3	75	8	7	87.5	26	23	88.5	9	9	100
St. Vincent's (NY)	9	7	77.8	18	17	94.4	2	1	50	10	9	90
St. Vincent's (SI)	6	5	83.3	9	8	88.9	1	1	100	15	14	93.
	=	=	===	==	=	===	===	==	==	=	==	==
TOTALS	121	87	71.9	144	116	80.6	224	170	75.9	124	114	91.

Table 6. City of New York Premature Center Statistics Survival Percentages (by Weight) 1965
Total All Centers

			White			
W-: 14 O	T			T	T	r
Weight Group	Born In	No. Survived	% Survival	Born Out	No. Survived	% Survival
Under 500 gms.	16	0	0	2	0	0
501-750 gms.	53	0	0	12	Ō	0
751-1000 gms.	83	18	21.7	48	21	43.7
1001-1250 gms.	84	45	53.6	75	49	65.3
1251-1500 gms.	89	54	60.7	134	102	76.1
1501-1750 gms.	184	144	78.3	195	172	88.2
1751-2000 gms.	247	227	91.9	203	192	94.6
2001-2500 gms.	1503	1473	98	85	75	88.2
TOTALS	2259	1961	86.8	754	611	<del>===</del> 81
1017120	2200	1301	L	754	011	01
			Nonwhite			
Under 500 gms.	113	0	0	3	0	0
501-750 gms.	125	1	0.8	13	3	23.1
751-1000 gms.	123	35	28.5	44	20	45.5
1001-1250 gms.	153	92	60.1	75	58	77.3
1251-1500 gms.	208	154	74.0	123	112	91.1
1501-1750 gms.	281	250	89.0	155	149	96.1
1751-2000 gms.	349	334	95.7	166	161	97
2001-2500 gms.	1654	1638	99	92	91	98.9
TOTALS	3006	2504	83.3	<del>===</del> 671	594	<del>===</del> 88.5
1017120	3000				594	66.5
		White	e and Nonwhite			
Under 500 gms.	129	0	0	5	0	0
501-750 gms.	178	1	0.6	25	3	12
751-1000 gms.	206	53	25.7	92	41	44.6
1001-1250 gms.	237	137	57.8	150	107	71.3
1251-1500 gms.	297	208	70	257	214	83.3
1501-1750 gms.	465	394	84.7	350	321	91.7
1751-2000 gms.	596	561	94.1	369	353	95.7
2001-2500 gms.	3157	<u>3111</u>	98.5	177	166	93.8
TOTALS	5265	4465	84.8	1425	1205	84.6

Survival Rate (Under 500 grams)

•			V	/hite					No	nwhite		
Hospital	Born In	Sui	rvival	Born Out	Sur	vival		Sur	vival	<b>D</b>	Sur	vival
	BOIN III	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	2	0	0		_		3	0	0		_	
Bellevue	_	_	_	_		_	_	_	_	_	_	_
Bronx	3	0	0	l	_		2	ol	0	_		_
Elmhurst	_	_		_	_				_	_	_	
Flushing		_	<del></del>	_	_	_	<b>!</b> _	_	_	l –	_	
Harlem	_	_	_	_	_	_	18	0	0	_	_	
Jewish Brooklyn	_	_	_	_	_		18 3	ō	Ö-		_	٠
Kings County	2	0	0	1	0	0	70	ō	ŏ	2	0	0
Lincoln		_	_	_	_	_	5	0	Ö		_	_
L. I. Jewish	1	0	0	_	_	_	_	_	_	_	_	
Mt. Sinai	1	0	0	_	_		_	_	_	_		
New York	1	0	Ó	1	0	0	_	_		1	o	0
Queens Gen.	2	0	0		_	_	10	0	0		_	_
St. Vincent's (NY)	2	0	0		_	_	1	Ō	Ŏ.	_	_	_
St. Vincent's (SI)	2	0	Õ	_	_	_	1	Ō	Ŏ	{ . <u> </u>	_	
TOTALS	16	<u> </u>		<u>=</u>	<u> </u>	<del></del>	113	<u> </u>	<u> </u>	<u></u>	<del></del>	0

Table 6 (Continued)
Survival Rate (501-750 grams)

			W	hite					No	onwhite		
Hospital		Sur	/ival		Sur	vival	_	Sur	vival	5 0 1	Sur	vival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	9	0	0	_	_	_	8	0	0	-	_	-
Bellevue	3	0	0	_		_	2	0	0	2	0	0
Bronx	6	0	0		_	_	7	0	0		-	_
Elmhurst	3	0	0	_	_	_	6	0	0	1	0	.0
Flushing	_	_	_	_			_	_	-	1	0	0
Harlem		_		<b>–</b> .	-	_	29	0	0	1	0	0
Jewish Brooklyn	2	o	0	3	0	0	6	0	0	_	_	· —
Kings County	4	0	0	_	_	-	38	0	0	3	.0	- 0
Lincoln	4	0	0	_	_	_	8	0	0	-	_	_
L. I. Jewish	2	0	0	1	0	0	_	· —	_	1	0	0
Mt. Sinai	7	0	0	_	_	_	2	0	0	1	0	0
New York	7	0	0	1	0	0	2	0	0	- 2	2	100
Queens Gen.	1	0	0	3	0	0	15	1	6.7	1	1	100
St. Vincent's (NY)	3	0	0	2	0	0	2	0	0	-	-	_
St. Vincent's (SI)	2	0	0	2	0	0	_	-	_	i –	-	
		=	==	==	=	=	=	=	=		=	==
TOTALS	53	0	0	12	0	0	125	1	0.8	13	3	23.1

			W	hite					Non	white		
Hospital		Sur	vival		Sur	vival		Sur	vival	Born Out	Sur	vival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	13	1	7.7	7	2	28.6	7	1	14.3	2	1	50
Bellevue	7	1	14.3	3	1	33.3	3	1	33.3	2	0	0
Bronx	14	1	7.1	1	0	0	6	0	. 0	2	1	50
Elmhurst	5	0	0	1	1	100	10	4	40	2	1	50
Flushing	5	2	40	6	3	50	_	-		4	3	75
Harlem		_	_	_	-	_	30	9	30	3	0	0
Jewish Brooklyn	3	2	66.7	5	2	40	8	3	37.5	4	2	50
Kings County	_	_	_	-	_	_	35	9	25.7	5	1	20
Lincoln	- 6	2	33.3	1	1	100	4	1	25	3	2	66.7
L. I. Jewish	4	2	50	9	6	66.7	-	-	-	6	4	66.
Mt. Sinai	5	2	40	4	1	25	-	-	_	3	2	66.
New York	7	1	14.3	6	2	33.3	1	1	100	4	1	25
Queens Gen.	5	2	40	1	1	100	18	6	33.3	1	1	100
St. Vincent's (NY)	5	1	20	2	0	0	-	-	-	1	0	0
St. Vincent's (SI)	4	1	25	2	1	50	1	0	0	2	1	50
/ (/		=	=	=	=	==	==	=	==	=	=	-
TOTALS	83	18	21.7	48	21	43.7	123	35	28.5	44	20	45.

Table 6 (Continued)
Survival Rate (1001–1250 grams)

			W	/hite					N	onwhite		
Hospital	Born In	Sui	rvival	Born Out	Su	rvival		Su	rvival		Su	rvival
	Dom m	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	9	4	44.4	9	3	33.3	8	5	62.5	6	6	100
Bellevue	7	3	42.9	3	2	66.7	6	3	50	3	3	100
Bronx	7	0	0		-	-	12	7	58.3	4	3	75
Elmhurst	4	4	100	4	2	50	3	0	0	3	1	33.3
Flushing	6	4	66.7	- 2	0	0	_		-	_	_	_
Harlem	-	-	-		_	<u> </u>	28	23	82.1	- 6	4	66.7
Jewish Brooklyn	10	9	90	7	3	42.9	23	11	47.8	10	8	80
Kings County Lincoln	4	2	50	_	_	-	34	20	58.8	4	3	75
L. I. Jewish	1	1	100	3	2	66.7	9	7	77.8	-		_
Mt. Sinai	4	4	100	21	13	61.9	-		_	12	8	66.7
New York	11	3	27.3	11	10	90.9	2	2	100	5	4	80
Queens Gen.	11	7	63.6	6	5	83.3	3	2	66.7	5	5	100
St. Vincent's (NY)	3	2	66.7	2	2	100	23	12	52.2	3	. 2	66.7
St. Vincent's (N1)	5	2	40	3	3	100	-	-	-	- 5	4	80
Oc. Vincent's (31)	==	0	0	4	4	100	<b>2</b>	<u>0</u>	0	9		77.8
TOTALS	84	45	53.6	75	49	65.3	153	92	60.1	75	58	77.3

. *			W	hite					Nor	nwhite		
Hospital	Born In	Sur	vival	2. 0.	Sur	vival		Su	rvival		Sui	rvival
	BOTH III	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	8	3	37.5	9	5	55.6	9	5	55.6	8	8	100
Bellevue	8	4	50	7	5	71.4	4	2	50	8	6	75
Bronx	4	1	25	6	5	83.3	13	10	76.9	6	5	83.3
Elmhurst	6	6	100	14	13	92.9	9	4	44.4	. 3	3	100
Flushing	11	8	72.7	4	2	50	5	2	40	6	5	83.3
Harlem	_	-	-	2	2	100	36	30	83.3	9	8	88.9
Jewish Brooklyn	2	2	100	10	7	70	18	13	72.2	9	8	88.9
Kings County	5	-0	0	2	0	0	69	52	75.4	8	7	87.5
Lincoln	9	4	44.4	1	1	100	16	13	81.2	2	2	100
L. I. Jewish	3	3	100	20	15	75	_`	_	_	18	17	94.4
Mt. Sinai	9	7	77.8	20	16	80	6	6	100	8	6	75
New York	11	7	63.6	8	7	87.5	3	3	100	4	4	100
Queens Gen.	2	.0	0	6	6	100	19	13	68.4	10	9	90
St. Vincent's (NY)	9	. 7	77.8	12	9	75	_	_	_	8	. 8	100
St. Vincent's (SI)	2	2	100	13	9	69.2	1	1	100	16	16	100
		=			=	===	_	=	==	<del>==</del> .	=	===
TOTALS	89	54	60.7	134	102	76.1	208	154	74	123	112	91.1

Table 7. City of New York Premature Center Statistics Survival Percentages (by Weight) 1967
Total All Centers

		• • • • • • • • • • • • • • • • • • • •	Mil Celifeis			
			White			
Weight Group	Born In	No. Survived	% Survival	Born Out	No. Survived	% Survival
Under 500 gms.	19	0	0	3	0	0
501-750 gms.	36	0	0	14	4	28.6
751-1000 gms.	58	12	20.7	35	19	54.3
1001-1250 gms.	83	47	76.6	73	51	69.9
1251-1500 gms.	127	77	60.6	103	85	82.5
1501-1750 gms.	162	130	80.2	160	142	83.7
1751-2000 gms.	235	214	91.1	221	208	94.1
2001-2500 gms.	<u>1398</u>	<u>1358</u>	<u>97.1</u>	<u>91</u>	<u>83</u>	<u>91.2</u>
TOTALS	2118	1838	86.8	700	592	84.6
	· · · · · · · · · · · · · · · · · · ·		Nonwhite			
Under 500 gms.	100	0	0	1	0	0
501-750 gms.	107	3	2.8	11	2	18.2
751-1000 gms.	108	19	17.6	32	18	56.2
1001-1250 gms.	129	71	55.0	83	63	75.9
1251-1500 gms.	164	131	79.9	95	87	91.6
1501-1750 gms.	236	219	92.8	142	136	95.8
1751-2000 gms.	331	314	94.9	154	147	95.5
2001-2500 gms.	1297	1281	98.8	55	<u>51</u>	92.7
TOTALS	2472	2038	82.4	573	504	88
		Whit	e and Nonwhite	)		
Under 500 ams.	119	0	0	4	0	0
501-750 gms.	143	3	2.1	25	6	24
751-1000 gms.	166	31	18.7	67	37	55.2
1001-1250 gms.	212	118	55.7	156	114	73.1
1251-1500 gms.	291	208	71.5	198	172	86.9
1501-1750 gms.	398	349	87.7	302	278	92.1 94.7
1751-2000 gms.	566	528	93.3	375	355	
2001-2500 gms.	2695	2639	97.9	146	134	91.8
TOTALS	4590	3876	84.4	1273	1096	86.1
IOIALO	1 4000	1 00.0	1		l	<u> </u>

			W	hite					Non	white		
Hospital		Sur	vival		Sur	vival		Sur	vival	Born Out	Sur	vival
-	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	_	_		_	_	_	4	0	Ó	_	-	_
Bellevue	. 3	0	0	-	-	-	1	0	0	_	-	-
Bronx	1	0	0	-	-	· <del></del>	2	0	0	_	-	_
Brooklyn	1	0	0	_	-	-	4	0	0	-	-	-
Elmhurst	2	0	0	-	-	_	1	0	0	_	-	
Flushing	_	-	-	-	-		-	-	_	-	-	_
Harlem	-	-		-	-	_	31	0	0	_	-	_
Jewish Brooklyn	_	-	-	-	-	<u> </u>	_	-	_	_	=	_
Kings County	2	0	0	1	0	0	48	0	0	1	0	0
Lincoln	2	0	0	1	0	0	_	-	_	-	_	_
L. I. Jewish	-	-	_	-	-	-	_	_	_	_	-	
Mt. Sinai	1	0	0	-	-	-	1	0	0	_	-	
New York	1	0	0	_	-	-	_	_	_	_	-	_
Queens Gen.	1.	0	0	1	0	0	6	0	0	_	-	_
St. Vincent's (NY)	1	0	0	-	1 -	-	1	0	0	/ -	-	-
St. Vincent's (SI)	4	0	0	-	_		1 _1	0	0	·		
TOTALS	19	0	0	3	0	0	100	0	0	1	0	0

Table 7 (Continued)
Survival Rate (501-750 grams)

			W	hite .					Nor	white		
Hospital	Born In	Sur	vival	B 0 4	Sur	vival		Sur	vival		Sui	vival
	DOM III	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	6	0	0	1	0	0	5	0	0	_	_	_
Bellevue	5	0	0	2	1	50	1	0	0	_		_
Bronx	3	0	0		_	_	2	0	0	_	_	_
Brooklyn	3	0	0		_		6	0	0	3	1	33
Elmhurst	4	0	0	1 1	0	0	1	0	0	1	0	0
Flushing		_	_	_	_	_	_		_	_	_	_
Harlem	_		_	_	_	_	26	1	3.8	_	l _	_
Jewish Brooklyn		_	_		_	_	4	1	25		_	
Kings County	1	0	0	1	0	0	33	1	3	1.	1	100
Lincoln	4	0	0	1	0	0	8	0	0	3	3	100
L. I. Jewish	4	0	0	2	1	50	_	_	_	_	_	_
Mt. Sinai	2	0	0	_		_	_	_		_	_	_
New York	1	0	0		_	_	3	0	0	_		_
Queens Gen.		_	_	2	1	50	17	0	0	1	0	0
St. Vincent's (NY)	1	0	0	2	1	50	1	0	0	2	1	50
St. Vincent's (SI)	2	0	0	2	o	0	_	-	_	_	_	-
	=	=	===	===	=	==	=	=	=		=	=
TOTALS	36	0	0	14	4	28.6	107	3	2.8	11	2	18

	T			i			<del></del>					
			w	hite					Nor	white		
Hospital	Born In	Sur	vival	D0-1	Sur	vival		Sui	vival		Sur	vival
	DOIN IN	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	6	1	16.7	-	_	_	3	1	33.3	_	_	_
Bellevue	4	0	0	4	1	25	3	0	0		_	-
Bronx	6	1	16.7	4	1	25	8	4	50	1	1	100
Brooklyn	1	0	0	2	2	100	2	0	0	7	3	42.9
Elmhurst	2	0	0	3	1	33.3	3	0	0		_	
Flushing	1	0	0	1	1	100	1	0	0		_	_
Harlem		_	-	_ `	_	_	16	4	25	4	2	50
Jewish Brooklyn	3	1	33.3	2	1	50	7	2	28.6	2	0	0
Kings County	5	0	0	1	1	100	43	4	9.3	5	2	40
Lincoln	6	0	0	_		_	43 7	2	28.6	1	1	100
L. I. Jewish	3	2	66.7	3	1	33.3		_	_	4	3	75
Mt. Sinai	16	5	31.2	5	3	60.0	1	1	100	1	1	100
New York	2	1	50	3	3	100	5	١٥	0	3	3	100
Queens Gen.	1	0	0	2	1	50	8	1	12.5	1	1	100
St. Vincent's (NY)	1	0	0	4	2	50	1	0	0	3	1	33.3
St. Vincent's (SI)	1	1	100	1	1	100		_	_		_	_
	=	=	==	==	=		==	=			=	=
TOTALS	58	12	20.7	35	19	54.3	108	19	17.6	32	18	56.2

Table 7 (Continued)
Survival Rate (1001-1250 grams)

			Wi	nite					Non	white		
Hospital		Surv	rival	_	Sur	vival	D In	Surv	ival	Born Out	Sur	vival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Doin out	No.	%
Babies	7	5	71.4	1	1	100	9	4	44.4	5	3	60
Bellevue	7	4	57.1	- 5	2	40	1	0	∈0	2	2	100
Bronx	4	1	25	5	2	40	5	3	60	1	1	100
Brooklyn	3	0	0	2	2	100	1	0	0	12	8	66.
Elmhurst	5	4	80	6	3	50	2	1	50	5	4	80
Flushing	5	3	60	6	3	50	_	-		1	1	100
Harlem	_	-	_	_	_	-	19	14	73.7	1	1	100
Jewish Brooklyn	3	3	100	5	4	80	18	9	50	9	8	88.
Kings County	_	-	l · —		-	-	42	19	45.2	7	4	57. 100
Lincoln	12	4	33.3	1	0	0	11	7	63.6	1	1	1
L. I. Jewish	7	3	42.9	11	9	81.8	1	-	-	14	8	57. 100
Mt. Sinai	6	3	50	6	4	66.7	1	4	80	6	6	1
New York	13	10	76.9	4	4	100	2	2	100	5	5	100
Queens Gen.	3	3	100	3	2	66.7	1	8	57.1	4	2	50 100
St. Vincent's (NY)	5	4	80	14	11	78.6	<b>i</b>   -	-	-	8	8	1 .
St. Vincent's (SI)	3	0	0.	4	=	100	= =	=	=	= $=$ $=$	$\frac{2}{2}$	==
TOTALS	83	47	56.6	73	51	69.9	129	71	55	83	63	75

			W	nite					Non	white		
Hospital		Sur	rival		Sur	vival		Surv	rival	Born Out	Surv	ival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Boin Out	No.	%
D. h.i.e.	11	7	63.6	2	2	100	9	9	100	5	4	80
Babies	12	7	58.3	7	4	57.1	2	1	50	6	5	83.3
Bellevue	9	4	44.4	2	2	100	9	7	77.8	1	3	100
Bronx	4	2	50	10	9	90	3	3	100	18	18	100
Brooklyn	9	6	66.7	4	3	75	2	2	100	2	2	100
Elmhurst	10	5	50	4	2	50	_	-	_	2	2	100
Flushing		_	_	2	2	100	38	31	81.6	1	1	100
Harlem	8	6	75	5	5	100	22	18	81.8	3	3	100
Jewish Brooklyn	0	0	0	3	3	100	46	34	73.9	4	2	50
Kings County	'	5	55.6	1	1	100	11	6	54.5	5	3	60
Lincoln	9		66.7	24	21	87.5	_	-		11	11	100
L. I. Jewish	6	4	81.8	6	6	100	5	5	100	4	4	100
Mt. Sinai	22	18	1	8	7	87.5	1	3	100	11	11	100
New York	4	3	75	2	1	50	10	9	90	7	7	100
Queens Gen.	_	-	-	_	12	85.7		2	66.7	6	6	100
St. Vincent's (NY)		6	42.9	1	5	55.6	1	1	100	7	5	71.
St. Vincent's (SI)	8	4	50	9		35.0		<u>-</u>	===	==	$\mid$ =	1=
TOTALS	127	77	60.6	103	85	82.5	164	131	79.9	95	87	91

Table 8. City of New York Premature Center Statistics Survival Percentages (by Weight) 1968
Total All Centers

Weight Group         Born In         No. Survived         % Survival         Born Out         No. Survived         % Survival           Under 500 gms.         22         0         0         3         0         0           501-750 gms.         51         1         2         18         0         0           751-1000 gms.         76         18         23.7         37         19         51.4           1001-1250 gms.         70         34         48.6         64         47         73.4           1251-1500 gms.         104         75         72.1         135         117         86.7           1501-1750 gms.         159         134         84.3         208         185         88.9           1751-2000 gms.         245         228         93.1         261         247         94.6           2001-2500 gms.         1341         1304         97.2         100         90         90           TOTALS         2068         1794         86.8         8         13         0         0           501-750 gms.         100         8         8         13         0         0           501-750 gms.         105         29										
Weight Group	Born In	No. Survived	% Survival	Born Out	No. Survived	% Survival				
	22	0	0	3	0	0				
	51	1		18		1 -				
	76	18	23.7		19					
1001-1250 gms.	70	34	48.6		, -					
		75	72.1	135	117					
		134	84.3	208	185					
	245	228	93.1	261						
2001-2500 gms.	1341	1304	97.2	100	90					
TOTALS	2069	1704	===	===						
TOTALS	2006	1/94	86.8	826	705	85				
			Nonwhite							
	87	0	0	1	n	0				
	100	8			_					
751-1000 gms.	105	29		42	26	_				
1001-1250 gms.		66	56.9							
1251-1500 gms.	151	125	82.8	88	80	90.9				
1501-1750 gms.	222	189	85.1	128	119	93				
1751-2000 gms.	323	312	96.6	178	174	97.8				
2001-2500 gms.	1228	1218	99.2	88	85	96.6				
TOTALS	2332	1947	83.5	590	<del>===</del> 524	===				
					524	88.8				
	·	White	e and Nonwhite	•		÷				
Under 500 gms.	109	0	0	4	0	0				
501-750 gms.	151	9	6	31	Ō	Ö				
751-1000 gms.	181	47	26	79	45	57				
1001-1250 gms.	186	100	53.8	116	87	75				
1251-1500 gms.	255	200	78.4	223	197	88.3				
1501-1750 gms.	381	323	84.8	336	304	90.5				
1751-2000 gms.	568	540	95.1	439	421	95.9				
2001-2500 gms.	2569	2522	98.2	188	175	93.1				
TOTALS	4400	3741	85	1416	1229	86.8				

			W	hite					Nor	nwhite		
Hospital	Born In	Şur	rvival	Born Out	Sur	vival	Barra Ia	Sui	vival	D	Sur	vival
	50111 111	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	2	0	0	_	_	_	1	0	0		_	. –
Bellevue	3	0	0	_	_	_	1 1	0	0		_	_
Bronx	3	0	0	_		_	2	0	0			_
Brooklyn	_	_	_	_	_	·	3	0	0	_	_	
Elmhurst	. 1	0	0	_	_	_	1 1	Ö	0	_		
Flushing	1	0	0		_	_		_	· _			_
Harlem	2	0	0	_	_	_	17	0	0		_	
Jewish Brooklyn			_		_		2	ō	Ŏ	_		_
Kings County	1	0	0	<del>.</del>	_	_	53	ō	Ŏ			_
Lincoln	3	0	0	1	0	0				_	_1	_
L. I. Jewish	·	_	_	_	_	_			_	_		
Mt. Sinai	5	0	0	1	0	O	_ '	_	_	: _		
New York		_	_	1	ő	ŏ	_	_ [	_		_ 1	
Queens Gen.	_	_	_ :		_	_	4	0	0	`	_	_
St. Vincent's (NY)	1	ol	0			_			_			_
St. Vincent's (SI)		_	_		_	_	3	0	0	1	0	0
	==	==	===	==	==			=			<u> </u>	_
TOTALS	22	0	0	3	0	0	87	0	0	1,	0	C

Table 8 (Continued)
Survival Rate (501-750 grams)

			W	hite					Non	white		
Hospital	i	Sur	vival		Sur	vival		Sur	vival	D	Sur	vival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	6	0	. 0	2	0	0	6	1	16.7	_	- 1	_
Bellevue	5	0	0	-	-	_	1	0	0	1	0	0
Bronx	7.	0	0	-	-	_	3	0	0	-	- 1	_
Brooklyn	3	0	0	2	0	- 0	3	0	0	1	0	0
Elmhurst	1	0	0	2	.0	0	5	0	0	2	0	0
Flushing		-	_	_	-	_	_ `	_	-	1	0	0
Harlem	2	0	0	_	-	_	19	4	21.1	-	-	
Jewish Brooklyn	2	1	50	- :	-	_	7	2	28.6	<u> </u>	-	_
Kings County	1	0	0	2	0	0	36	1	2.8	2	0	0
Lincoln	3	0	0	_	-		4	0	0	1	0	0
L. I. Jewish		-	<u> </u>	1	0	0	1	0	0	1	0	0
Mt. Sinai	3	0	0	3	0	0	1	0	0		-	_
New York	7	0	0	4	0	0	3	0	0	-	· —	-
Queens Gen.	2	0	0		-	_	10	0	0	- '	-	-
St. Vincent's (NY)	6	0	0	1	0	0	-	-	-	2	0	0
St. Vincent's (SI)	3	0	0	1	0	0	1	0	0	2	0	0
		=	==	=	=	==	=	=		=	=	==
TOTALS	51	1	2	18	0	0	100	8	8	13	0	0

			W	hite					Non	white		
Hospital		Sur	vival		Sur	vival	_	Sur	vival	D	Sur	vival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	12	2	16.7	5	3	60	7	1	14.3	2	1	50
Bellevue	3	0	0	. 2	1	50	2	0	0	_	_	
Bronx	8	2	25	1	1	100	5	4	80	_	-	-
Brooklyn	4	1	25	3	1	33.3	3	1	33.3	6	4	66.7
Elmhurst	1	0	0	1	1	100	3	2	66.7	1	0	0
Flushing	3	2	66.7	1	0	. 0		-		2	1	50
Harlem	-1	0	0	1	0	0	13	2	15.4	1	1	100
Jewish Brooklyn	1	0	0	1	0	0	10	4	40	5	3	60
Kings County	2	0	0	5	2	40	43	9	20.9	6	2	33.3
Lincoln	5	0	0		-	` - ·	2	2	100	_	-	-
L. I. Jewish	5	2	40	- 5	4	80	-	-	-	4	3	75
Mt. Sinai	17	8	47.1	4	3	75	-	-	_	<b>–</b>	-	-
New York	5	0	0	3	1	33.3	5	3	60	4	2	50
Queens Gen.	2	0	0	_	-	-	9	0	0	3	1	33.3
St. Vincent's (NY)	3	0	0	5	2	40	2	1	50	8	8	100
St. Vincent's (SI)	4	1	25	_	-	-	1	0	-0	<u> </u>	-·	-
	<b> </b> ==	=	==	=	=	===	_	=	==	===	=	===
TOTALS	76	18	23.7	37	19	51.4	105	29	27.6	42	26	61.9

Table 8 (Continued)
Survival Rate (1001-1250 grams)

			W	hite					Nor	nwhite		
Hospital	Born In	Sui	rvival	B O-4	Sui	vival		Sui	rvival		Sui	rvival
	DOIN IN	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	. 5	1	20	.—	_		8	4	50	1	1	100
Bellevue	3	2	66.7	2	1	50	4	3	75	2	1	50
Bronx	7	4	57.1	1	1	100	6	3	50	3	2	66.7
Brooklyn	3	2	66.7	4	2	50	_	_	_	11	10	90.9
Elmhurst	2	1	50	2	1	50	7	3	42.9	_	_	_
Flushing	2	0	0	4	3	75	_	_	_			l _
Harlem	3	1	33.3	3	1	33.3	21	15	71.4	_	_	l _
Jewish Brooklyn	2	2	100	5	4	80	15	9	60	4	2	50
Kings County		_	_	_	_		31	15	48.4	2	1	50
Lincoln	5	1	20	3	1	33.4	3	1	33.3	3	3	100
L. I. Jewish	6	2	33.3	9	8	88.9	_	_	_	7	5	71.4
Mt. Sinai	10	7	70	6	5	83.3	3	0	0	5	4	80
New York	13	6	46.2	4	4	100	3	3	100	1	1	100
Queens Gen.	3	2	66.7	6	6	100	10	7	70	4	3	75
St. Vincent's (NY)	5	3	60	7	5	71.4	2	0	0	3	3	100
St. Vincent's (SI)	1	0	0	8	5	62.5	3	3	100	6	4	66.7
	=	==		=	=		_	_	=		=	===
TOTALS	70	34	48.6	64	47	73.4	116	66	56.9	52	40	76.9

			W	hite					Non	white		
Hospital	Born In	Sur	vival		Sur	vival		Sui	vival		Sui	vival
	born in	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	6	4	66.7	7	7	100	5	4	80	2	1	50
Bellevue	7	6	85.7	9	9	100	4	4	100	6	5	83.3
Bronx	14	9	64.3	6	5	83.3	10	9	90	_	_	_
Brooklyn	6	5	83.3	10	10	100	1	1	100	13	12	92.3
Elmhurst	7	3	42.9	8	5	62.5	3	2	66.7	2	2	100
Flushing	10	9	90	9	6	66.7	2	2	100	1	1	100
Harlem	3	1	33.3	4	4	100	23	19	82.6	3	3	100
Jewish Brooklyn	6	5	83.3	6	6	100	22	17	77.3	11	9	81.8
Kings County	1	1	100	6	6	100	40	32	80	6	5	83.3
Lincoln	7	4	57.1	2	1	50	6	5	83.3	5	4	80
L. I. Jewish	3	2	66.7	15	9	73.3	1	1	100	9	8	88.9
Mt. Sinai	13	10	76.9	11	10	90.9	7	5	71.4	9	9	100
New York	13	9	69.2	8	7	87.5	4	4	100	6	6	100
Queens Gen.	1	1	100	10	10	100	21	18	85.7	4	4	100
St. Vincent's (NY)	2	2	100	16	14	87.5	1	1	100	7	7	100
St. Vincent's (SI)	5	4	80	8	6	75	1	1	100	4	4	100
	=	=			=	==			=		=	=
TOTALS	104	75	72.1	135	115	85.1	151	125	82.8	- 88	80	90.9

Table 9. City of New York Premature Center Statistics Survival Percentages (by Weight) 1969
Total All Centers

			White			
Weight Group	Born In	No. Survived	% Survival	Born Out	No. Survived	% Survival
Under 500 gms.	14	0	0	3	0	0
501-750 gms.	37	2	5.4	14	1	7.1
751-1000 gms.	55	10	18.2	37	19	51.4
1001-1250 gms.	84	41	48.8	87	58	66.7
1251-1500 gms.	98	67	68.4	120	101	84.2
1501-1750 gms.	150	119	79.3	214	198	92.5
1751-2000 gms.	322	302	93.8	231	210	90.9
2001-2500 gms.	1345	1309	97.3	125	110	88.0
TOTALS	2105	1850	87.9	831	697	83.9
	l		Nonwhite			
Under 500 gms.	95	0	0	4	0	0
501-750 ams.	93	3	3.2	20	3	15
751-1000 gms.	104	32	30.8	35	6	17.1
1001–1250 gms.	113	65	57.5	61	46	75.4
1251-1500 gms.	160	135	84.4	98	82	83.7
1501-1750 gms.	194	168	86.6	128	117	91.4
1751-2000 gms.	312	303	97.1	189	181	95.8
2001-2500 gms.	1156	1140	98.6	263	261	99.2
	===		82.9	798	696	87.2
TOTALS	2227	1846	<u> </u>		090	1 07.2
		Whit	e and Nonwhite	<del>,</del>		
Under 500 gms.	109	0	0	. 7	0	0
501-750 gms.	130	5	3.8	34	4	11.8
751-1000 gms.	159	42	26.4	72	25	34.7
1001-1250 gms.	197	106	53.8	148	104	70.3
1251-1500 gms.	258	202	78.3	218	183	83.9
1501-1750 gms.	344	287	83.4	342	315	92.1
1751-2000 gms.	634	605	95.4	420	391	93.1
2001-2500 gms.	2501	2449	97.9	388	371	95.6
TOTALS	4332	3696	85.3	1629	1393	85.5

	····		W	hite	,				Non	white		
Hospital		Sur	vival		Sur	vival		Sur	vival	Born Out	Sur	vival
·	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	2	0	0			_	3	0	0		-	
Bellevue		_			-		_	-	_	-	-	_
Bronx	1	0	0	1	0	0	1	0	0	_	-	_
Brooklyn	_		_	-	-	_	2	0	0	1	0	0
Elmhurst	_	_	_	1	0	0	2	0	0	1	0	0
Flushing	1	0	0	_	-	-	-	-	_	_	-	_
Harlem	4	0	0	i –	-	- \	23	0	0	] ]	0	0
Jewish Brooklyn		-	-	_	-	-	_	-	-	_	-	_
Kings County	2	0	0	_	- ·	_	59	0	0		_	_
Lincoln	-	_	_	-	-	_	2	0	0	_	-	_
L. I. Jewish	_	-	-	_	-	_	_	-	-	_	-	_
Mt. Sinai	1	0	0	-	-	_	_	-		_	-	
New York	1	0	0	1	0	0		-	_		-	
Queens Gen.	1	0	0	-	-	-	3	0	0	_	_	0
St. Vincent's (NY)	_	-	-	_	-	-	-	-	-	2	0	U
St. Vincent's (SI)	1	0	0_					=	l <u> </u>			
TOTALS	14	0	0	3	0	0	95	0	0	5	0	0

Table 9 (Continued)
Survival Rate (501-750 grams)

		,		W	hite					Nor	nwhite		
Hospital	Bori	- In	Sur	vival	B 0.4	Sur	vival		Sur	vival		Sur	vival
	DUI		No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies		2	2	100	. <del>-</del>	_	_	4	0	0		_	_
Bellevue		1	0	0	!	_	_		_		_	_	_
Bronx		1	0	. 0	2	0	-0	1	0	.0	_		_
Brooklyn		3	0	0	1	0	0	- 3	0	0	1	0	0
Elmhurst		3	0	0	3	Ó	0	2	0	0	1	0	. 0
Flushing		5	0	0	- :	. <u> </u>	_	1	0	0	_		_
Harlem		<del></del> .	-	l –		_		18	2	11.1	1 1	0.	0
Jewish Brooklyn		1 .	0	0	_			4	0	0		_	_
Kings County		1	0	0	_	_	_	38	1	2.6	2	0	0
Lincoln		1	0	0	2	.0	0	5	. 0	0		_	_
L. I. Jewish		4	0	0	1	1.	100	1.	0	0	3	1	33.3
Mt. Sinai		5	0	0	-	_	l —	_	_	_	4	1	25
New York		7	0	0	3	0	0	4	0	0.	1	0	0
Queens Gen. 🔪			_	_	1	0	0	10	0	0	4	0	0
St. Vincent's (NY)			· -	_	1	0	0	2	0	0	2	0	0
St. Vincent's (SI)		3	0	0	/	_	_	_			1	1	100
	=	=	=	==		=	==	==	=	====	== .		=
TOTALS	3	7.	2	5.4	14	1	7.1	93	3	3.2	20	3	15

Survival Rate (751-1000 grams)

			W	hite		J.			Nor	nwhite		
Hospital	Born In	Sui	vival	<b>D</b> 0	Sur	vival		Sui	rvival		Sur	vival
	born in	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	6	0	0		_	_	-				_	
Bellevue	1/	. 1	100	3	2	66.7	_		_	3	0	0
Bronx	4	1	25	4	1	25	8	Q.	0	1	0	0
Brooklyn	4	0	0		_	_	3	1	33.3	5	1	20
Elmhurst	5	1	20	3	2	66.7	2	0	0	_	_	_
Flushing	2	0	0	4	2	50	2	, 1	50	1	0	0
Harlem	_			1	0	0	16	3	18.7			_
Jewish Brooklyn	3	2	66.7	1	1	100	22	12	54.6	2	0	0
Kings County	4	1	25	3	2	33.3	31	7	22.6	10	3	30
Lincoln	3	1	33.3	_	_	_	` 4	1	25	1	0	0
L. I. Jewish	3	0	0	2	1	50	_	-	_	5	1	20
Mt. Sinai	7	0	0	3	1	63.3	1	1	100	1	0	0
New York	5	2	40	4	2	50	4	2	50	1	0	0
Queens Gen.	1	0	0	2	1	50	11	4	36.4	3	1	33.3
St. Vincent's (NY)	_	_		4	2	50			_	2	0	0
St. Vincent's (SI)	7	1	14.3	3	2	66.7	_	1 -	_		_	- <u> </u>
	===	=	===	=	= .	===		_	===	=	=	
TOTALS	55	10	18.2	37	19	51.4	104	32	30.8	35	6	17.1

Table 9 (Continued)
Survival Rate (1001-1250 grams)

			w	hite		. 1			Non	white		
Hospital		Sur	vival		Sur	vival		Sur	vival	Da O	Sur	vival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	12	2	16.7	3	1	33.3	7	3	42.9	2	0	0
Bellevue	5	1	20	8	5	62.5	3	1	33.3	3	3	100
Bronx	3	1	33.3	6	4	66.7	3	- 1	33.3	4	4	100
Brooklyn	3	1	33.3	5	3	60	_	-	-	7	4	57.1
Elmhurst	5	2	40	5	3	60	1	0	0	4	4	100
Flushing	6	4	66.7	4	3	75	_	-	_	4	4	100
Harlem	1 -	0	0	2	0	0	19	13	68.4	3	2	66.7
Jewish Brooklyn	5	4	80	4	2	50	27	16	59.3	4	3	75
Kings County	- 3	3	100	4	3	75	28	15	53.6	8	5	62.5
Lincoln	2	0	0	2	2	100	4	2	50	_	-	-
L. I. Jewish	5	4	80	16	11	68.7		_	-	5	3	60
Mt. Sinai	8	5	62.5	5	4	80	1	- 1	100	4	3	75
New York	16	10	62.5	11	7	63.6	4	4	100	3	3	100
Queens Gen.	2	1	50	_	_	_	12	6	50	4	. 3	75
St. Vincent's (NY)	2	1	50	6	6	100	3	2	66.7	4	3	75
St. Vincent's (SI)	6	<u>2</u>	33.3	6	4	66.7	<u></u> <u>1</u>	1	100	2	2	100
TOTALS	84	41	48.8	87	58	66.7	113	65	57.5	61	46	75.4

			·w	hite					Non	white		
Hospital		Sur	vival		Sur	vival		Sur	vival	50 °	Sur	vival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	10	7	70	6	4	66.7	14	12	85.7	5.	5	100
Bellevue	8	6	75	13	10	76.9	8	6	75	6	5	83.3
Bronx	10	9	90	. 7	5	71.4	7	7	100	2	2	100
Brooklyn	4	4	100	11	9	81.8	4	4	100	14	11	78.6
Elmhurst	6	3	50	5	5	100	5	4	80	2	2	100
Flushing	3	1	33.3	5	5	100	1	1	100	2	2	100
Harlem			_	3	3	100	19	15	78.9	4	4	100
Jewish Brooklyn	9	4	44.4	10	8	80	19	19	100	11	8	72.7
Kings County	_	-	_	5	4	80	35	28	80	8	7	87.5
Lincoln	5	4	80	4	3	75	` 10	5	50	3	3	100
L. I. Jewish	9	6	66.7	15	15	100	_	_	-	9	5	55.5
Mt. Sinai	15	12	80	. 7	7	100	4	2	50	4	4	100
New York	10	6	60	8	6	75	7	7	100	6	5	83.3
Queens Gen.	_ `	_	_	7	6	85	24	22	91.7	9	9	100
St. Vincent's (NY)	7	4	57.1	9	7	77.8	2	2	100	5	5	100
St. Vincent's (SI)	2	1	50	5	4	80	1	1	100	8	5	62.5
				=	=	=	=	=	==	=	=	===
TOTALS	98	67	68.4	120	101	84.2	160	135	84.4	98	82	83.7

Table 10. City of New York Premature Center Statistics Survival Percentages (by Weight) 1970
Total All Centers

		· · · · · · · · · · · · · · · · · · ·				
	T	·	White		<u> </u>	· 
Weight Group	Born In	No. Survived	% Survival	Born Out	No. Survived	% Survival
Under 500 gms.	11	0	0	1	0	0
501-750 gms.	33	. 0	0	12	1 1	8.3
751-1000 gms.	61	12	19.7	39	18	46.2
1001-1250 gms.	76	35	46.1	81	49	60.5
1251-1500 gms.	103	71	68.9	118	98	83.1
1501-1750 gms.	172	154	89.5	202	179	88.6
1751-2000 gms.	271	247	91.1	228	211	92.5
2001-2500 gms.	1323	1291	97.6	133	126	94.7
TOTALS	2050	1810	88.3	814	682	83.8
			Nonwhite		· · · · · · · · · · · · · · · · · · ·	
Under 500 gms.	63	0	0	3	0	0
501-750 gms.	80	o o	ŏ	7	ő	١ ٥
751-1000 gms.	99	27	27.3	40	22	55
1001-1250 gms.	122	75	61.5	62	47	75.8
1251-1500 gms.	164	125	76.2	104	95	91.3
1501-1750 gms.	219	205	93.6	153	144	94.1
1751-2000 gms.	319	308	96.6	185	180	97.3
2001-2500 gms.	1470	1451	98.7	81	75	92.6
TOTALS	2536	2191	86.4			
				635	563	88.7
· · · · · · · · · · · · · · · · · · ·	·	White	and Nonwhite			· ·
Under 500 gms.	74	0	0	4	0	0
501-750 gms.	113	. 0	0	19	1	5.3
751-1000 gms.	160	39	24.4	79	40	50.6
1001–1250 gms.	198	110	55.6	143	96	67.1
1251-1500 gms.	267	196	73.4	222	193	86.9
1501-1750 gms.	391	359	91.8	355	323	91
1751-2000 gms.	590	555	94.1	413	391	94.7
2001-2500 gms.	2793	2742	98.2	214	201	13.9
TOTALS	4586	4001	87.2	1449	1245	<del></del> 85.9

			V	/hite					No	nwhite		
Hospital	Born In	Sui	vival	Born Out	Sur	vival		Sui	vival	2	Sui	vival
	DOI III	No.	%	Bom Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	1	0	0		_				_	_		
Bellevue	_	_		_	-	_	_	· _ :	_			_
Bronx	_		_	<u> </u>	_	_	l _	_		_	_	
Brooklyn	1	0	0			_	_	_	_		_	_
Elmhurst	_	_	_	_		_		_				_
Flushing	_	_			_	_	_		_	_	_	
Harlem	1	0	0	_			16	0	0		_	
Jewish Brooklyn	_	_	_		_		2	Ö	ŏ			
Kings County	2	. 0	0	_	_		40	Ö	ő	1	0	0
Lincoln	2	0	Ŏ.	_	_						l "i	·
L. I. Jewish		: <u> </u>	_	_:	_			-	_		_	_
Mt. Sinai	3	0	0									_
New York	_			_	_	_		_		_	_	
Queens Gen.	_	_ [		, _	_	_	5	0	0	1	0	0
St. Vincent's (NY)	1.	0	0		_			0	J		0	0
St. Vincent's (SI)			_	1	0	0		_ [	_	' '	"	U
TOTALS	11	<u></u>	0	<u> </u>	=	===	63	=	<del>_</del>	3	=	0

Table 10 (Continued)
Survival Rate (501-750 grams)

Babies   2   0   0   -   -   -   1   0   0   0   0   0   0   0   0   0			white	Non			. (								
No.	rvival	Sur	D O4	vival	Sur				Survival			Survival			Hospital
Bellevue	%	No.	Born Out	%	No.	Born In	%	No.	Born Out	%	No.	Born In			
Bellevue	0	0	1	0	0	1	_	_	_	0	0	2	Babies		
Bronx         3         0         0         -         -         -         2         0         0         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         - <td>_</td> <td>  -  </td> <td>-  </td> <td>0</td> <td>0</td> <td>2</td> <td></td> <td>  _ </td> <td>_</td> <td>0</td> <td>0</td> <td></td> <td>Bellevue</td>	_	-	-	0	0	2		_	_	0	0		Bellevue		
Elmhurst 2 0 0 3 0 0 — — — — — — — — — — — — — — —	-		-	0	0	2	_	_		0	0	3	Bronx		
Flushing       4       0       0       -       -       -       1       0       0       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -<	0	0	2	0	0	3		_	·	0	0	1	Brooklyn		
Harlem  Jewish Brooklyn  2 0 0 3 0 0 Kings County  2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 2 0 0 0	-	-	-	-	_	_ `		0	3	. 0	0	2	Elmhurst		
Jewish Brooklyn     2     0     0     -     -     -     3     0     0     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     - <td>_</td> <td><u> </u></td> <td>-  </td> <td>0</td> <td>0</td> <td>1</td> <td>· -</td> <td>  -  </td> <td></td> <td>0</td> <td>0</td> <td>4</td> <td>Flushing</td>	_	<u> </u>	-	0	0	1	· -	-		0	0	4	Flushing		
Kings County       2       0       0       2       0       0       29       0       0       2       0         Lincoln       6       0       0       -       -       -       1       0       0       -       -       -         L. I. Jewish       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -       -	-	_	- "	0	0	19	_	-		_	- 1	_ :	Harlem		
Lincoln 6 0 0 1 0 0 1		-	-	. 0	0	3	_	-		0	0	2	Jewish Brooklyn		
L. I. Jewish	0	0	2	0	0	29	0	0	2	0	0	2	Kings County		
Mt. Sinai     2     0     0     2     1     50     2     0     0     1     0       New York     6     0     0     5     0     0     -     -     -     -     -       Queens Gen.     2     0     0     -     -     -     17     0     0     1     0       St. Vincent's (NY)     -     -     -     -     -     -     -     -     -     -     -       St. Vincent's (SI)     -     -     -     -     -     -     -     -     -     -	-	-	-	0	0	. 1		-	_	0	0	6	Lincoln		
New York 6 0 0 5 0 0	-	_	_		-	_	_	-	_	_ :	-	_	L. I. Jewish		
New York     6     0     0     5     0     0     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     -     <		-	1	0	0	2	50	1	2	0	0	2	Mt. Sinai		
St. Vincent's (NY)	-	_	-		-		0	0	5	0	0	6	New York		
St. Vincent's (NY)	0	0	1	0	0	17	<b>–</b> .	-	_	0	0	2	Queens Gen.		
	-	-	_	_	'-	-	_		-		-	-	St. Vincent's (NY)		
	.							_			<u> </u>		St. Vincent's (SI)		
TOTALS 33 0 0 12 1 8.3 80 0 0 7 0	0	0	7	ď		90	0.2	1	12				TOTALC		

			, W	hite		Nonwhite							
Hospital		Sur	vival		Sur	vival		Sur	vival	Born Out	Sur	vival	
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%	
Babies	9	0	0	1	1	100	4	1	25	_	-	_	
Bellevue	-	_		2	1	50	3	2	66.7	1	1	100	
Bronx	9	3	33.3	4	2	50	7	0	0	1	0	0	
Brooklyn	2	0	0	1	1	100	2	0	0	6	4	66.	
Elmhurst	5	1	20	1	0	0	1	0	0	1	0	0	
Flushing	4	1	25		_	_	1	0	0	2	1	50	
Harlem		_	_			_	25	5	20	-	-	-	
Jewish Brooklyn	3	0	0	3	1	33.3	9	4	44.4	5	5	100	
Kings County		_	_	1	0	0 、	31	.8	25.8	7	1	15	
Lincoln	6	0	0	_		_ `	4	2	50	_	-	-	
L. I. Jewish	_	_	_	6	3	50	-	_	_	2	2	100	
Mt. Sinai	11	3	27.3	5	2	40	1	0	0	5	3	60	
New York	5	2	40	2	1	50		-	-	1	1	100	
Queens Gen.	2	1	50	3	1	33.3	10	4	40	5	3	60	
St. Vincent's (NY)	1	0	0	4	1	25	-	-	_	2	1	50	
St. Vincent's (SI)	4	1	25 ===	6	4	66.7	1 ==	1	100	2	0		
TOTALS	61	12	19.7	39	18	46.2	99	27	27.3	40	, 22	55	

Table 10 (Continued)
Survival Rate (1001-1250 grams)

			W	hite		Nonwhite							
Hospital	Born In	Sui	rvival	Born Out	Sur	vival	D 1	Su	rvival		Su	rvival	
	00111111	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%	
Babies	9	5	55.6	3	2	66.7	7	4	57.1	_	_	_	
Bellevue	1	1	100	5	4	80	_	_	_	2	2	100	
Bronx	- 7	2	28.6	7	4	57.1	8	7	87.5	2	2	100	
Brooklyn	2	0	0	4	1	25	1	0	0	8	5	62.5	
Elmhurst	8	5	62.5	1	0	0	1	1	100	2	1	50	
Flushing	4	2	50	2	0	0	_	_	_	6	5	83.3	
Harlem	1	1	100	2	2	100	25	19	76	1	0	0	
Jewish Brooklyn	3	. 1	33.3	3	2	66.7	12	10	83.3	7	5	71.4	
Kings County	1	1	100	_	· _		40	17	42.5	5	3	60	
Lincoln	7	3	94.3	1	0	0	4	2	50			_	
L. I. Jewish	2	0	0	6	3	50	1 1	1	100	8	5	62.5	
Mt. Sinai	10	5	50	5	- 4	80	2	2	100	3	3	100	
New York	16	8	50	17	9	52.9	4	2	50	7	6	85.7	
Queens Gen.	_	_	_	4	2	50	13	8	61.5	5	4	80	
St. Vincent's (NY)	2	0	0	11	8	72.7	1	0	0	3	3	100	
St. Vincent's (SI)	3	1	33.3	10	8	80	3	2	66.7	3	3	100	
	==	=	==	== :	=	=	=	=	===	_ <u> </u>	<u> </u>	=	
TOTALS	76	35	46.1	81	49	60.4	122	75	61.5	62	47	75.8	

			w	hite		Nonwhite							
Hospital	Born In	Su	vival	Borr Out	Survival			Survival			Sui	vival	
	BOTH III	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%	
Babies	16	9	56.2	4	3	75	12	12	100	_	_	_	
Bellevue	4	3	75	7.	6	85.7	1	1	100	5	5	100	
Bronx	9	7	77.8	5	3	60	1	10	90.9		_	_	
Brooklyn	8	5	62.5	9	7	77.8	2	2	100	22	22	100	
Elmhurst	10	6	60	6	- 5	83.3	7	7	100	1	1	100	
Flushing	4	4	100	7	6	85.7	3	2	66.7	1	1.	100	
Harlem	_	_	_	1	1	100	29	22	75.9	2	2	100	
Jewish Brooklyn	3	- 2	66.7	3	3	100	15	11	73.3	6	4	66.7	
Kings County	3	3	100	_			49	34	69.4	8	7	87.5	
Lincoln	7	4	57.1	1	1	100	13	7	53.8	1	1	100	
L. I. Jewish	- 5	5	100	23	20	87	_	_	_	13	12	92.3	
Mt. Sinai	15	12	80	3.	3	100	7	7	100	5	5	100	
New York	8	-5	62.5	17	13	76.5	3	2	66.7	17	16	94.2	
Queens Gen.	1	1	100	9	8	88.9	7	5	71.4	5	5	100	
St. Vincent's (NY)	6	3	50	14	11	78.6	2	_	'	13	10	76.9	
St. Vincent's (SI)	4	2	50	9.	8	88.9	3	3	100	5 5	4	70.9 80	
	===	_			=	===	ا نے ا		===	==	=	===	
TOTALS	103	71	68.9	118	98	83.1	164	125	76.2	104	95	91.3	

Table 11. City of New York Premature Center Statistics Survival Percentages (by Weight) 1971
Total All Centers

	White											
Weight Group	Born In	No. Survived	% Survival	Born Out	No. Survived	% Survival						
Under 500 gms.	7	0	0	2	0	1 N 10						
501-750 gms.	44	1	2.3	- 11	<b>0</b>	0						
751-1000 gms.	52	9	17.3	34	12	35.3						
1001-1250 gms.	74	27	36.5	75	52	69.3						
1251-1500 gms.	82	58	70.7	85	69	81.2						
1501-1750 gms.	158	134	84.8	144	127	88.2						
1751-2000 gms.	237	216	91.1	217	205	94.5						
2001-2500 gms.	1182	1147	97.0	164	141	86.0						
TOTALS	1836	1592	86.7	732	606	82.8						
			Nonwhite									
Under 500 ams.	28	0	0	1	0	0						
501-750 gms.	63	3	4.8	14	2	14.3						
751-1000 gms.	88	17	19.3	43	15	34.9						
1001-1250 gms.	92	63	68.5	59	44	74.6						
1251-1500 gms.	140	116	82.9	94	82	87.2						
1501-1750 gms.	193	183	94.8	133	120	90.2						
1751-2000 gms.	271	258	95.2	189	185	97.9						
2001-2500 gms.	1205	1192	98.9	127	122	96.1						
			===	660	570	86.4						
TOTALS	2080	1832	88.1	<u> </u>	570	00.4						
		Whit	e and Nonwhite		·							
Under 500 gms.	35	0	0	3	0	0						
501-750 gms.	107	4	3.7	25	2	8.0						
751-1000 gms.	140	26	18.6	77	27	35.1						
1001-1250 gms.	166	90	54.2	134	96	71.6						
1251-1500 gms.	222	174	78.4	179	151	84.4						
1501-1750 gms.	351	317	90.3	277	247	89.2						
1751-2000 gms.	508	474	93.3	406	390	96.1						
2001-2500 gms.	2387	2339	98.0	291	263	90.4						
TOTALS	3916	3424	87.4	1392	1176	84.5						

			W	hite		Nonwhite							
Hospital		Sur	vival		Survival			Survival		Born Out	Sur	vival	
-	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%	
Babies	2	0	0	_	_	_	_	_	-	· -	-	_	
Bellevue	1	0	0	_	_	-	-	-	-	-	-	_	
Bronx	_	_	-	1	0	0	2	0	0	_	_	_	
Brooklyn	1	0	. 0			-	-		-	_	-	-	
Elmhurst		-	-	-	-	_	-	-		-	_	. –	
Flushing		-	_	-	-		_		_	_		_	
Harlem	_ `	-	-	-	-	- `	5	0	0	_	-	_	
Jewish Brooklyn	_		-	-	-	_	1 1	0	0	-		_	
Kings County	. 3	0	0	_	-	-	16	0	U		_		
Lincoln	_	-	-	_	-	-	1	_	0	_			
L. I. Jewish	_	l –	-	- 1	-	_	1	0		-			
Mt. Sinai		-	-	-	-	_	-	_	_	1	0	0	
New York	_	-	-	1	0	0	_	0	0		J 5		
Queens Gen.	_	-	-	-	-	_	2	0	0	1 - <u>-</u>		_	
St. Vincent's (NY)	_	-	-		-	_	2	-	_		l _	_	
St. Vincent's (SI)			l		,-				<del></del>	==		==	
TOTALS	7	0	0	2	0	0	28	0	0	1	0	0	

Table 11 (Continued)
Survival Rate (501-750 grams)

			W	hite					Nor	white		
Hospital	Born In	Sur	vival	В. О.	Sur	vival		Sur	vival		Sur	vival
	DOTH III	No.	%	Born Out	No.	%	Born in	No.	%	Born Out	No.	%
Babies	4	0	0		_	-	2	0	0		-	_
Bellevue	1	0	0	1	0	.0	_	_			_	_
Bronx	5	1	20	_			3	0	0	1	0	0
Brooklyn	4	0	- 0				1	1	100	3	1	33.3
Elmhurst	_	_	_	1	0	0	2	0	0	1	0.	0
Flushing	3	0	0	_	_	_		_	_		_	
Harlem	_	_	-	_	_		13	1	7.7	_ :		_
Jewish Brooklyn	1	0	0	_	_		5	0	0	4	0	0
Kings County	6	0	0	_	_	_	16	0	Ö	_		_
Lincoln	4	0	. 0		_			_	_	_		_
L. I. Jewish	2	0	0	3	0	0	_		_			_
Mt. Sinai	5	.0	0	2	0	0	1	0	0	1	0	0
New York	3	0	0	3	0	0	4	0	Ö	4	1	25
Queens Gen.	6	0	0		_	·	14	1	7.1			
St. Vincent's (NY)		_	· -	1	0	0	2	0	0	_	_	_
St. Vincent's (SI)		l a — :	_		_	_		_		_		_
	=	=	==	=	=	===		==		=	=	
TOTALS	44	1	2.3	. 11	0	0	63	3	4.8	14	2	14.3

## Survival Rate (751-1000 grams)

			W	hite					Nor	white		٠
Hospital	Born In	Sur	vival	Born Out	Sur	vival	Dave to	Sur	vival	B O4	Sur	vival
	DOTAL III	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	1	0	0	3	0	0	5	0	0	2	1	50
Bellevue	1	0	0	2	0	0	_	_		3	2	66.7
Bronx	6	0	0	<del>-</del>		-	8	1	12.5	-	_	_
Brooklyn	<u> </u>	-	- :	- 3	1	33.3	1	0	0	3	2	66.7
Elmhurst	1	1	100	2	1	50	_	_	·	· _	_	
Flushing	3	1	33.3	-	-	_	2	1	50	1	1	100
Harlem	_	_	_	. 1	0	0	15	3	20	1	0	0
Jewish Brooklyn	1	0	0	4	2	50	5	. 3	60	7	0	. 0
Kings County	5	0	0	_	_		30	5	16.7	4	0	0
Lincoln	10	2	20	1	1	100	0			_	_	_
L. I. Jewish	-8	1	12.5	6	3	50	_	_		3	0	0
Mt. Sinai	- 5	2	40	6	2	33.3	1	0	0	5	2	40
New York	3	0	0	4	2	50	1	0	0	12	-5	41.7
Queens Gen.	5	2	40	· —	-	_	14	2	14.3	,		_
St. Vincent's (NY)	_	: .—	-	1	0	0	4	2	50	2	2	100
St. Vincent's (SI)	. 3	0	0	1	0	.0	2	0	0	· –	_	_
	=	=		=	=			=			=	
TOTALS	52	9	17.3	34	12	35.3	88	17	19.3	43	15	34.9

Table 11 (Continued)
Survival Rate (1001-1250 grams)

			w	hite					Non	white		
Hospital	S	Sur	vival		Sur	vival		Sur	vival	D	Sur	vival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	7	2	28.6	5	3	60	5	4	80	_	_	_
Bellevue	6	2	33.3	5	3	60		_	_	8	6	75
Bronx	6	2	33.3	9	- 5	55.6	3	- 3	100	- '	-	_
Brooklyn	. 5	2	40	4	4	100	4	3	75	13	11	84.6
Elmhurst	2	1	50	2	1	50	3	2	66.7	2	2	100
Flushing	6	4	66.7	3	1	33.3	2	1	50	1	1	100
Harlem	. –	_	-	_	_	-	18	17	94.4	1	0	0
Jewish Brooklyn	1	1	100	4	3	75	7	3	42.9	9	6	66.7
Kings County	4	0	0	2	2	100	19	10	52.6	6	5	83.3
Lincoln	8	3	37.5	'	_	_	6	5	83.3	_	-	-
L. I. Jewish	11	6	54.5	10	9	90	1	0	0	10	7	70
Mt. Sinai	11	3	27.3	10	7	70	4	3	75	4	2	50
New York	4	1	25	12	8	66.7	2	1	50	1	-0	0
Queens Gen.	2	0	0	.2	2	100	15	9	60	1	1	100
St. Vincent's (NY)		-	_	3	1	33.3	3	2	66.7	3	3	100
St. Vincent's (SI)	. 1.	0	0	4	3	75	-		-	_	-	-
·	=	=	=	=	=	===	===	=	==	==	=	=
TOTALS	74	27	36.5	75	52	69.3	92	63	68.5	59	44	74.6

Survival Rate (1251-1500 grams)

	. :		W	hite					Non	white		
Hospital	Born In	Sur	vival	Born Out	Sur	vival	Born In	Sur	vival	Born Out	Sur	vival
	DOTH III	No.	%	Born Out	No.	%	Born III	No.	%	Born Out	No.	%
Babies	5	2	40	2	2	100	7	7	100	1	1	100
Bellevue	10	. 7	70	11	8	72.7	1	1	100	8	5	62.5
Bronx	13	10	76.9	5	3	60	12	10	83.3	2	2	100
Brooklyn	4	0	- 0	7	6	85.7	2	2	100	16	15	93.7
Elmhurst	2	1	50	_	-	-	1	0	0	2	1	50
Flushing	8	7	87.5	7	7	100	1	1	100	2	2	100
Harlem			_ '	_	-	–	27	26	96.3	3	3	100
Jewish Brooklyn	4	4	100	6	5	83.3	20	18	90	19	17	89.5
Kings County	6	5	83.3	1	0	0	37	24	64.9	13	10	76.9
Lincoln	8	6	75	_	-		8	5	62.5	-	-	-
L. I. Jewish	2	1	50	10	9	90	-	_	-	4	3	75
Mt. Sinai	8.	. 5	62.5	8	6	75	3	3	100	7	7	100
New York	5	5	100	11	10	90.9	4	3	75	. 6	- 5	83.3
Queens Gen.		l		3	2	66.7	13	12	92.3	4	4	100
St. Vincent's (NY)	2	2	100	4	3	75	2	2	100	5	5	100
St. Vincent's (SI)	5	3	60	10	8	80	2	2	100	2	2	100
	=	=	==	=		===		=	=	=	=	=
TOTALS	82	58	70.7	85	69	81.2	140	116	82.9	94	82	87.2

Table 12. City of New York Premature Center Statistics Survival Percentages (by Weight) 1972
Total All Centers

501–750 gms. 751–1000 gms. 1001–1250 gms. 1251–1500 gms. 1501–1750 gms. 1751–2000 gms. 2001–2500 gms.  TOTALS  Under 500 gms. 751–1000 gms. 1251–1500 gms. 1251–1500 gms. 1251–1500 gms. 1751–2000 gms. 1751–1750 gms.	14 27 51 65 83 33 15 51 ==============================	0 1 24	% Survival 7.1 7.4 25.5 52.3 68.6 88.7 93.0 97.7 87.9  Nonwhite 0 1.9 29.3	8orn Out  1 20 55 65 94 154 169 163 721	No. Survived  0 4 26 41 72 138 154 146 581	% Survival  0 20 47.3 63.1 76.6 89.6 91.1 89.6 80.6
501–750 gms. 751–1000 gms. 1001–1250 gms. 1251–1500 gms. 1501–1750 gms. 1751–2000 gms. 2001–2500 gms.  TOTALS  Under 500 gms. 751–1000 gms. 1251–1500 gms. 1251–1500 gms. 1251–1500 gms. 1751–2000 gms. 1751–1750 gms.	27 51 65 83 33 15 51 =============================	2 13 34 57 118 200 929 1354	7.4 25.5 52.3 68.6 88.7 93.0 97.7 87.9 Nonwhite	20 55 65 94 154 169 163 721	26 41 72 138 154 146 581	20 47.3 63.1 76.6 89.6 91.1 89.6 80.6
751-1000 gms. 1001-1250 gms. 1251-1500 gms. 1501-1750 gms. 1751-2000 gms. 2001-2500 gms.  TOTALS  Under 500 gms. 501-750 gms. 1251-1000 gms. 1251-1500 gms. 1251-1500 gms. 1251-2000 gms. 1501-1750 gms. 1751-2000 gms.	51 655 83 33 15 51 =============================	13 34 57 118 200 929 1354	25.5 52.3 68.6 88.7 93.0 97.7 87.9 Nonwhite	55 65 94 154 169 163 721	26 41 72 138 154 146 581	47.3 63.1 76.6 89.6 91.1 89.6 80.6
1001–1250 gms. 1251–1500 gms. 1501–1750 gms. 1751–2000 gms. 2001–2500 gms.  TOTALS  Under 500 gms. 501–750 gms. 1251–1500 gms. 1251–1500 gms. 1501–1750 gms. 1751–2000 gms.	65 83 33 15 51 39 26 53 82 85	34 57 118 200 929 1354	52.3 68.6 88.7 93.0 97.7 87.9 Nonwhite	65 94 154 169 163 721	41 72 138 154 146 581	47.3 63.1 76.6 89.6 91.1 89.6 80.6
1251-1500 gms. 1501-1750 gms. 1751-2000 gms. 2001-2500 gms. 2001-2500 gms.  TOTALS  Under 500 gms. 501-750 gms. 1001-1250 gms. 1251-1500 gms. 1501-1750 gms. 1751-2000 gms. 2001-2500 gms. 201-2500 gms. 201-2500 gms. 201-2500 gms. 201-2500 gms. 301-751-2000 gms. 201-2500 gms. 301-751-2000 gms. 301-750 gms.	83 33 15 51 39 = 26 53 82 85	57 118 200 929 1354	68.6 88.7 93.0 97.7 87.9 Nonwhite	94 154 169 163 721	41 72 138 154 146 581	76.6 89.6 91.1 89.6 80.6
1501-1750 gms. 1751-2000 gms. 2001-2500 gms. 2001-2500 gms.  TOTALS  Under 500 gms. 501-750 gms. 1001-1250 gms. 1251-1500 gms. 1501-1750 gms. 1751-2000 gms. 2001-2500 gms. 2001-2500 gms. 201-2500 gms. 201-2500 gms. 201-2500 gms. 301-751-2000 gms. 301-751-2000 gms. 301-751-2000 gms. 301-751-2000 gms. 301-751-2000 gms. 301-751-750 gms. 301-750 gms.	33 15 51 == 39 26 53 82 85	118 200 929 1354	88.7 93.0 97.7 87.9 Nonwhite	154 169 163 721	138 154 146 581	89.6 91.1 89.6 80.6
1751-2000 gms. 2 2001-2500 gms. 99 TOTALS 153  Under 500 gms. 501-750 gms. 1001-1250 gms. 1251-1500 gms. 2001-2500 gms. 2001-2500 gms. 2001-2500 gms. 1001-1250 gms. 13001-1250 gms. 13001-1250 gms. 13001-1250 gms. 13001-1250 gms. 115001-1250	15 51 == 39 = = 53 82 85	200 929 1354 0 1 24	93.0 97.7 87.9 Nonwhite 0 1.9	169 163 721 3 14	154 146 581 0 2	91.1 89.6 80.6
2001-2500 gms. 99 TOTALS 155  Under 500 gms. 501-750 gms. 1001-1250 gms. 1551-1500 gms. 1651-1751-2000 gms. 29 2001-2500 gms. 29 TOTALS 175  Under 500 gms. 99 TOTALS 175  Under 500 gms. 1001-750 gms. 11501-750 gms. 1	51 ====================================	929 1354 0 1 24	93.0 97.7 87.9 Nonwhite 0 1.9	163 721 3 14	154 146 581 0 2	91.1 89.6 80.6
TOTALS 153  Under 500 gms. 501-750 gms. 1001-1250 gms. 1251-1500 gms. 1501-1750 gms. 161751-2000 gms. 29001-2500 gms. 29001-2500 gms. 1751-1000 gms. 501-750 gms. 1751-1000 gms. 1501-750 gms. 1751-1000 gms. 1501-750 gms. 1501-750 gms. 1501-750 gms. 1501-1250 gms. 15001-1250 gms. 15001-1	26 53 82 85	0 1 24	87.9 Nonwhite 0 1.9	721 3 14	581 0 2	80.6
Under 500 gms. 501-750 gms. 751-1000 gms. 1001-1250 gms. 1251-1500 gms. 1501-1750 gms. 1751-2000 gms. 2001-2500 gms. 9 TOTALS  Under 500 gms. 501-750 gms. 501-750 gms. 1751-1000 gms. 18501-750 gms. 18501-750 gms. 19501-750 gms.	26 53 82 85	0 1 24	Nonwhite 0 1.9	3 14	0 2	0
Under 500 gms. 501-750 gms. 751-1000 gms. 1001-1250 gms. 1251-1500 gms. 1501-1750 gms. 1751-2000 gms. 2001-2500 gms. 9 TOTALS  Under 500 gms. 501-750 gms. 501-750 gms. 11001-1250 gms. 11001-1250 gms.	26 53 82 85	0 1 24	Nonwhite 0 1.9	3 14	0 2	0
501-750 gms. 751-1000 gms. 1001-1250 gms. 1251-1500 gms. 1501-1750 gms. 1751-2000 gms. 2001-2500 gms. 2001-2500 gms. 301-750 gms. 401-750 gms. 501-750 gms. 501-750 gms. 751-1000 gms. 11001-1250 gms.	53 82 85	0 1 24	0 1.9	14	2	
501-750 gms. 751-1000 gms. 1001-1250 gms. 1251-1500 gms. 1501-1750 gms. 1751-2000 gms. 2001-2500 gms. 9  TOTALS  Under 500 gms. 501-750 gms. 501-750 gms. 11001-1250 gms. 11	53 82 85	1 24	1.9	14	2	
751-1000 gms. 1001-1250 gms. 1251-1500 gms. 1501-1750 gms. 1751-2000 gms. 2001-2500 gms.  TOTALS  Under 500 gms. 501-750 gms. 751-1000 gms. 11001-1250 gms. 11	82 85	24			,	14.3
1001–1250 gms. 1251–1500 gms. 1501–1750 gms. 1751–2000 gms. 2001–2500 gms.  TOTALS  Under 500 gms. 501–750 gms. 751–1000 gms. 13 1001–1250 gms.	85		29.3	E4		
1251–1500 gms. 9 1501–1750 gms. 10 1751–2000 gms. 29 2001–2500 gms. 9 TOTALS 173  Under 500 gms. 501–750 gms. 13 1001–1250 gms. 13				51	31	60.8
1501–1750 gms. 16 1751–2000 gms. 2! 2001–2500 gms. 9: TOTALS 17:  Under 500 gms. 501–750 gms. 15 1001–1250 gms. 15		43	50.6	70	43	61.4
1751–2000 gms. 2! 2001–2500 gms. 9: TOTALS 17:  Under 500 gms. 501–750 gms. 751–1000 gms. 1: 1001–1250 gms. 1:	94	74	78.7	76	64	84.2
2001-2500 gms. 9 TOTALS 17: Under 500 gms. 501-750 gms. 15: 751-1000 gms. 15: 1001-1250 gms. 15:	60	137	85.6	127	117	92.1
TOTALS 17:  Under 500 gms. 501-750 gms. 751-1000 gms. 1: 1001-1250 gms. 1:	53	243	96.0	171	166	97.1
Under 500 gms. 501–750 gms. 751–1000 gms. 13	73	958	98.5	129	124	96.1
501–750 gms. 13 751–1000 gms. 13 1001–1250 gms. 15	<del>=</del> = =	1480	<del></del> 85.7	641	<del></del> 547	<del>===</del> 85.3
501–750 gms. 13 751–1000 gms. 13 1001–1250 gms. 15	- <u> </u>	White	and Nonwhite		<u> </u>	
501–750 gms. 13 751–1000 gms. 13 1001–1250 gms. 15	39	0	0	4	0	0
751–1000 gms. 13 1001–1250 gms. 15	80	3	3.7	34	6	17.6
1001-1250 gms. 15	33	37	27.8	106	57	53.8
	50	77	51.3	135	84	62.2
1251-1500 gms. 1	77	131	74.0	170	136	80.0
			87.0	281	255	90.7
	93	255		1		
2001–2500 gms. 193	93 68	255 443	94.7	340	320	94.1
TOTALS 326	68			340 292	320 270	94.1 92.5

## Survival Rate (500 grams)

			W	/hite					Noi	nwhite		
Hospital	Born In	Sui	vival	Born Out	Sur	vival	B 1-	Sur	vival	B O	Sui	vival
	BOIN III	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	_	_		_	_	_		_	_	_	_	<u>, –                                     </u>
Bellevue	_	_	_	1	0	0	1	0	0	_		_
Bronx	1	0	0	-	_	_	1	o	0	_		_
Brooklyn	4	0	0	_	-				_	_	_	
Elmhurst	_	_ [		- 4 -	_				_	<b>—</b> ,: :	_	_
Flushing	_	-	<b>—</b> .	<del>-</del> -	-	_				1	—	
Harlem		-	_	-		_	`2	0	0	_		
Jewish Brooklyn	_	-	_	] -	_		_	-		2	0	0
Kings County	_	_			-		15	0	0			-
Lincoln	2	0	0	_	- !		_	_	_		_	
L. I. Jewish	3 2	0	0	-	_	_ *	l -	_	· —	_		·
Mt. Sinai	2	0	0	_	_	·	1 1	0	.0	1	0	0
New York	,;	-	. —	-						— <sub>5,1</sub> ,1	_	_
Queens Gen.	-	_	_	] –	_	-	6	lol	0	_	_	_
St. Vincent's (NY)	1	1	100	_	_	_	_	-		_		_
St. Vincent's (SI)	1	0	0	_	1 22	_	_	-	_	. –	_	-
TOTALS	14	1	7.1	<del>-</del>	<u></u>	0	26	<u></u>	0	3		0

Table 12 (Continued)
Survival Rate (501-750 grams)

			W	hite					Non	white		
Hospital		Sur	vival		Sur	vival		Sur	vival		Sur	vival
e de la companya de	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	1	0	0	_	_	-	7	0	0	2	0	0
Bellevue	1	0	0	_		-	_	_	. <b>_</b>	1	0	0
Bronx	2	0	0	1	0	0	2	0	0		_	_
Brooklyn	2	.0	. 0	1	0	0	2	0	0	2	0	0
Elmhurst	1	0	0	_		-	1	0	0	_	_	
Flushing	_	-	_	2	1	50	1	0	0			-
Harlem	_	_		_	_		8	0	0	_	_	-
Jewish Brooklyn	1	0	0	4	1	25	3	0	0	5	e 0	0
Kings County	3.	0	. 0	_	-	_	19	0	0	_	e	-
Lincoln	6	2	33.3	_	_	-	2	1	50	_	_	_
L. I. Jewish	2	0	0	1	0	0	_	_	_	2	1	50
Mt. Sinai	·	_		2	0	0	_	_	_	_	_	
New York	- 2	0	0	2 7	1	14.3	1	0	0	1	1	50
Queens Gen.	. 1	0	Ō	_	_	_	4	0	0	_	_	_
St. Vincent's (NY)	2	0	0	2	1	50	_	_	_	_		
St. Vincent's (SI)	3	0	0		_		3	0	0	1	0	0
	=	=	=	=		==	=	=	=		=	==
TOTALS	27	2	7.4	20	4	20	53	1	1.9	14	2	14.3

Survival Rate (751-1000 grams)

			W	hite					Non	white		
Hospital	B	Sur	vival		Sur	vival		Sur	vival	D	Sur	vival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	* <u>-</u> '	_	_	3	2	66.7	7	1	14.3	4	2	50
Bellevue	2	0	0	4	1	25		_	_	3	1	33.3
Bronx	1	0	0	2	2	100	9	3	33.3	1	1	100
Brooklyn	2	0	0	1	1	100	1	1	100	5	4	80
Elmhurst	8	1	12.5	<u>`</u> :	_	_	2	1	50	_	_	
Flushing	3	1	33.3		_	_	_	_	_		_	_
Harlem	_	_		1	0	0	20	5	25	2	2	100
Jewish Brooklyn	2	0	0	8	3	37.5	5	1	20	13	10	76.9
Kings County	6	0	0	1	1	100	17	3	17.6	1	0	0
Lincoln	- 6	- 2	33.3	_	_	_	5	3	60	_	_	_
L. I. Jewish	5	3	60	8	3	37.5	1	0	0	9	5	55.6
Mt. Sinai	2	1	50	9	4	44.4	2	1	50	4	2	50
New York	9	4	44.4	16	8	50		_	_	6	3	50
Queens Gen.	1	0	0	1	0	0	11	5	45.5	_	_	_
St. Vincent's (NY)	2	1	50	_	_	_	1	0	0	1	0	0
St. Vincent's (SI)	2	0	0	1	1	100	1	O	0	2	1	50
	==	=	===	==	=	=	=	=		=	=	=
TOTALS	51	13	25.5	55	26	47.3	82	24	29.3	51	31	60.8

Table 12 (Continued)
Survival Rate (1001-1250 grams)

	.nvi		W	hite					Nor	nwhite		
Hospital	Born in	Sui	vival	Born Out	Sur	vival	Born In	Sur	vival	Born Out	Sur	vival
	Dom III	No.	%	Doin Out	No.	%	BOTH III	No.	%	Born Out	No.	%
Babies	3	0	0	_	_	_	1	0	0	1	1	100
Bellevue	1	0	0	6	3	50	3	2	66.7	3	3	100
Bronx	7 -	. 4	57.1	3	2	66.7	5	0	0	3	3	100
Brooklyn	4	3	75	4	2	50	2	: 1	50	14	8	57.1
Elmhurst	4	- 3	75		_	_	1	0	0	_	_	F
Flushing	4	2	50	3	3	100	_	<u> </u>	_	_	l	<u></u>
Harlem	1	1	100	<u> </u>		l –	26	10	38.5	1	1	100
Jewish Brooklyn	2 .	0	0	5	1	20	13	9	69.2	15	7	46.7
Kings County	1 - v2 - v2	, <u> </u>	_	_	_	_	16	9	56.2	1	1	100
Lincoln	11	5	45.5		_	<del> </del>	5	3	60			
L. I. Jewish	5	. 3	60	14	11	78.6	_	_	_	12	6	50
Mt. Sinai	10	7	70	8	5	62.5	3	3	100	8	6	75
New York	4	3	75	13	10	76.9	3	2	66.7	8	4	50
Queens Gen.	1	1	100	_			6	3	50	1	1	100
St. Vincent's (NY)	2	1	50	4	2	50	_		-	3	2	66.7
St. Vincent's (SI)	6	1	16.7	5	2	40	1	1	100			
	=	=	==	=	=	=	=	=			-=	==
TOTALS	65	34	52.3	65	41	63.1	85	43	50.6	70	43	61.4

### Survival Rate (1251-1500 grams)

	ote.		W	hite					Non	white		
Hospital	Born In	Su	vival	B 0-4	Sur	rvival		Sui	rvival	5	Sur	vival
ing.	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	10	4	40	6	5	83.3	7	3	42.9	3	2	66.7
Bellevue	5	4	80	10	5	50	_	_	-	3	3	100
Bronx	6	6	100	7	4	57.1	7	7	100	2	0	0
Brooklyn	7	6	85.7	8	8	100	3	2	66.7	15	12	80
Elmhurst	5	2	40	、2.	2	100	3	3	100	4	3	75
Flushing	5	- 5	100	4	3	75	2	1	50	1	0	0
Harlem -		_	-	_		_	21	18	85.7	1	1	100
Jewish Brooklyn	2	1	50	4	- 1	25	8	7	87.5	17	15	88.2
Kings County	6	4	66.7	1	1	100	20	16	80	1	1	100
Lincoln	12	10	83.3	_	_		4	4	100		_	_
L. I. Jewish	6	5	83.3	19	15	78.9	_	_ '	_	9	8	88.9
Mt. Sinai	9	6	66.7	8	6	75	. 4	3	75	8	8	100
New York	3	1	33.3	10	8	80	3	2	66.7	5	4	80
Queens Gen.	2	1	50	2	1	50	9	6	66.7	4	4	100
St. Vincent's (NY)	3	2	66.7	5	5	100	2	1	50	1	1	100
St. Vincent's (SI)	2	0	0	8	8	100	1	1	100	2	2	100
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	==	=	=	==	=	==	=	=	=	=	=	===
TOTALS	83	57	68.7	94	72	76.6	94	74	78.7	76	64	84.2

Table 13. City of New York Premature Center Statistics Survival Percentages (by Weight) 1973
Total All Centers

			White			
Weight Group	Born In	No. Survived	% Survival	Born Out	No. Survived	% Survival
Under 500 gms.	6	0	0	1	0	0
501-750 gms.	21	2	9.5	21	5	23.8
751-1000 gms.	41	12	29.3	46	26	56.5
1001-1250 gms.	55	34	61.8	60	37	61.7
1251-1500 gms.	67	53	79.1	103	74	71.8
1501-1750 gms.	123	107	87.0	142	126	88.7
1751-2000 gms.	204	189	92.6	160	142	88.8
2001-2500 gms.	641	616	96.1	160	135	84.4
TOTALS	1158	1013	87.5	693	545	78.6
	1		Nonwhite	L		
Under 500 gms.	16	0	0	2	0	0
501-750 ams.	29	3	10.3	13	1	7.7
751-1000 ams.	57	25	43.9	41	23	56.1
1001–1250 gms.	77	43	55.8	47	33	70.2
1251-1500 gms.	78	61	78.2	74	60	81.1
1501-1750 gms.	174	161	92.5	115	106	92.2
1751-2000 gms.	242	232	95.9	156	147	94.2
2001-2500 gms.	809	787	97.3	114	109	95.6
2001-2300 gms.	309		<del>37.3</del>		103	
TOTALS	1482	1312	88.5	562	479	85.2
		Whit	e and Nonwhite			
Under 500 gms,	22	0	0	3	0	0
501-750 gms.	50	5	10.0	34	6	17.6
751-1000 gms.	98	37	37.8	87	49	56.3
1001-1250 gms.	132	77	58.3	107	70	65.4
1251~1500 gms.	145	114	78.6	177	134	75.7
1501-1750 gms.	297	268	90.2	257	232	90.3
1751-2000 gms.	446	421	94.4	316	289	91.5
2001-2500 gms.	1450	1403	96.8	274	244	89.0
TOTALS	2640	2325	88	1255	1024	81.6

## Survival Rate (under 500 grams)

			W	hite					Nor	nwhite		
Hospital		Sur	vival	<b>D</b> 10.	Sur	vival	<b>.</b>	Sur	vival	Born Out	Sur	vival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	_	_		_	_			_	-			1 <u>- 1                                 </u>
Bellevue		-	.—		-			-	_		-	_
Bronx					_	_	1	0	0	_		· —
Brooklyn		-			-			_		_	-	
Elmhurst	_	-	_ '		-		l –					. — .
Flushing	·			_		_	-	_	_		-	_
Harlem		_	<b>—</b> ·		-		5	0	0		-	_
Jewish Brooklyn	_			1 -	0.	0	1	0	0	1	0	0
Kings County '	4	0	0	_	_ '		4	0	0	] 1	0	0
Lincoln	_	-	_	-	-	. —	. 1	0	0	-	_	
L. I. Jewish	2	0	0	_	_	—	_	-		-		_
Mt. Sinai	_		_		-	_	_		:	-	-	_
New York	_	-		-	-	_	-		· —	'	_	_
Queens Gen.		_		-	-	_	2	0	0	· -	_	-
St. Vincent's (NY)	_		_	_			_	-	_		-	. —
St. Vincent's (SI)		-	-	l –	-	_	2	0	0	-	1 - 1	_
TOTALS	6	=	0	=	0	0	16	0	0	2	<u> </u>	0

Table 13 (Continued)
Survival Rate (501-750 grams)

			W	hite					Nor	white		
Hospital	Born In	Sur	vival	D	Sur	vival		Sur	vival		Sur	vival
	DOM: III	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	_	_	_	_	_	_	2	0	0	_	1	-
Bellevue	2	0	0	1	1	100		_		_	_	_
Bronx	-	_	- :	1	0	0	4	0	0	_		7. <u>4</u> .
Brooklyn	6	2	33.3	1	0	0	_	_		3	0	0
Elmhurst	1	0	0	_	_	_	_	_	_	_	_	
Flushing	_	_	_		_			_		· <u></u>	_	
Harlem		_		· -	_	_	5	0	0		_	_
Jewish Brooklyn	1	0.	0	-	_	_	4	1	25	3	1	33.3
Kings County	2	0	0		_	_	2	o	0	_	·	
Lincoln	_	_	_	_	_		1	0	0		_	-
L. I. Jewish	2	0	0	5	1	20	1	Ö	0	3	0	0
Mt. Sinai	1	0	0		2	100	2	2	100	1	0	0
New York	2	0	0	2 7	1	14.3	_	_		2	0	Ö
Queens Gen.	1	0	0		_	_	7	0	Ö		_	
St. Vincent's (NY)	1	o	0	2	0	0	_	_	_	1	0	0
St. Vincent's (SI)	2	0	0	<u></u>	0	<u> </u>	_1	9	0		=	=
TOTALS	21	2	9.5	21	5	23.8	29	3	10.3	13	1	7.7

## Survival Rate (751-1000 grams)

			Ŵ	hite	1 <u>-</u> 1				Nor	white		¥ .
Hospital	Born In	Sur	vival	B O4	Sui	rvival		Sui	rvival		Sur	rvival
	BOTH III	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	4	2	50	4	2	50	6	1	16.7	1	0	0
Bellevue	3	1	33.3	6	2	33.3	_		_	1	0	0
Bronx	1	0	0	2	0	0	3	0	0	1	0	ō
Brooklyn	3	1	33.3	2	2	100	2	1	50	5	1	20
Elmhurst	1.	0	0	1	1	100	2	1	50	2	1	50
Flushing	1	0	0	1	1	100					_	_
Harlem	_	_				_	13	9	69.2	_	_	_
Jewish Brooklyn	1	0	0	5	2	40	11	5	45.4	10	4	40
Kings County	5	0	0	_		_	5	. 0	0	1	1	100
Lincoln	4	1	25	_	_		\ \	_	_			
L. I. Jewish	5	3	60	11	5	45.4	1	0	0	6	4	66.7
Mt. Sinai	7	4	57.1	2	2	100	6	2	33.3	6	6	100
New York	2	0	0	11	9	81.8	3	3	100	8	6	75
Queens Gen.	_	_	_		_	_	4	2	50	_		′-
St. Vincent's (NY)	1	0	0	_	_	_	1	1	100		1771 	
St. Vincent's (SI)	3	0	Ö	1	0	. 0				_	_	
		=	==	=			_				=	
TOTALS	41	12	29.3	46	26	56.5	57	25	43.9	41	23	56.1

Table 13 (Continued)
Survival Rate (1001–1250 grams)

			W	hite		*			Non	white		
Hospital		Sur	vival		Sur	vival		Sur	vival	D O4	Sur	vival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	3	1	33.3	6	2	33.3	. 1	0	0	1	1	100
Bellevue	2	2	100	8	5	62.5		_	_	-	-	- , -
Bronx	6	3	50	4	3	75	5	5	100	1	1	100
Brooklyn	4	2	50	3 -	2	66.7	5	2	40	. 5	4	80
Elmhurst	4	3	75	1	0	0	4	- 3	75	1	1	100
Flushing	1	1	100	2	1	50		_	-		-	_
Harlem	· .	_		· · ·	_	_	21	14	66.7	-		-
Jewish Brooklyn	1	1	100	5	2	40	6	2	33.3	11	c 9	81.
Kings County	-2	1	50	1	. 1	100	2	1	50	1	0	0
Lincoln	11	7	63.6	_	-	-	8	5	62.5	_	_	_
L. I. Jewish	3	3	100	9	8	88.9	_	-	_	- 11	8	72.
Mt. Sinai	4	4	100	6	3	50	5	3	60	3	3	100
New York	7	3	42.9	10	6	60	6	3	50	. 9	4	45
Queens Gen.		_		1	1	100	8	4	50	1.	1	100
St. Vincent's (NY)	2	2	100	2	2	100	4	1	25	3	1	33
St. Vincent's (SI)	<u>5</u>	1 =	20	2	1	50	<u>2</u>	O	0		=	_
TOTALS	55	34	61.8	60	37	61.7	77	43	55.8	47	33	70.

## Survival Rate (1251-1500 grams)

			W	hite			. :		Non	white		
Hospital		Sur	vival	5	Sur	vival		Sur	vival	Born Out	Sur	vival
	Born In	No.	%	Born Out	No.	%	Born In	No.	%	Born Out	No.	%
Babies	7	4	57.1	8	4	.50	5	5	100	2	1	50
Bellevue	11	8	72.7	4	- 3	75		-	-	3	2	66.7
Bronx	6	3	50	6	4	66.7	8	5	62.5	1	0	0
Brooklyn	7	5	71.4	9	8	88.9	4	3	75	16	14	87.5
Elmhurst	1 .	1	100	3	1	33.3	4	3	75	_	-	_
Flushing	3	3	100	6	4	66.7	1	1	100	3	. 3.	100
Harlem		_	_	-	_	l. —	12	8	66.7	-	-	
Jewish Brooklyn	6	4	66.7	15	13	86.7	12	10	83.3	20	17	85
Kings County	. 3	3	100	2	2	100	3	3	100	1	1	100
Lincoln	. 4	4	100	1	11,	100	7	5	71.4	2	2	100
L. I. Jewish	2	2	100	16	14	87.5	2	0	0	7	7	100
Mt. Sinai	3	2	66.7	6	3	50	5	5	100	. 7	3	42.9
New York	4	4	100	15	11	73.3	1	1	100	8	7	87.5
Queens Gen.	4	4	100	_	-	-	11	10	90.9	2	1	50
St. Vincent's (NY)	3	3	100	5	0	0	3	2	66.7	2	2	100
St. Vincent's (SI)	3	3	100	7	6	85.7	-	-		-		-
	==	=	==	=	===	==	=	=		=	=	==
TOTALS	67	53	79.1	103	74	71.8	78	61	78.2	74	60	81.1

Table 15. Neonatal Survival by Birth Weight (< 1000 grams) Province of Quebec

Table 14. Deaths/1000 Livebirths — 1966-1973 State of Oregon/United States

	1966	1967	1968	1969	1970	1971	1972	1973
Neonatal Mortality			1				- : . · · ·	
United States	17.2	16.2	15.9	15.6	15.1	14.2	13.6	13.0
Oregon	15.1		14.3					10.5
Premature Mortality Oregon (1001-								
2500 gms)	115.7	101.5	106.3	83.7	87.6	97.2	86.7	72.2

Birth Weight (gm)	Number Liveborn	Number Survived	% Survived	Number Stillbirths	% Stillbirths
501-550	101	0	0.0	80	44.2
551-600	117	0	0.0	73	38.3
601-650	75	1	1.3	59	44.0
651-700	136	2	1.5	79	36.7
701-750	93	3	3.2	50	35.0
751-800	97	4	4.1	51	34.5
801-850	83	. 8	9.6	39	32.0
851-900	83	9	10.8	36	30.2
901-950	123	18	14.6	74	37.6
951-1000	103	18	17.5	54	34.3

Table 16. Referral Neonatal Intensive Care Results for 501-1000g Infants Admitted 0-24H Age to Montreal Children's Hospital 1970-1974 Inclusive

Birth Weight	Number		Deaths	Survi	vors (disch	arged alive)
(gm)	Admissions	0 – 7 Days	After 7 Days	Number	%	Number on Respirators Who Survived
501-550	1	1 s <b>1</b> fe	0	0	0	(0)
551-600	3	2	1	Ô	0	, (0)
601-650	4	4	0	. 0	. 0	(0)
651-700	12	11	1	o.	. 0	(0)
701-750	. 8	6	n	2	25	
751-800	13	. 7	4	2	25 15	(1/2)
801-850	15	9	3	2		(0/2)
851-900	9	5	2	3	20	(0/3)
901-950	19	8		2	22	(0/2)
951-1000	20	10	7 2	4 8	21 40	(2/4) (5/8)
Subtotals						44.
501-750	28	24	; • <b>2</b>	2		(4 (0)
751-1000	76	39	18	19	7 25	(1/2) (7/19)
Total	104	63	20	21	32	(8/21)

Figures courtesy Miss Collinge, M.Sc.N., Montreal Children's Hospital, Quebec, Canada

These infants were transferred from the following hospitals, and include for practical purposes all 501-1000 gm survivors from these hospitals.

St. Mary's	Livebirths 1970-1974	. 1	Livebir	ths 1970-1974
Lachine General	7000	Catherine Booth		6000
Reddy Memorial	3100	Santa Cabrini		6600
Montreal General	2000	Queen Elizabeth		4600
Bellechasse	6900	Brome Missisquoi		2300
Lakeshore	8700	Plattsburgh, N.Y.		5000
	7300	Jean Talon		6800
Notre-Dame	9400	Saranac Lake, N.Y.		1500
Barrie Memorial	1200	Lasalle General		6800

TOTAL POPULATION REPRESENTED = 85,200 CONSECUTIVE LIVEBIRTHS

21 Survivors 501-1000 gm/ $\pm$  85,200 livebirths = rate of 2.5/10,000 livebirths.

Table 17. Neonatal Survival By Birth Weight Stanford University Medical Center

			7 17							<u> </u>		
Birth Weight (gm)	Number Liveborn	Gesta	er Died ational (wks) >28	Number Survived	% Survived	Number Stillborn	Number Liveborn	Numbe Gesta Age (	tional	Number Survived	% Survived	Number Stillborn
				1964		:				1965		
Less than 500	. 0	0	0	0	0	7	1	1	0	0	0.0	1.
501-550	1	1	0	0	0	3	2	2	_	0	0.0	1
551-600	1	. 1	. 0	. 0	0	2	0	_	_	_	_	0
601-650	0	. 0	0	_	<del>.</del>	0	1	1	_	0	0.0	0
651-700	0	0	0 .	_	_	1	0	0	_	_		1
701-750	0	0	0	. <u></u>	_	2	0	0			-	0
751-800	0	0	0		_	2	0	0	_			0
801-850	1	1	0	_	_	2	0	0	_	_	_	0
851-900	. 1	1	. 0	0	. 0	.0	1	1	_	0	0.0	0
901-950	0	0	0.	·	·	0	3	2		. 1	33.3	1
951-1000	0	0	; · 0	-	_	0	4	2		2	50,0	0
TOTAL	4	4	0.	0	0	19 (82.6%)	12	9	_	3	7.5	4 (25%)
				1966						1967		
Less than 500	0	_		_		. 1	1	1	0	0	0.0	1
501-550	0	_	_		_	0	0	_	_	_	_	2
551-600	0	_			<u> </u>	1	1	1	0	0	0.0	2
601-650	0			· · ·	_	1	0	_	_	_		1
651-700	. 2	2	. 0	0	0	0	2	1	0	1	50.0	2
701-750	1	1	0	0	0	0	0	_	_	_	_	1
751-800	0	_		_	_	2	1	1	0	0	0.0	. 0
801-850	. 0	_				1	3	1	1	1	33.3	1 .
851-900	2	2	. 0	0	0	0	1	0	0	. 1	100.0	1
901-950	. 1	1	0	0	0	0	4	4	0	0	0.0	0
951-1000	. 0	_			-	0	2	1	0	1	50.0	0
TOTAL	6	6	_	0	0	6 (50%)	15	10	1	4	26.7	11 (42.3%)
			3.0	1968						1969		
Less than 500	4	4	0	0	0	1	1	1	0	0	0.0	3
501-550	0	0 .	0	_		0	0	0	0	_	_	0
551-600	0	0	0	_	_	0	1	1	0	0	0.0	1
601-650	0	0	0		<del></del>	0	0	0	0	· _	-	0
651-700	1	1	0	0	0	0	1	1	0	0	0.0	2
701-750	0	0 -	0	-	-	0	0	0	0	<u>-</u>	_	3
751-800	0	0	0	-	_	0	1	. 1 ,	0	0	0.0	. 0
801-850	0	0	0			<sup>3</sup> 1	0	0	0	_	_	0
851-900	1	1	0	0	0	. 1	. 1	1	0	0	0.0	. 0
901-950	1	1	0	. 0	. 0	<b>~</b> 0	3	2	0	. 1	33.3	0
951-1000	0	0	0			0	1	0	0	1	100.0	0
TOTAL	7	7	0	0	0	3 (17.6%)	9	7	0	2	22.2	9 (50%)

Table 17. (Continued)

Birth Weight (gm)	Number Liveborn	Gesta	er Died itional (wks) >28	Number Survived	% Survived	Number Stillborn	Number Liveborn	Gesta	er Died itional (wks) <28	Number Survived	% Survived	Number Stillborn
				1970						1971	1 /	
Less than 500	1	1	0	0	0.0	1	1	1	0	0	0.0	2
501-550	2	2	0	0	0.0	0	0	0	0	_	· -	0
551-600	. 2	1	0	1	50.0	0	1	1	0	0	0.0	2
601-650	0	0	0	_	_	0	1	1	0	0	0.0	0
651-700	2	2	0 -	0	0.0	0	1	1	0	0	0.0	1
701-750	0	0	0	· <u> </u>	·	0	0	0	0		· '	0
751-800	0	0	0	_	_	· 0	. 0	0	0	_	·	0
801-850	2	- 1	0	1	50.0	0	0	0	0	_	1 <b>-</b> 1	0
851-900	1	1	0	0	0.0	0	2	2	0	0	0.0	0
901-950	3	3	0	0	0.0	0	0	0	0	_	- <del>-</del>	1
951-1000	4	3	1	0	0.0	, 0	4	1	0	3	75.0	0
TOTAL	17	14	1	2	11.8	1	10	7	0	3	30.0	6
						(5.6%)						(37.5%)
				1972						1973		
Less than 500	2	2	0	0	0.0	1	1	1	0	. 0	0.0	1
501-550	0	0	. 0	0	0.0	0	0	0	0		<del></del> -	1
551-600	1	1	0	0	0.0	0	0	0	0	<del></del>	. <u>.</u> .	0
601-650	2	2	0	ō	0.0	0	.0	0	0	_	_	0
651-700	1	0	1	0	0.0	0	0	0	0	_	1 <u>1</u>	2
701-750	1	1	0	0	0.0	1	2	2	0	0	0.0	ō
751-800	0	0	0	U	0.0	0	2	2	0	0	0.0	Ö
801-850	0 .	0	. 0		_	0	1	1	0	0	0.0	0.1
851-900	0	0	. 0		_	0	o	0	0	U	- -	2
901-950	2	1	0	1	- -		1	1	0	1	50.0	0
951-1000	1	Ö	0	1	50.0 100.0	1	2 2	2	0	0	0.0	Ô /
TOTAL	10	7	1,	2	20.0	3	10	9	0	1	10.0	7
					- N. L.	(23.1%)	120 42 (7.4)					(41.2%)
			· · · · · · · · · · · · · · · · · · ·	1974	# **							
Less than 500	0	0	0	—	. <del>-</del>	3						
501-500	1	1	0	0	0.0	1					Ass. A	
551-600	1	1	Q	0	0.0	0	Í		, n			
601-650	0	0	0	_	_	0	•				·	37.
651-700	0	0	0	_	_	0						
701-750	2	2	0	0	0.0	1						14, 34
751-800	0	0	0			1	].		•			
801-850	1	1	0	<i>i</i> 0	0.0	2						
851-900	1	1	0	0	0.0	0						
901-950	o	0	0			0	<b> </b> .					Say Say
951-1000	1	1	0	0	0.0	0						gila.
TOTAL		<del></del>								i		
TOTAL	7	7	0	0	0.0	8 (53.3%)						
	•											

Table 18. Neonatal Survival by Birth Weight and Gestational Age Liveborns — Birth Weights < 1000 grams — 1963-1973 University of Colorado Medical Center, Denver

Birth Weight (gms)	24	26	28	Ges 30	tation	al Age 34	(wks) 36	38	Unknown	Total Number	Number Survived	% Survived
7/1/63 — 6/30/64												
Less than 450												
451-500									4			
501-550	1											
551-600	3									1 3	0	0
601-650	3									. 3	. 0	0
651-700							1				,	
701-750												18 B 30
751-800		1								1	Ö	0
801-850		•								•	,	, <b>U</b>
851-900							1			1	0	0
901-950		- 5 -		2		t - ·	* -			2	1	50
951-1000								100		2		50
					<del></del>							
TOTAL	4	1	<del></del>	2			1			8	1	12.5
7/1/64 — 6/30/65									1.04			
Less than 450										,		
451-500												
501-550												
551-600											_	
601-650	1									1	0	0
651-700	1 2									1	0	0
701-750	2								1	3	0	0
751-800									1	1	0	0
801-850	1									1	0	0
851-900									1	1	0	0
901-950	·	1					,			1	· 0	0
951-1000		1								1	0	0
951-1000		2					-			2	1	50
TOTAL	5	4							3	12	1	8.3
7/1/65 - 6/30/66												
Less than 450												
451-500												. A
501-550				1						1	0	0
551-600	2									· 2	0	0
601-650		1								1	0	0
651-700	2									2	0	0
701-750	2									2	0	0
751-800	1									1	0	0
801-850	. 1									1	. 0	0
												, ,
851-900												
901-950												

Table 18 (Continued)

Birth Weight (gms)	24	26	28	Ges 30	tationa 32		(wks) 36	38	Unknown	Total Number	Number Survived	% Survived
7/1/66 — 6/30/67			<del></del>		;	<del></del>	· · · ·	.,	· /			
							-					
Less than 450												
451-500												-
501-550		1								1	0	0
551-600	-											1.
601-650	.1									1	.0	0
651-700	1									1 .	. 0	0
701-750	, <b>1</b>									1	0	0
751-800			1							1	0	0
801-850	1	:								1	0	0
851-900			1							1	1	100
901-950		1	2							3	2	66.6
951-1000												
TOTAL	4	2	4			· · ·	· · · · ·			10	3	30
7/1/67 — 6/30/68												
1 4b - 450												
Less than 450												
451-500											·	
501-550	4											
551-600 601-650	<b>1</b>	2						•		1 2	0	0
651-700	:	2								2	U	U
701-750			1							1	0	0
751-800	1		•							1	0	0
801-850	1	1	1							3	0	00
851-900	•	•	•							3	U	00
901-950						1				1	0	0
951-1000						•				•		•
TOTAL	3	3	2			1	**.	1	<del></del>	9	O .	0
			-		<del>,,</del>	•	.,					
7/1/68 — 6/30/69												
Less than 450												
451-500												
501-550											,	1
551-600	1								1	2	0	0
601-650	1	1							1	2	ő	o
651-700		•							•	_	_	
701-750												
751-800	l											
801-850	1	2								2	0	0
851-900										_	-	
901-950	1	1	1							3	0	0
951-1000												
TOTAL	2	4	1						2	9	0	.0.

Table 18 (Continued)

Birth Weight (gms)	24	26	28	Gest 30	ationa 32	Age (wks) 34 36	38	Unknown	Total Number	Number Survived	% Survived
7/1/69 — 6/30/70											
Less than 450										:	
451-500										:	
501-550	.3								3	0	0
551-600									J		
601-650	١.	1							1	0	0
651-700										į	
701-750	l										
751-800		1							1	0	0
801-850	1	1						1 1	3	0	0
851-900	l	1							1	0	0
901-950	1.	1							1	0	0
951-1000		1			e	2) 40 004		. 1	2	0	0
TOTAL	4	6	. 4.					2	12	0	0
7/1/70 — 6/30/71					ż						
Less than 450						5.4					
451-500											1
501-550											
551-600											
601-650	2								2	0	0
651-700				1					1	0	0
701-750	1	1	1	•					3	o .	0
751-800	1	•	•						1	0	Ö
801-850	1	1							2	. 0	0
851-900									ļ		- P
901-950		1							- 1	0	0
951-1000		1							1		
TOTAL	5	4	1	1					11	0	0
7/1/71 — 6/30/72											
1	1										
Less than 450	•										
451-500											
501-550 551-600											
601-650	•	*									
651-700	•									1	
701-750		2							2	0	0
751-800	1	4							1	0	0
801-850	Ι'								'	]	"
851-900	1	1							2	0	o
901-950	1	4	1						6	0	0
951-1000		•	•				rije.				
TOTAL	3	7	1				.,		11	0	0

Table 18 (Continued)

Birth Weight (gms)	24	26	28	Gest	tationa 32	1 Age 34	(wks) 36	38	Unknown	Total Number	Number Survived	% Survived
7/1/72 — 6/30/73							*.	<del></del>				
							,					
Less than 450												
451-500												
501-550												
551-600												
601-650	1		1							2	0	0
651-700												
701-750												
751-800	1	1								2	0	0
801-850		ν,		1						1	. 0	0
851-900	1			1						2	0	0
901-950		1							1	2	1	50
951-1000									·		V.	
TOTAL	3	2	1	2					1	9	1	11.1

Table 19. Neonatal Survival by Birth Weight
Birth Weights < 1000 Grams - 1963-1973
Boston Hospital for Women

Birth Weight (gm)	Number Livebirths	Number Survived 28 Days	% Survival	Number Fetal Deaths	% Fetal Deaths
<500	33	0	0.0	93	73.8
501-550	12	0	0.0	19	61.3
551-600	25	0	0.0	16	39.0
601-650	20	1.	- 5.0	15	42.8
651-700	31	2	6.4	21	40.4
701-750	28	2	7.1	14	33.3
751-800	28	1	3.6	15	34.9
801-850	18	3	16.6	12	40.0
851-900	26	3	11.5	12	31.6
901-950	41	6	14.6	8	16.3
951-1000	31	13	41.9	15	32.6
Total	293	31	10.6	240	45.0

Table 20. Neonatal Survival by Birth Weight and Gestational Age
Liveborns — Birth Weights <1000 Grams — 1970-1974
University of Minnesota Medical Center, Minneapolis — Neonatal I. C. U.

Birth Weights (gms)													1
Less than 450 451-500 501-550 501-560 501-560 501-560 501-560 501-560 501-560 501-700 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750 701-750		24	26	28					38	Unknown			
451-500 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	1970		4	····		<u></u>						-	
\$1500	Less than 450									ļ			
551-600	451-500	1									1	0	0
001-650 651-700 701-750 2 2 0 0 0 751-800 801-850 1 1 0 0 0 0 901-950 951-1000 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0													
661-700 701-750 701-750 701-750 801-850 801-850 801-850 801-850 1 1 1 1 3 0 0 0 901-950 901-950 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1				1	ı						7	U	U
701-750						,							
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951-1000  TOTAL 3 2 2 3 1 1 11 1 9.1  1971 Less than 450 451-500 1 0 0 0  551-600 1 0 0 0  601-650 651-700 1 1 0 0 0  701-750 1 0 0 0  801-850 851-900 2 2 2 2 100 901-950 1 1 0 0 0  951-1000  TOTAL 3 3 2 2 1 10 2 20  1972 Less than 450 451-500 1 0 0 0 0  1 1 1 1 0 0 0 0  1 1 0 0 0 0			1		1					1	1	i	1
TOTAL 3 2 2 3 1 1 11 1 9.1  1971 Less than 450 451-500 1 0 0 601-650 651-700 1 1 0 0 601-650 1 0 0 701-750 1 0 0 801-850 851-900 2 2 2 0 0 801-850 851-900 1 1 1 0 2 20  1972 Less than 450 451-500 1 0 0 501-550 1 0 0 951-1000 1 0 0 601-650 1 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0 0 601-650 0 0 0 0				:		1						1	
1971 Less than 450 451-500 1 501-550 551-600 1 1 0 0 0 001-650 651-700 1 1 0 0 0 701-750 1 1 0 0 0 801-850 851-900 2 2 2 2 100 901-950 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	951-1000	<u> </u>				2					2	U	<u> </u>
Less than 450 451-500 1 501-550 551-600 1 1 0 0 0 601-650 651-700 1 1 0 0 0 701-750 1 1 0 0 0 701-750 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	TOTAL	3	2	? ;	2	3	44. ·	, , AF	٠. ٠	1	11	1	9.1
Less than 450       451-500       1       0       0         501-550       1       0       0         651-700       1       1       0       0         651-700       1       1       0       0         701-750       1       1       0       0         801-850       851-900       2       2       2       2       100       0         901-950       1       1       2       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0        0       0       0       0       0       0       0       0       0       0       0       0       0       0       0        0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0	1971						1.0	et each					14 60%
451-500													
501-550         1         0         0           551-600         1         0         0           651-700         1         1         0         0           701-750         1         1         0         0           751-800         1         1         0         0           801-850         2         2         2         2         100           801-950         1         1         2         0         0           951-1000         1         1         2         0         0           TOTAL         3         3         2         2         100         2         2           1972         Less than 450         451-500         1         1         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0         0			1								1	0	0
551-600       1       1       0       0         601-650       1       1       0       0         651-700       1       1       0       0         751-800       1       1       0       0         851-900       2       2       2       100         901-950       1       1       2       0       0         951-1000       1       2       0       0       0         TOTAL       3       3       2       2       10       2       20         1972         Less than 450       451-500       1       1       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       <		j	4.					National Control		1 m 1			
601-650		1									1	0	0
651-700													
701-750			1	1							1	0	1
751-800		1									1		1
851-900 901-950 1 1 1		1			1						2	0	0
901-950 951-1000	801-850				•	;							
951-1000  TOTAL 3 3 2 2 10 2 20  1972 Less than 450 451-500 1	851-900					2					1	1	1 .
TOTAL 3 3 2 2 10 2 20  1972 Less than 450 451-500 1 1 0 0 501-550 1 1 0 0 601-650 2 2 0 0 651-700 701-750 1 1 1 2 2 0 0 751-800 1 1 1 2 2 0 0 751-800 1 1 1 2 2 0 0 851-900 1 1 1 1 2 2 2 50 851-900 1 1 1 1 2 2 2 50 851-900 1 1 1 1 2 2 2 1 50 951-1000 3 0 0	901-950		•	1	1						2	0	0
1972 Less than 450 451-500	951-1000										1	<u> </u>	<u> </u>
Less than 450 451-500	TOTAL	. 3	3 :	3	2	2					10	2	20
451-500       1       0       0         501-550       1       0       0         551-600       1       1       0       0         601-650       2       2       0       0         651-700       0       0       0       0       0         701-750       1       1       2       0       0       0         751-800       1       1       1       2       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0		1											
501-550       1       0       0         551-600       1       1       0       0         601-650       2       2       0       0         651-700       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0												_	
551-600       1       0       0         601-650       2       2       0       0         651-700       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0       0 <td></td> <td>1 '</td> <td>1</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>1</td> <td></td> <td></td>		1 '	1								1		
601-650       2         651-700         701-750       1       1       2       0       0         751-800       1       1       2 (26-30)       4       1       25         801-850       1       1       2 (28-29)       4       2       50         851-900       1       1       1 (24-28)       3       0       0         901-950       1       1       2       1       50         951-1000       3       3       0       0			1						1		1	4	1
651-700 701-750 1 1 1 751-800 1 1 1 2 (26-30) 801-850 1 1 1 2 (28-29) 851-900 1 1 1 1 (24-28) 901-950 951-1000 3 3 0 0				1									
701-750         1         1         2         0         0           751-800         1         1         1         2(26-30)         4         1         25           801-850         1         1         2(28-29)         4         2         50           851-900         1         1         1(24-28)         3         0         0           901-950         1         1         2         1         50           951-1000         3         3         0         0				2							2	1 0	"
751-800					_								
801-850					1					0 (00 00)		4	
851-900 1 1 1 1 (24-28) 3 0 0 0 901-950 1 1 1 2 1 50 951-1000 3 3 0 0			_	1		1					1	1	
901-950 951-1000 951-1000 951-1000 951-1000 951-1000 951-1000 951-1000 951-1000		- 1	-										
951-1000 3 3 0 0			1							1 (24-28)		1	50
3371000						1							7 1
TOTAL 4 5 7 2 5 23 4 17.4	951-1000				ა						<u> </u>		
	TOTAL	:	4	5	7	2				5	23	4	17.4

Table 20 (Continued)

Birth Weights (gms)	24	26	28		nal Age (w ? 34 ;		Unknown	Total Number	Number Survived	% Survived
1973		,	·	1-1-12						
Less than 450		4			the second of			,		1
451-500										
501-550										
551-600										
601-650	1		1					1		
651-700		1	•					1	0	0
701-750	1	1						'1	0	0
751-800		3						3	0	0
801-850		•						3	0	"
851-900	1			1			2 (25-33)	4	0	
901-950				. 1			3 (23-32)	5	1	0
951-1000	'	1		1			5 (23-32) 5 (27-33)	7	1	20 14.3
TOTAL	2	6	1	· <b>3</b>			10	22	2	9.1
TOTAL 1974	2	6	1	3			10	22	2	9.1
	2	6	1	3		Taylar d	10	22	2	9.1
1974	2	6	1	3		· · · · · · · · · · · · · · · · · · ·	10	22	2	9.1
1974 Less than 450	2	6	1	3		· · · · · ·	10	22	2	9.1
1974 Less than 450 451-500	2	6	1	3			10	22		
1974 Less than 450 451-500 501-550 551-600 601-650		6	1	3		· · · · · · · · · · · · · · · · · · ·	10		0	9.1
1974 Less than 450 451-500 501-550 551-600		6	1	3			10			
1974 Less than 450 451-500 501-550 551-600 601-650 651-700 701-750		6	1	3		·	10			0
1974 Less than 450 451-500 501-550 551-600 601-650 651-700 701-750 751-800		1 1	1	3			10	1	0	0
1974 Less than 450 451-500 501-550 551-600 601-650 651-700 701-750 751-800 801-850		1 1	2	3		-	10	1 1 1	0	0 0 0
1974 Less than 450 451-500 501-550 551-600 601-650 651-700 701-750 751-800 801-850 851-900		1 1		3			10	1	0 0 0	0
1974 Less than 450 451-500 501-550 551-600 601-650 651-700 701-750 751-800 801-850 851-900 901-950	1	1 1	2	3			10	1 1 1 2	0 0 0	0 0 0
1974 Less than 450 451-500 501-550 551-600 601-650 651-700 701-750 751-800 801-850 851-900	1	1 1	2	3		· · · · · · · · · · · · · · · · · · ·	10	1 1 1 2	0 0 0	0 0 0

Table 21. Neonatal Survival by Birth Weight and Rate of Stillborns by Birth Weight

Birth Weights < 1000 Grams — 1973-1974

Cincinnati General Hospital

LIVEBORN:							
Weight (gms)		1973				1974	
weight (gins)	Total		Survived		Total		Survived
0-250							
251-500	3				7		
501-550	4		1		1		
551-600	. 3		1		2	•	600
601-650	. 4				3		
651-700	•				2		
701-750	3				3	;	
751-800	3				à.		
801-850	2		1	•	6		
851-900	2				3		1
901-950	2		1	9	3		
951-1000	: <b>4</b>				. 3		2
	Comb	ined Surv	vivors Two	Years = 7/63 =	11%	*	
			<del> </del>	<del></del>			
STILLBORN:							det i
500-550					2		All Maria
551-600					3		
601-650	3						
651-700							
701-750	3				2		
751-800	. 1						1 1 1 1 1 1 1
801-850					. 1		
851-900	1		7.1.4		. 1		
901-950					1 1		
951-1000	3				1		
							· · · · · · · · · · · · · · · · · · ·
THERAPEUTIC	ABORTIONS:						
		1973				1974	
		N=33				N=50	
			•				

Table 22. Neonatal Survival by Birth Weight and Gestational Age
Liveborns — Birth Weights < 1000 grams — 1965-1974
University of California, San Francisco — Totals (Inborn and Outborn)

1965 Birth Weight (gms)	24	26	28	Gest	tational 32	Age 34	(wks) 36	38	Unknown	Total Number	Number Survived	% Survived
Less than 450 451-500 501-550 551-600 601-650										-:		
651-700 701-750 751-800 801-850			1							1	0	0 100
851-900 901-950 951-1000		1	1 1 1							1 2 1	0 0 0	0 0 0
TOTAL		1	5					*		6	1	16.7
1966												
Less than 450 451-500 501-550 551-600	1	1						-		1	0	0
601-650 651-700 701-750	1	•								1	0	0
751-800 801-850 851-900 901-950 951-1000		1	1 2					· .		1 1 3	0 1	0 100 33.3
TOTAL	2	4	3							9	2	22.2
1967 Less than 450 451-500 501-550	1									1	0	0
551-600 601-650 651-700 701-750	1	1	ŧ.							2	0	0
751-800 801-850 851-900 901-950	2 1	1								2 1 1	1 0 0	50 0 0
951-1000		1								1	1	100
TOTAL	5	3								8	2	25

Table 22 (Continued)

		3 1 4	<i>F</i> -						<del>-                                    </del>			
1968 Birth Weight (gms)	24	26			tional 32	Age ( 34	(wks) 36	38	Unknown	Total Number	Number Survived	% Survived
Less than 450 451-500		** • •										
501-550 551-600 601-650 651-700	1			1 .						1	0	0 0
701-750 751-800 801-850 851-900 901-950 951-1000	1	1 1 3	1 2	1	1	1				2 4 4 3 2	0 1 2 1	0 25 50 33.3 50
TOTAL	. 2	6	4	3	1.	.1	n in History		* - 1	17	5	29.4
1969												
Less than 450 451-500 501-550												
551-600 601-650 651-700	1									1 1	0 0 0	0 0 0
701-750 751-800 801-850	1	1								2	1	100
851-900 901-950 951-1000		1	1	1	,-					2 2	1 2	50 100
TOTAL	3	3	1	2			arter to		1 / L 1 / L	9	4	44.4
1970												
Less than 450 451-500 501-550												
551-600 601-650 ** 651-700	1					·				1	0	0
701-750 751-800 801-850			r				**					
851-900 901-950 951-1000		1	<u> </u>	2						1	0	50 0
TOTAL	1	1		2						4	1	25

Table 22 (Continued)

1971   Birth Weight (gms)						<u> </u>						<del></del>
451-500 501-550 551-600 501-650 651-700 701-750 71 1 1 2 2 0 0 751-800 801-850 901-950 91-950 1 1 1 0 0 951-1000 1 1 0 0  TOTAL 2 5 7 0 0   1972  Less than 450 451-500 501-550 551-600 601-650 751-800 1 1 0 0 801-850 1 1 0 0 801-850 1 1 0 0 801-850 1 1 0 0 801-850 1 1 0 0 801-850 1 1 0 0 801-850 1 1 0 0 801-850 1 1 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 801-850 1 1 0 0 0 0 801-850 1 1 0	Birth Weight	24	26	28				38	Unknown			
651-700 701-750 751-800 801-850 801-850 81 901-950 91-950 951-1000 1  TOTAL 2 5 7 0 0   1972  Less than 450 451-500 501-650 551-600 601-650 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 901-950 90	451-500 501-550 551-600				**		,					
801-850	651-700		1		~					. 2	0	0
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851-900 901-950 901-950 951-1000 1 1 1 1 25 951-1000 1 1 1 3 27.3  1973  Less than 450 451-500 501-550 551-600 1 701-750 1 701-750 1 701-750 1 1 2 801-850 851-900 901-950 901-950 901-950 901-950 901-950 1 1 2 50 2 1 1 2 50 2 1 1 2 50 2 1 1 2 50 2 50	651-700 701-750 751-800		1							1	0	0
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Less than 450 451-500 501-550 551-600 1 601-650 3 651-700 1 1 0 0 701-750 1 1 0 0 751-800 1 1 2 301-850 1 1 0 0 0 851-900 901-950 2 1 1 2 5 0 951-1000 1 1 2 5 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	TOTAL		6	3	2					. 11	3	27.3
451-500       501-550         551-600       1       0       0         601-650       3       3       1       33.3         651-700       1       1       0       0         701-750       1       1       0       0         751-800       1       1       2       4       1       25         801-850       1       2       4       1       0       0         851-900       901-950       2       1       1       4       2       50         951-1000       1       1       1       2       5       1       20												
801-850     1     1     0     0       851-900     901-950     2     1     1     4     2     50       951-1000     1     1     1     2     5     1     20	451-500 501-550 551-600 601-650 651-700 701-750	1	1	2						3 1 1	1 0 0	33.3 0 0
TOTAL 3 9 4 1 1 20 5 25	801-850 851-900 901-950		1	. 1	1	. 1			2	1 4	0 2	0 50
	TOTAL	3	9	4	1	1.				20	5	25

Table 22 (Continued)

1974 Birth Weight (gms)	2	4	26	28	Ges 30	tationa 32	al Age 34	(wks) 36	38	Unknown	Total Number	Number Survived	% Survived
,	a#						· · · · · · · · · · · · · · · · · · ·						
Less than 450													
451-500			1								1	0	0
501-550	1										1	o ·	0
551-600	1										1	0.	0
601-650	1										1	lo	0
651-700	1									1	2	0	0
701-750	1									1	2	Ö	0
751-800	1		3	2	1						7	2	28.6
801-850	١.		1								1	0	0
851-900	1		1	.1							2	0	o
901-950				3	2					1	6	6	66.7
951-1000	1			1						3	5	2	40
TOTAL		7	6	7	3					6	29	8	27.6

# Table 23. Neonatal Survival by Birth Weight Birth Weights < 1000 Grams - 1974 University of Arizona, Tucson

2 Hospitals

Live Births — 9000

University Hospital – #  $9 < 1000 \,\mathrm{gms}$ 

Tucson Medical Center − # 17 < 1000 gms

Birth	UNIVE	RSITY HO	SPITAL %	TUCSON	MEDICAL		4	TOTAL	÷ • • •
Weight	Number	Survived	% Survived	Number	Number Survived	% Survived	Number	Number Survived	% Survived
Under 500	0	_	_	0	<u>-</u>	<del>_</del>	0	_	
501-550	0	-	_	0		_	0		i, . —
551-600	0		_	0	_	_	0	_	
601-651	0	_		1	0	0	1	0	. 0
651-700	0	_	_ ·	3	1	33.3	3	1	33.3
701-750	0		_	3	0	0	3	0	0
751-800	1	0	0	0	_	· <u> </u>	1	0	0
801-850	3	0	0	0		_	3	0	0
851-900	3	2	66.7	2	2	100	5	4	80
901-950	1	1	100	3	1 '	33.3	4	2	50
951-1000	1	0	0	5	2	40	6	2	33.3
	= '	==	===	=	=			, <u> </u>	=
TOTAL	9	3	33.3	17	6	35.3	26	9	34.6

Table 24. Neonatal Survival by Gestational Age - 1966-1974 Royal Victoria Hospital Montreal, Quebec, Canada

Gestational Age (wks)	Number Livebirths Over 500 gm	% Survival	% Survival Excluding Deaths from Malformation, Hydrops
20	1	0.0	0.0
21	5	0.0	0.0
22	8	0.0	0.0
23	5	0.0	0.0
24	14	0.0	0.0
25	<b>23</b>	8.7	9.0
<b>26</b>	41	19.4	20.5
27	33	51.5	54.8
28	25	76.0	76.0
29	44	70.4	77.6
30	51	78.4	83.3
31	67	88.1	90.8
32	70	91.4	97.0

Table 25. Neonatal Survival by Gestational Age - 1964-1974 Royal Victoria Hospital, Montreal University of California, San Francisco **University of Colorado** 

Gestational Age (wks)	Number Livebirths	Number Survivors	% Survivors
Less than 24	31	0	0.0
24	58	0	0.0
25	43	3	6.9
26	82	13	15.8
27	54	23	42.5
28	67	31	46.2
29	50	32	64.0
30	63	45	71.4
31	71	61	85.9
32	72	65	90.2

Table 26. Survival Rates of 501-1000 Gram Livebirths 1920 - 1974 With Neonatal Intensive Care in Maternity Hospital of Birth

	1920 Finland*		5-1957 ork City**		6-1970 /.H.*** Discharged	1971-1974 R.V.H.*** Discharge			
Birth Weight (gms)	30 days %	7 days	28 days %	7 days %	Alive %	7 days %	Alive %		
501-750		0	0	3	3	11	4 ,		
751-1000	10	11	9	28	16	61	35		

<sup>\*</sup>Yllpo's experience in Finland, published in Hess, Premature and Congenitally diseased infants, Lea &

\*\*\*Royal Victoria Hospital, Montreal.

Febiger, Philadelphia and New York, 1922, p. 375. (for infants 600-1000 gm).
\*\*For white infants receiving intramural care in hospital of birth, in 10 premature Centers, New York City, in Silverman, W.A., Premature Infants, E. C. Dunham, Editor, Third Edition, New York, Paul B. Hoeber, Inc., 1961, pp. 484-487.

Table 27. Number of Mortalities by Birth Weight — 1966-1974 (Excluding Antenatal Referrals and Abortions)
Royal Victoria Hospital
Montreal, Quebec, Canada

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	ANTENATAL REFERRALS 1971-1974	8/1		7		7	_	4	_	_		С	9	<b>پ</b> ر	73	<u>.</u>	24		117
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1		N/D																	_
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L		S/B				-						7	_	_	_		_		
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			920	000	920	92	750	800	820	006	920	951-1000	1250	1500	2000	2500	2500	Incidence LBW	500/Tc
		÷	501-550	551-600	601-650	651-700	701-750	751-800	801-850	851-900	901-950	951	1001-1250	1251-1500	1501-2000	2001-2500	Over 2500	Incide	501:2

S/B — Stillbirths
L/B — Livebirths
N/D — Neonatal Deaths
A To discharge from Hospital
Liberalised abortion from 1971
The Royal Victoria Hospital became a center for referral of high-risk pregnancies in 1971.

Table 28. Fetal Deaths - 1966-1973 Los Angeles County-University of Southern California Medical Center

Year	Alive on Admission to Delivery Service	Fetal Deaths	Fetal Death Rate/1000	Number Patients Monitored	% Patients Monitored		
1966-69	37,013	804	23	_	3 0		
1970	9,654	157	16	1,798	18		
1971	9,303	155	16	2,337	15		
1972	9,318	137	15	2,828	30		
1973	10,319	136	13	3,329	** - <b>32</b>		

Table 29. Intrapartum Fetal Deaths — 1970-1973 Los Angeles County-University of Southern California Medical Center

	Monitored	Unmonitored
Total patients	9,871	28,722
Fetal deaths	15	108
Rate/1000	1.5	3.7

Table 30. Fetal Mortality — 1968-1972
Parkland Hospital, University of Texas Southwestern Medical School

Year	Live Births	Fetal Deaths	Fetal Death Rate/1000	Neonatal Death Rate/1000
1968	5,955	126	21	23
1969	6,347	122	19	24
1970	6,779	142	21	18
1971	6,939	127	18	15
1972	6,772	124	18	16

Table 31. Neonatal Survival — 1970-1973

Los Angeles County/University of

Southern California Fetal Monitoring

en en de la companya de la companya La companya de la co	Monitored	Unmonitored
< 1500 grams		
Live Births	112	448
Neonatal Survivals	60	183
Survival %	54	40.8
1000-1500 grams		
Live Births	82	279
Neonatal Survivals	53	161
Survival %	64.6	57.7%
< 1000 grams		*.
Live Births	30	169
Neonatal Survivals	7	22
Survival %	23.3	13.0

Table 32. Neonatal Mortality — 1966-1973
Deaths/1000

	LAC-USC*	University of Oregon
1966-69	26	19.4
1970	18	11.0
1971	15	14.2
1972	12	9.8
1973	9.5	10.1

<sup>\*</sup>Los Angeles County/University of Southern California.

APPENDIX C

#### Table 36. Data Collection Form

Please check appropriate year when procedure was started: (1964-1974)

Obstetrical Improvements		64	65	66	67	68	69	70	71	72	73	74
1. Antenatal high risk clinic												
2. Amniocentesis								İ				
bilirubinoid pigment	64								1			
chromosomal anomalies	69-70						1			ļ		•
sex determination	69-70							l	1			
inborn errors of metabolism	69-70						Ì		1			1
intrauterine transfusion	63-67											1
fetal maturity - L/S ratios	70-71					-		1				
bilirubin	67							1	1			
creatinine	65-66											
3. Sonography - anomalies	72											
fetal maturity	72											
placental localization	72											
4. Amnioscopy – color of amniotic fluid and vernix	73-73											
5. Other evaluations of fetal well being									1			
maternal urine - E <sub>3</sub> , estriol	65-70							1	1			
maternal blood - human plasma lactogen	72								l			
fetoprotein	73							1	1	İ		
contraction stress test	73											
6. Beta methasone for lung maturation	73					-						
7. Drugs to arrest premature labor:			,									
MgSO <sub>4</sub>	64							l.				
alcohol	68-69	'										
Beta sympathomimetic	73											
8. Fetal monitoring												
Heart rate & uterine pressure activity	70-71							1	1			1
Beat-to-beat analysis of HR	72							1	ļ	İ		
Evaluation of pre-ejection phase (EKG and HR) Monitoring of fetal respirations	74											
Fetal EEG	74							l	!			
Fetal scalp ph												
Resuscitation in delivery room												
Better trained personnel - nurses	65											
neonatal fellows at									İ			
problem deliveries	68-73							1	l			
Thermal regulation	66							1				
More aggressive intubation & suctioning	69							1				
Umbilical artery & vein acid base	69											
Correction of acidosis	69											
Transitional nursery on the delivery floor												
Observation							Ì		1	· 3		
Stabilization of ill newborns			'									
Neonatal Intensive Care Unit	64-65							<u> </u>				

Table 36. (Continued)

		64	65	66	67	68	69	70	71	72	73	74
Transport System	70									-		
Regionalization of Newborn Care	70-71											
Personnel:				,					14			
1. Specially trained nurses	65						ř					
2. Neonatal fellows	65				1							
3. Anesthesiologist	69-70					l		-				
4. Respirator technicians	71											
Equipment: with alarm systems												
Continual oxygen monitors	68-69			1				ŀ				
Apnea monitors	66-68											
Heart rate monitors	66-68											
					ļ					100		
Humidity monitors	70-72		}									
Thermal monitors (thermidor probes)	67								1			
Blood pressure monitors: Doppler	72			ļ								
Ultra sound		1							1.			
				1				1				
Transducers for direct arterial blood pressure					ŀ							: 1
measurements	70-72	1		1								
Improved ambu bags (>40% O <sub>2</sub> )	66			1 .						ŀ		
	. 4" 	1				ľ						
Microchemistries:	**				l		1	ŀ				
Arterial & capillary blood gas monitoring	64	Ì		1				1				•
Electrolytes	64					١.	l					
Ca, glucose, Mg	64			1		1			1			
Bilirubin	64	1					l					١.
Bilirubin binding	71	1	l	•			1			1		
Total proteins	64	1	1									
	64	1	1								ŀ	
Alb/glob		1			1	į	1			1		İ
Protein electrophoresis	64	]	1		1				1	1		l
Hematology studies: routine	64	1	1									1
Coagulation studies	69-70		]		1	l		1				
G6PD	69-70		1		1	İ	1					
Liver chemistries	64	1	1	1			ļ ·	1		1		
Coombs, type & crossmatch	64	1	Ì	ļ	l			1		22.0		
Viral studies			1		1	1						
Metabolic disease screening	68		1						1			
					1	ŀ	100				ŀ	
Procedures:			1		1			1.		j		
Early feeding (note 4, 6, 12 or 24)	69-70	1		1	l	1	1		l	1		
Umbilical artery catheterization for blood sampling	na 69	1							l			
Radial & temporal arterial punctures or cath		1							İ			
monitoring for oxygenation	69								1:			
Mechanical ventilation	68						1	1	1		1	
PEEP (positive end expiratory pressure)	70-71				1	1	1	1	.		1	
CPAP (continuous positive airway head box)						1			1		1	1
nasal prongs	74			1			1			1		1
Negative pressure vent	• •		1			1	1					l
	60-60				1	1	1				l	1.
Phototherapy - intermittent	68-69		1	1							1	
continuous	68-69	1	1	1	1	1	1	1	1			
Intravenous hyperalimentation	70	1		1		1	1	1		1		1
Nasojejunal feeding	73-74					<u></u>		<u>L</u>	<u></u>	<u> </u>	<u> </u>	

Table 33. Neonatal Survival by Birth Weight and Gestational Age — 1958-1968 and 1971-1973

Denver Children's Hospital

	Gestational Age	Birth Weight	Number Live Births	Number Survived	% Survived
1958-1968	< 30 wks	<1000 gms (½ SGA)	89	7	8
	< 30 wks	1000-1500	77	29	37.7
	30-34 wks	1000-1500 (½ SGA)	70	44	62.9
	30-34 wks	1500-2000	154	124	80.5
	34-38 wks	2000-2500	523	506	96.7
	TOTAL		913	710	77.8
1971-1973	< 30 wks	<1000 gms (½ SGA)	28	1	3.6
	< 30 wks	1000-1500	27	11	40.7
	30-34 wks	1000-1500 (½ SGA)	22	15	68.2
	30-34 wks	1500-2000	48	43	89.6
	34-38 wks	2000-2500	231	224	96.9
	TOTAL		356	294	82.6

Table 34. Neonatal Survival by Birth Weight — 1965-1974
University of California at San Francisco
Changes in Survival (%)

	1965 — 19	69	1970 — 1974				
Birth Weight	Number Liveborn	% Surviving	Number Liveborn	% Surviving			
901-950	6	17	8	50			
951-1000	6	50	4	75			
1001-1250	30	57	. 32	66			
1251-1500	35	66	42	83			
1501-2000	151	90	120	94			
2001-2500	493	92	441	99			
> 2500	9,110	99.6	6,879	99.7			

Table 35. Distribution of Livebirths by Weight Group/1000 Livebirths
Royal Victoria Hospital, Montreal, Quebec

<i>5</i>	1966-1970			1971-1974 (Excluding Antenatal Referrals & Abortions
501-750	30/13320	2.25	21/8487	2.47
751-1000	42/13320	3.15	19/8487	2.24
1001-1250	43/13320	3.23	13/8487	1,53
1251-1500	51/13320	3.83	30/8487	3.53
1501-2000	196/13320	14.7	109/8487	12.8
2001-2500	643/13320	48.3	358/8487	42.2
Over 2500	12315/13320	924.5	7937/8487	935.2
Subtotals				
501-1000	72/13320	5.4	40/8487	4.7
1001-2500	933/13320	70.0	510/8487	60.1

Liberalised abortion began in 1971.

Table 36. (Continued)

		64	65	66	67	68	69	70	71	72	73	74	
Cardiac catheterization techniques	65												
Cardiac surgery	64		1	1	l				1				ı
Aggressive gastrointestinal surgery	64	1		1	İ								l
Evaluation of gestational age:	64	1							l.				l
pE	69	1			·								l
Neurological exam	70	1									4 .		l
Nerve conduction time	70	-											
EEG													
			ŀ										
Antibiotics:		1	1			, ·							
Ampicitlin	69												
Kanamycin	65	İ											ı
Gentamycin	70-1												l
Penicillinase resistant antibiotics	65	1										1	
		1						5 1					l
Routine monitoring of Hct & Hb electrolytes,	65-66				,	:				100			
dextrostix & glucose, Ca	-7	-		. (							1.		l
													ĺ
ICU Nurses:	,		-67		-						sie g		ľ
1. specially trained	64-65											-	l
2. Umb cath care & blood drawing	69-70	1					-	5			5111		
3. Dextrostix monitoring	70	1											
4. oro-nasotracheal care	70											**	ı
5. Ambuing	65			·	16.1				4. <sup>8</sup>				ĺ
6. heelstick blood drawing (except type & cross)	70							, 1	r:		-		
7. starting peripheral IV's	, Y												
		1											
Treatment Improvements:													
Anesthesia		1											
Post-op care												1	
Surgical techniques							, '			* 0.0			ĺ
Resuscitation									1				
RDS, meconium aspiration					İ			5 A 2 .					l
Hypoglycemia					-								ĺ
Hypocalcemia										€ .			
Polycythemia										¢°			l
Coagulation defects													ļ .
Sepsis Rx							1.7		N-				
Erythroblastosis fetalis							-				1		ĺ
Metabolic disorders				. ]									ĺ
Drug doses													
Environmental stimulation						l					1		

If you have any comments, please feel free to add.

Case Reports of Infants Who Survived at Birth Weights Less Than 601 Grams or Gestational Ages of 24 Weeks or Less

#### Case Report 1

#### UNIVERSITY OF CINCINNATI MEDICAL CENTER

This was a 580-gram black female infant born by breech extraction with prolapsed cord on 9/3/73 with estimated gestational age of 25-27 weeks. The Apgars were 5 and 8 at 1 and 5 minutes, respectively. On physical examination the newborn appeared to be between 24-26 weeks of gestation with no abnormal physical findings. Shortly after birth the infant developed severe respiratory distress with possible sepsis. An umbilical artery catheter was placed to monitor blood gases which was found by x-ray later to be free in the peritoneum. In addition to respiratory distress the newborn experienced several episodes of apnea and bradycardia during the first three days of life. These were treated by frequent "ambuing." Additional problems concerning this infant were: (1) Anemia, which required two transfusions. (2) Nutrition: on day 5 nasogastric tube was passed by continuous gavage feedings. In addition, aminosol was given by peripheral intravenous drip. These modes were continued for three weeks when gavage feedings were begun at every 3-hour interval. (3) Phototherapy was used for several days to prevent hyperbilirubinemia. The highest bilirubin recorded was 4.5 milligram percent.

The infant was discharged at three months of age with a weight of 2270 grams; head circumference, chest circumference and length were all below the tenth percentile. On follow-up visit at 17 months of age the neurological exam is within normal limits. Her size is still small. She's just walking now and has a vocabulary of about ten words, but it is felt by the examining physician that she is slow in her development.

#### Case Report 2

#### UNIVERSITY OF MARYLAND HOSPITAL

DOB: 11/17/72

DOB:

9/3/73

This is a 539-gram black female infant born to a 29-year-old gravida 5, para 5, A-positive, VDRL-negative mother with approximate gestational age of 28 weeks. The Appars were 0 at 1 minute and 4 at 5 minutes. The physical exam revealed a small immature female infant with head circumference of 21 cm, chest circumference of 18 cm, length of 31 cm, and no abnormal findings.

Hospital course: At two hours of age an umbilical artery catheter was passed and arterial blood gasses were obtained; pH was 7.21;  $pCO_2$  was 46;  $pO_2$  was 34; BE was -10;  $HCO_3$  was 17.5. The infant was placed in 60 percent oxygen

Case Record: E.H.

Date of Birth: 7/17/74
Date of Discharge: 9/23/74

This 580-gram female infant who was 29 weeks by obstetrical estimate was admitted to Colorado General Hospital on 7/17/74 having been transferred from Weld County Hospital in Greeley, Colorado, where she had been delivered at 7:00 p.m. on that day of cesarean section. Her mother is a 27-year-old gravida I, para 0 woman without previous medical illness. Her pregnancy had been uncomplicated until 25 weeks when she developed ankle swelling which was treated with hydrodiuril. Despite the diuretic therapy, her edema persisted; and on 7/12/74 she was found to have elevated blood pressure which was treated with hydrodiuril and Serpasil. On the day prior to delivery the mother was found to have increased edema, proteinuria, and hypertension and was, therefore, admitted to the hospital. During two days in the hospital she had increasing symptoms with hyperreflexia and jitteriness and blood pressure determinations to as high as 240/160. She was treated with Valium, phenobarbital, Diazoxide, Lasix, Apresoline, Serpasil, and magnesium sulfate. By the evening of 7/17 it was elected to terminate the pregnancy for maternal indications, as she had not yet responded to medical management of her hypertensive disease.

Essentially it was planned to do a hysterotomy termination of the pregnancy which was done under Flouthane, nitrous oxide, Vistaril, and atropine. The infant was resuscitated immediately after delivery and had Apgars of 3 at 1 minute and 8 at 5 minutes. She required positive pressure resuscitation via an endotracheal tube, was given oxygen from the first three to five minutes of life; and at this time the child breathed spontaneously and was able to be extubated. Initial gases in an F:02 of 45 percent showed a pO2 of 229, a pCO2 of 39, and a pH of 7.30. Her dextrostix was satisfactory and she was begun on an infusion via an umbilical artery catheter of Dlow at 2 cc/hour. Arrangements for transfer to Colorado General Hospital were promptly made and the child arrived here at approximately 3 hours of age. On physical examination here the child's weight was 580 grams, her length was 34 cm, blood pressure was 62 systolic, temperature was 35.8 axillary, pulse was 160, respiratory rate was 54, and head circumference was 24 cm. The child was incredibly small, but pink, an active newborn without significant clinical respiratory distress. General physical examination was completely within normal limits. Gestational age assessment by physical criteria gave a gestational age of approximately 33 to 34 weeks, by neurological assessment the gestational age was estimated between 30 and 32 weeks; therefore, an overall clinical assessment of gestational age averaged 32 to 33 weeks. The child's entire hosptial course was remarkably benign. She slowly tolerated the introduction to PM-60/40 feedings and had only mild to moderate apnea responding to stimulation over her first week in the hospital. She initially required feeding by constant intragastric drip but by the end of two weeks was able to move to intermittent gavage feeding schedule. She demonstrated steady weight gain so that at the end of two weeks in the hospital her weight was up to 840 grams. The remainder of her hospital course was completely benign with the only problems

being that of caloric intake and weight gain which continued smoothly. At the time of discharge on 9/23/74, her weight was up to 1940 grams; her general physical and neurological examination were completely within normal limits; and on follow-up examinations in the last four months, she has continued to be a thriving healthy vigorous child, who is a delight to her family.

This interesting child demonstrates not only viability at under 600 grams but also the fact that severe intrauterine growth retardation may occur in infants of this birth weight; thus, not all extremely low birth weight infants can be guaranteed to be immature. The valuation of this infant for other potential causes of intrauterine growth retardation including metabolic diseases and congenital infections was completely normal, and it is presumed that the etiology of her growth retardation was the maternal hypertensive disease.

#### Case Report 5

A PREMATURE INFANT WEIGHING LESS THAN ONE POUND AT BIRTH WHO SURVIVED AND DEVELOPED NORMALLY

DOB: 6/6/37

Baby McG. was born about 10:30 p.m., on June 6, 1937, fifteen minutes after my arrival. The child was the third born to the mother, who was 28 years of age at the time. The birth was approximately two months premature. The delivery was normal. The child was alive but so extremely small that I did not expect survival, since there was no incubator available. The nurse bathed the baby in warm olive oil, wrapped it in cotton, and placed it in a basket in a warm oven. No scales were at hand, so the actual birth weight was not obtained, but it was by far the smallest living baby I had ever seen. Shortly after birth the nurse gave the baby two drops of brandy in warm water from an eye dropper. Greatly to my surprise the nurse called me on the telephone the following morning to inform me that the infant was still alive and to request feeding instructions. About 11 a.m., June 7th, the day following birth, the nurse took the baby to a local grocery store, and weighed him on the grocery scales in the presence of the proprietor and another person. The weight of the baby at that time was 14 ounces, as the accompanying affidavit confirms. For two days the child was given feedings of two drops of brandy and a few drops of corn syrup in warm water from a dropper. On the third day the child was given lactogen, in a dilution of one teaspoonful to one ounce of water, and since that time has been fed lactogen in the full strength dilution (1 part lactogen to 7 parts water), with progressive increases in volume as the baby grew older. For the first ten days of life the child took several droppers of formula each hour. At ten days on the infant was able to suck, and, therefore, was fed from a bottle on a twohour schedule. During the first two weeks the baby was kept in a warm oven at night.

The weight at 2 months was 3 pounds, at 4 months 6 pounds, at 7 months 9-3/4 pounds, at which time the body length was 24-1/4 inches. The child has been generally healthy and normal as to its physical and mental condition.

Cereal, vegetable puree, and other usual additions were made to the diet at 6 months.

At present the child is 12 months old, weighs 13 pounds 12 ounces, and measures 25-1/4 inches.

J.S. Monro, North Sydney, N.S. Canadian Medical Association Journal 40:69-70, 1939

NOTE: Dr. Behrman included the following case reports in Appendix C:

- "Case Reports," The Canadian Association Journal 40:69-70, January 1939.
- Lelek, K., Limanowski, J., and Hager-Malecka, B., "A Three-Month Old Infant With a Birthweight of 450 Grams," *Pediatria Polska*, 1973, T. XLVIII, 2, (in Polish).

and given bicarbonate. The following day oxygen was lowered to 40 percent and by day 3 she no longer required any oxygen.

On day 2 phototherapy was begun to prevent hyperbilirubinemia and was continued for several days. Oral feedings of 1 cc every two hours by gavage were begun on day 3 when the weight of the infant was only 482 grams. Another problem was persistent metabolic acidosis which was treated with frequent sodium bicarbonate, given either intravenously or by mouth. This persisted for about two weeks. On day 13 of life, episodes of apnea occurred and this continued for another two weeks. At this same time there was a hematocrit drop of 5 points and hypernatremia. A sepsis workup was done. The infant's weight gain was acceptable but the head circumference appeared to grow too rapidly in the first two months of life, but by the third month it was proportional to the other parameters of weight and length. At about 3 months of age the infant was discharged with a weight of 2693 grams, with a head circumference of 33-1/2 cm, a length of 14-1/4 inches, and a hematocrit of 34. Physical examination revealed a bilaterally flattened head with separated sutures; eyes were normal; the rest of the physical, including neurological, exam was normal at discharge. The infant was again seen at 11 months when the weight was 7144 grams and length was 27 inches. No abnormal nuerological findings were noted. At 2 years of age she was again seen and was thought to be normal neurologically and developmentally.

# Case Report 3

UNIVERSITY OF ARIZONA AT TUCSON

DOB: 12/30/74

This is a 624-gram, 24-week gestation, female infant born to a para 3, gravida 1, abortion 2 mother with a bicornuate uterus. The Apgars were good at birth and the physical exam was normal except for extreme immaturity. At age 1-1/2 days she developed episodes of apnea and over-perfusion of the lungs due to a patent ductus arteriosus. Nasal CPAP was begun with no improvement in her condition and she was placed on mechanical ventilation with high oxygen concentration. Two days after ventilation was started because of worsening of her condition due to severe pulmonary edema secondary to congestive heart failure, she was taken to surgery and the PDA was ligated. After surgery the lungs cleared and she only required 25 percent oxygen and intermittent mechanical ventilation for two weeks, mainly for apnea. During this period she received intravenous hyperalimentation by peripheral IV. She did well until 2-1/2 months of age, having been gavage fed with progestamil and off the ventilator and oxygen, when she developed abdominal distention and hematest-positive stools. The diagnosis by x-ray was necrotizing enterocolitis with air in the portal system, for which she is still being treated with IV hyperalimentation. The lowest weight recorded in this infant was 500 gm on the seventh day of life. She now weighs 600 gm.

13

# THE LAW RELATING TO EXPERIMENTATION WITH THE FETUS

A. M. Capron, LL.B.

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PD 304119-5 (15)

# The Law Relating to Experimentation with the Fetus

#### SYNOPSIS

- 1. The dead fetus (including tissues, fluids and other products of conception) may be used ex utero for research with the permission of either parent, provided that the other does not present an objection, under the terms of the Uniform Anatomical Gift Act; the only exceptions are those imposed by recent statutes in five states, which limit experimentation on an induced abortus to pathological examinations or the like (three states) or which require maternal (as opposed to paternal) consent (two states). Grave robbing statutes do not restrict experimentation if permission has been obtained under the UAGA. For research involving a dead fetus in utero, the consent of the pregnant woman should be sufficient. Caution and ignorance both suggest that the definition of "dead" fetus should for the moment be one which is "lifeless" (in the sense of having no signs of life, or at least no heartbeat); research with fetuses that have other signs of life although no possibility of "recovery" should fall into the category of experimentation on the "nonviable fetus."
- The viable fetus ex utero is a person in the eyes of the law, and its interest in life and well-being are clearly recognized by the civil and criminal Under the common law, this protection begins when the fetus is expelled or extracted from its mother, but at least one state has extended the criminal law protection to the point when birth begins and the common law recognized that a physician's duties of care commence at this point. Parents, or other guardians, may consent to beneficial experiments for such fetuses, and with proper safeguards may be able to give permission for riskless studies of scientific merit, although this point is not definitely settled in decisional law. The disqualification of the mother (and perhaps the father) of an aborted fetus to act as its guardian which is a feature of a number of recent statutes may affect fetal research. Such attempts to take away parental custody and control on the grounds that the mother has abandoned the fetus or is unable to take account of its interests seem unwise (because of the burden placed on state officials which they are ill-equipped to handle), misquided (because it is based on misapprehension of the significance of the decision to abort), unnecessary (because the interests of such fetuses are already protected by the law from parental abuse to the same degree as those of other children), and perhaps unconstitutional (because it chills exercise of the right to have an abortion and operates arbitrarily through presumptions rather than actual facts about parental choices).
- 3. The viable fetus *in utero* does not enjoy full protection, but the law does try to avoid prenatal injuries which will handicap or kill a person after birth; additionally, some jurisdictions have extended their notion of fetal

interests to recognize a right for its relatives and in some cases for its estate to sue for injuries to a viable fetus causing stillbirth. The limitation on these interests is, of course, the mother's right to an abortion necessary to protect her life or health even when that threatens the life or health of a viable fetus. This would not preclude the state from protecting the viable fetus in utero from possibly harmful experiments not connected with benefits to the mother's health or well-being or arising without her consent.

- The nonviable fetus ex utero has received the same respect and concern from the law as a viable fetus in the same position, although (in the absence of a statute directing otherwise) only normal sustenance and the prevention of pain but not heroic "lifesaving" attempts are required in caring for it. The reasons why "birth" was chosen as the point to begin full legal protection, even for the nonviable, may not apply to fetal research under careful supervision and with great attention paid to the determination of "nonviability"; thus a redefinition of the rights of the nonviable is conceivable. The question whether research of this type ought to be permitted is not a legal question, however, but a policy judgment to be reached on the basis of one's perception of the relative importance of the interests of the fetus, parents and society. If experimentation is limited to that which is intended to benefit the fetus or pose no harm, the authority to consent can be left with the parents as it is for viable fetuses. Were a wider scope of experimentation to be permitted, it would seem advisable to have outside review, which could inquire broadly into the parental decision to permit a fetus to participate or more narrowly into only whether the established criteria (on nonviability and the degree of risk and pain) have been met.
- 5. The nonviable fetus in utero has generally not been protected by the criminal law, except to the extent that injuries received antenatally are manifest after birth; the law of torts and property also regards birth as a necessary precondition for rights to vest in the previable fetus. This seems to manifest an understandable societal concern that persons not be burdened with prenatally imposed injuries, but the pregnant woman's right to a subsequent abortion presents an impediment to the clear authority otherwise passed by equity to intervene so as to prevent such irreparable harm befalling (potential) people. Any in utero research will require the woman's consent on her own behalf; the law seems to suggest, but does not demand, that someone also consent on behalf of the fetus. To locate the authority with the pregnant woman may be seen as creating a conflict of interest, yet to place it with someone else who could prevent her from participating would probably amount to an unconstitutional infringement on her right of privacy.

#### I. INTRODUCTION

This memorandum will address itself primarily to the two major questions on which the law can make a contribution to the discussion of the limits and conditions of fetal experimentation:

1. Which interests of the fetus are protected at what points in its development against which interests of other parties?

2. Since the fetus is unable to protect its interests, who speaks for it?

The first question focuses then on the issues of personhood and balancing, and the second on the issue of consent; in addition, the legal discussion will also suggest the means which are available, to the National Commission or other organs of government, for implementing decisions about the first two points.

Four categories of law are relevant to this discussion: constitutional, criminal, civil, and administrative. The Constitution is in large part a document that empowers people to do things—such as giving the President the authority to make treaties and the Congress the power to "lay and collect taxes." But in the context of regulating fetal research, the Constitution comes into play mostly as a limitation on what the state may do, directly or by legislative authorization to others. The provisions most likely to be invoked are the due process and equal protection clauses of the fourteenth amendment, although it is possible that other parts might be relevant. While it is imperative for American law-makers, including the National Commission, to have constitutional law in mind in drafting any legislation or regulations, it does not provide a particularly important source of the law on this subject because an examination of the constitutional cases most on point, such as Roe v. Wade, demonstrates the need to cut a layer deeper down into the underlying common law to which the Supreme Court turned in applying constitutional doctrine to the facts before it.

Consequently, this memorandum attempts to search out and organize the principles which can be derived from criminal and civil law decisions, as well as from more recent statutes which have not yet been the subject of much judicial interpretation. The common law of crimes (now typically codified) has given some protection to fetuses, under the heading of homicide and assault; much greater protection was given by statutory law on abortion, but this is an area still very much in flux in the wake of the 1973 decisions of the Supreme Court of the United States which in effect invalidated virtually all abortion laws then on the books. The civil law has also recognized the fetal interest in protection against negligent and intentional harm; this has found expression in rules concerning torts, property, and equity.

Administrative provisions that might be relevant to fetal experimentation are of two groups, those relating to the subjects and those relating to the researchers. First, each state has laws which provide for the registration of births (including stillbirths) and deaths. These provisions may affect the ways in which fetal subjects are handled and may provide guidance, which would be relevant to the criminal and civil law, on the status of the fetal material being used for research. Second are the disciplinary provisions which govern researchers, particularly those who are licensed to practice a profession and are thus exposed to penalties (e.g., censure or revocation of license) for conduct that violates the rules or norms established for the profession. Since such matters rest in the hands of the profession itself (although in some instances with state sanction) and are typically not well articulated as prospective rules, they add little to the law and will thus not be an important part of the material included in this memorandum.

Within the limitations imposed by a memorandum of this scope, an attempt will be made to indicate the variation among states which typifies the law on many of the points in issue here, as well as to trace the changes which have come about in the law over time. This memorandum does not pretend to touch on all the legal issues raised by fetal experimentation—indeed the growing body of law and commentary on the general issues of human experimentation is treated only tangentially. The current law on abortion is considered repeatedly because abortion forms the backdrop, both legally and clinically, for fetal experimentation. No "model statute" is offered, although the present state legislation, which seems largely the product of haste and emotion, is analyzed where appropriate. This analysis makes it plain that while the topic is very complex, anything put forward by the Commission should be as simple as possible because the rules will have to be applied by ordinary people, often hurriedly and without understanding.

The law operates by attempting to draw lines between what are often similar categories; thus, it is often accused of being arbitrary. But lawyers also are keenly aware of the precedential effect of each step that is taken. The Commission, too, should anticipate that the categories it draws rest on a blurred reality and tend not to hold fast in practice. Hence, some margin of error and some means of self-correction and adjustment must be included.

Any organizing framework has some problems, but it is hoped that the one used here serves the Commission's purposes. Rather than build the memorandum around legal categories (e.g., fetal interests shown by the criminal law, by the law of property, etc.), it was decided to structure it from the viewpoint of implementation—that is, according to types of research.

Analysis of both the major issues—the definition and balancing of fetal interests and consent—should be facilitated by examining separately the various types of fetal research, moving from experiments raising the fewest hard legal issues to those which pose increasingly difficult questions.

# II. DEAD FETUSES, TISSUES AND PRODUCTS OF CONCEPTION

The dead fetus and the products of conception (the placenta, umbilical cord, amniotic fluid, and so forth) may be desirable objects of study because of biomedical investigators' interest in: (1) learning about normal development, (2) observing whether substances cross the placenta, and (3) identifying any injuries to fetuses from products (drugs, cigarettes, food additives, etc.) used by pregnant women. Studies of the latter types might be commenced while the fetus was still in utero, by the measured administration of the substances, but they can also be conducted simply by studying the results of "natural experiments" after the abortion of a fetus who was exposed to a substance in the ordinary course of its development. There is also a great deal of interest in studying fetal cell differentiation and development in tissue culture, and in using such cultures for the study of viruses. Finally, organs from the recently dead fetus may be used in such as yet experimental procedures as thymus transplantation to infants with immune deficiency disease.

#### A. Uniform Anatomical Gift Act

All of this research would appear to be permissible under the Uniform Anatomical Gift Act (UAGA), which was promulgated by the National Conference of Commissioners on Uniform State Laws in July 1968 and was swiftly adopted in all fifty states and the District of Columbia, with only minor variations (none of which are germane to this discussion). A "decedent" under the Act is defined to include "a stillborn infant or fetus" (§ 1(b)), and a "part" of his body "includes organs, tissues, eyes, bones, arteries, blood, other fluids and other portions of a human body" (§ 1(e)). The purposes for which gifts under the Act may be used include "medical or dental education, research, advancement of medical or dental science, therapy or transplantation" (§ 3). Thus, the statute seems to indicate that research of the type being considered in this section is acceptable; the interests of medical science and of the immediate beneficiaries of research and therapeutic procedures is great enough to justify the use of dead fetuses, fetal issues and the products of conception, provided that proper consent is obtained.

The consent procedures established by the Act are of two types. The first, which is not relevant here, is that before his death "any individual of sound mind and 18 years of age or more" may make a gift to a medical institution (such as a hospital, school or organ bank) or a physician of "all or any part of his body," the gift to take effect upon his death (§ 2(a)). The UAGA also provides that if a decedent has not indicated a contrary wish, another person may make such a gift; the order of priority of persons who may give permission is set forth in six classes:

- "(1) the spouse,
  - (2) an adult son or daughter,
- (3) either parent
- (4) an adult brother or sister
- (5) a guardian of the person of the decedent at the time of death
- (6) any other person authorized or under obligation to dispose of the body." (§ 2(b)).

The first two classes clearly have no relevance in the case of fetal research. It is expectable that the donation of a dead fetus or fetal remains would thus usually be made by one or other of the parents. The statute specifies that a person may not make an anatomical gift if he or she has "actual notice of opposition by a member of the same or a prior class" (§ 2(b)) nor shall a donee accept a gift under these circumstances (§ 2(c)). Consequently, either parent would apparently be able to prevent the use of a dead fetus in an experiment by notifying the other parent and/or the investigator of his or her opposition. The statute does not, however, impose any obligation to make such inquiries (regarding the wishes of members of the same class); it presumes that a gift is valid "in the absence of actual notice" to the contrary, and insulates from criminal and civil liability anyone who proceeds "in good faith in accord with the terms of this Act" (§ 7(c)).

An experimenter desiring to use a fetus in an experiment could get valid permission from someone other than a parent only in the unusual situation that neither parent were "available at the time of death" (§ 2(b)).6 Thus, even if a guardian is appointed for a fetus prior to its death, he or she is not competent to give or withhold consent for the use of the fetus in an experiment after its death if the parents wish otherwise; only if a good faith effort to get the permission of either parent failed because they were "not available" would the guardian be authorized to act. It is also possible that the person who performs an abortion and is "under obligation to dispose of the body" (§ 2(b)(6)) might find him or herself left with the dead fetus by a woman who departed so suddenly and mysteriously that she was not available to give or withhold the necessary permission, which the abortionist would then be competent to make. Yet if a researcher intends to ask for a "gift" of the dead fetus or fetal remains, the UAGA would appear to require that he take the steps necessary to obtain permission from the parents rather than from the abortionist under a parental "unavailability" rationale (which would ordinarily be of dubious validity, given the requirement of "good faith" compliance with the statute).

The Act also provides that authorization for the gift may be given "after death or immediately before death" (§ 2(c)). Since the statute should be read in the context of the common law requirements on consent, the authorization should be both "informed" and "voluntary." It might therefore be questionable whether permission for an anatomical gift arising in the abortion context would be acceptable if it were obtained from a pregnant woman immediately before the fetus died, that is during the abortion process when she may not be in a clear frame of mind. It should nevertheless be possible to accommodate both the statute and the feelings of the parents; an explanation of the need for fetuses, fetal tissue or the products of conception could first be made to the pregnant woman (and the father of the fetus if he accompanies her) at the time that the abortion procedure itself is explained, and then permission for the anatomical gift could be obtained after the abortion was completed. In many instances, where the researcher's intention is to study the anatomy of the fetus or to use tissue for culture purposes, consent to proceed immediately is not needed. Only when the deterioration of tissues or organs (as in thymus transplantation) would jeopardize the success of the experiment is the need for a very prompt permission presented. Thus, such experiments can only go forward if and when the persons carrying them out feel confident that they will not be imposing an undue psychological burden on particular parents by seeking authorization from them immediately after a stillborn fetus has been aborted or an aborted fetus has died.

### B. Other Laws

Although the UAGA is the major provision of relevance to research on dead fetuses and fetal remains, a number of recent statutes modify in some measure the law on this subject, and some much older statutes may be thought to be relevant to this research as well.

In the past two years a large number of states have adopted new abortion statutes and some have also enacted special provisions on fetal experimentation. As a result, 14 states now have laws which restrict experimentation on aborted

fetuses, although the provisions in eight of these states, apply only to live or viable fetuses and the prohibition on research with "any aborted product of human conception" in the California statute excepts "fetal remains." The statutes in the remaining five states impose varying degrees of restriction on research with dead fetuses.

The least restrictive provisions are those of Massachusetts and South Dakota, which hardly change the law. The former states that: "No experimentation may knowingly be performed upon a dead fetus unless the consent of the mother has first been obtained, provided however that such consent shall not be required in the case of routine pathological study." This appears to be basically congruent with the UAGA, although it is unclear how "experimentation" could "knowingly" take place during "routine pathological study," since the research element would appear to lift such a pathological exam out of the category of the routine. The South Dakota provision is even more permissive. It prohibits only "experimentation with fetuses without written consent of the woman."10 The net effect of these two laws would seem simply to be that the father of the fetus is deprived of the authority (granted under the UAGA) to be the sole person consenting to the use of that fetus after death; the absence of maternal objection is no longer taken to be sufficient, rather the written consent of the mother is always required. Under the South Dakota statute the rest of the UAGA schema seems unaffected, so that the actual communicated objection of a father would still appear to be a bar to the use of his fetus; under the Massachusetts statute, an investigator who proceeded on the basis of the mother's consent despite the known objections of the father would not be exposed to criminal liability but he would not be immune from civil liability (to the father of a fetus) if he went beyond "transferring" the fetus and actually experimented upon it.

The remaining three statutes on fetal experimentation do have an impact on research with dead fetuses. Illinois and Indiana allow only pathological examination of, but not experimentation with, fetal tissues. Ohio narrows this permissible category to authorized autopsies; aside from such procedures "No person shall experiment upon or sell the product of human conception which is aborted."

It should be noted that all of these provisions, to the extent that they modify the UAGA rules on experimentation with dead fetuses and the like, apply only to the products of induced and not spontaneous abortions. Although the language in a number of them is broader, this must be read in the context of anti-abortion statutes which are speaking implicitly as well as explicitly of "the intentional destruction of the life of an embryo or fetus in his or her mother's womb of the intentional termination of the pregnancy . . . with an intention other than to increase the probability of a live birth or to remove a dead or dying unborn child," as the Missouri legislature put it. 13

The remaining set of laws which might affect the permissibility of experimentation with dead fetuses are grave robbing statutes, many of which date to the early nineteenth century. It is important to note that these would come into play only when the researcher has failed to get adequate consent for the use of the fetal remains.<sup>14</sup>

Although the applicability of grave robbing statutes may seem dubious, the most notorious actions brought against physician-investigators for fetal experimentation are being prosecuted under such a statute: on April 11, 1974, a grand jury indicted Drs. Leonard Berman, David Charles, Agneta Philipson and Leon Sabath for allegedly violating an 1814 Massachusetts statute when they studied the fetuses which had been aborted at Boston City Hospital after their mothers had taken an antibiotic. 15 The prosecution claims that the physicians did not have the authority to "remove or convey away" the "human body" of the fetuses or "the remains thereof," acts which are made a crime subject to imprisonment for up to three years. 16 The only relevant judicial interpretation of this statute is found in Commonwealth v. Slack, 17 where defendants had removed the body of a deceased man from the house of one of the defendants where he had died to that of a physician in another town, who wanted it for dissection. Defendants were convicted of removing and conveying away a human body without proper authorization. The conviction was reversed on appeal for failure to allege that the dead body was removed for the purpose of dissection. The Court stated that a literal construction of the statute would seem to prohibit removing or conveying away of any human body or the remains thereof for whatever purpose, even the internment of a dead body. The Court said that the provision was limited by the purposes of the statute which were to allow dead bodies to be used with the permission of the Board of Health, the overseers of the poor, or the selectman of the town for anatomical study, and to prevent the use of them in all other cases. The Court also held that the statute applied to dead bodies that were not dug up or removed from a cemetery.

The defendants in the present case possessed the requisite intent of using the aborted fetuses for dissection, and the fact that the aborted fetuses were not literally removed or conveyed anywhere but within the hospital grounds, coupled with the fact that their disposal was only detained, does not completely distinguish the facts in *Slack*, but only shortens the distance of removal and the time of disposal.

The grave robbing statutes in most other states are similar to the Massachusetts statute, and there is remarkably little judicial commentary on them that is relevant to the fetal research case. More recent statutes, such as the one enacted in Florida in 1972, except from their prohibition on "dealing in dead bodies" medical schools and other institutions that obtain the corpses for dissection or research.

The issues remaining unresolved, pending the final disposition of the Boston case, are whether the remains of a fetus (such as the abortuses removed by hysterotomy in the Boston City Hospital experiments) are "human bodies" within the scope of the grave robbing statutes, and whether the medical practice not to obtain explicit permission from women undergoing abortion for studies to be conducted on their abortuses is a valid defense to the charge of grave robbing. On the former issue, it seems doubtful that the legislatures had in mind the products of early pregnancy (i.e., first and possibly second trimester fetuses) when they drafted the grave robbing statutes, particularly in the nineteenth century. On the other hand, the permissibility of abortion does not mean that such fetuses do not possess "human bodies" even if they are not "persons" in the full sense of the law, as the Court declared in Roe v. Wade.

One likely way to resolve this issue is by looking to the statutes which define when a birth or death certificate must be filed; these are discussed in the following subsection.

The defendants in the Boston case would clearly like to take refuge in the medical practice of not seeking maternal consent for post-abortion examinations. As a matter of fairness, this may be a good argument; it indeed seems inequitable to penalize a few doctors for proceeding in good faith to do exactly what all their colleagues regularly do, particularly when it is at least arguable that an implied consent for the fetal examinations was given by the women when they gave informed consent to the manipulation of their own bodies -- since the purpose of the experiment could clearly be accomplished only if the investigators both gave the women the antibiotic and then examined the fetal tissues and organs for its presence. Yet as persuasive as this reasoning might be in negating negligence in a civil action against the doctor defendants, it is rather beside the point in a criminal action. The custom of a profession is no defense if it violates the law (e.g., were physicians routinely to engage in involuntary euthanasia this would not stop it from being homicide), and a prosecutor has discretion (subject to some small constraints on arbitrary or malicious abuse) as to whom among a group of wrongdoers he will prosecute. Thus, unless the custom of the profession, or the approval of an institutional committee on human studies, amounts to "lawful authority" for the "remov[ing] or convey[ing] away" of the fetuses, and thus complies with the statute, investigators who experiment on dead fetuses without parental permission (according to the procedures of the UAGA) are at risk of being convicted under grave robbing laws.

### C. Life and Death: Definition and Certification

In the discussion thus far we have assumed that it is apparent what a "dead fetus" is. Yet this is plainly not so. While it might be possible to get agreement that a particular fetus had so completely ceased all functioning that it was "dead," there would certainly be disagreement about the point in the process at which such a conclusion is proper and more fundamentally about whether the "death" being talked about is similar to the "death" we speak of in the case of a person. This question shades over into the related question of "viability"--if the judgment that a fetus is "nonviable" is based on the conclusion that its organ systems cannot function together in a coordinated fashion, then should it be considered "dead" although some parts of its functions can be kept working artificially for some time? (Since the National Commission has sought a separate memorandum on these questions, this subsection will be kept brief.)

In recent years the traditional understanding of death in human beings has become somewhat confused by medical developments which permit the artificial maintenance of respiration and circulation and by the ability of a heart removed from a "dead" person to function again in the recipient into whom it is transplanted. Medicolegal interchange and discussion has helped to clarify this field somewhat, however. There is an emerging agreement, both within the medical profession of and among the formulators of public policy, that it is possible to give a new articulation to the traditional understanding of death which can be employed in all cases, whether or not artificial means of support obscure the significance of the traditional life sign (heartbeat and breathing). A modern

definition, which recognized the interrelationship of the tripartite system as the basis for life and had death turn on the irreversible cessation of any necessary part, might be carried over into defining death in the fetus. Although on its face the problem of defining death in the fetus seems rather different, it is actually quite similar. In the fetus, the question is whether developing organ systems (e.g., heart, lung and brain) can be sustained to a point where they are capable of independent functioning, while in the child or adult, the question is whether injured organ systems can be sustained to a point where they will recover functioning.

In the case of the child or adult it may thus be proper to declare death despite a beating heart and respiring lungs if these functions are being artificially supported because of irretrievable cessation of total brain functions. Were it possible to achieve the necessary oxygen uptake through perfusion of a fetus that lacked functioning lungs and thereby to maintain circulation, such a fetus might be considered "dead" if it had no brain functions. Given the present technical difficulties of such a maintenance procedure and of making the necessary neurological findings, it seems likely that the definition of a "dead fetus" for purposes of the type of research considered in this section will be a narrower one. For the moment at least, fetuses which might be considered dead under the broader definition drawn with reference to general human death can be considered as subjects under the rubric of research on live, nonviable fetuses. The greater restrictions which accompany such research are merely a reflection of the public concern over the prospect of "exploitation" of apparently living, albeit hopeless, fetuses. It is sensible to distinguish (for purposes of their use in research, and for other purposes) between those beings, whether adults or fetuses, who are dead and those who are so close to being dead that further attempts at lifesaving are pointless. Yet it should be recognized that as more is learned about fetal development, and as new means are created for determining "viability" and for promoting it where possible, the time may come when some fetuses now designated, out of ignorance or caution, as "live but nonviable" will be seen as being properly described as "dead."

At present the laws on death certification provide little guidance on this question of "definition," but instead introduce another complication which cannot be ignored. In a number of states the special category of "fetal death" is recognized. This is typically defined as death prior to complete expulsion from the mother, evidenced after separation by the absence of life signs such as respiration, heartbeat, pulsation of the umbilical cord and movement of voluntary muscles.<sup>23</sup> In some jurisdictions, a regular death certificate must be filed in all cases of fetal death,<sup>24</sup> while in others such a certificate is required only after a stated period of gestation.<sup>25</sup> The more common practice, however, is for a special "fetal death" certificate to be filed, usually only after 20 weeks gestational age<sup>26</sup> but in some jurisdictions regardless of the length of the pregnancy.<sup>27</sup>

If a fetus is separated from its mother and shows signs of life (heartbeat, respiration, pulsation of the umbilical cord, or spontaneous movements of voluntary muscles) it is considered a "live birth" in most jurisdictions, although many apparently do not bother to define the term in their statutes.<sup>28</sup> A finding of "live birth," which requires that a birth certificate be filed, is not

dependent on the length of gestation nor on how long the signs of life persist in the fetus; if the life signs cease, a death certificate must be filed in addition to the birth certificate. Some states go further and require birth and death certificates to be filed for "stillborn children," but it is more usual to require only a report on those stillbirths that occur after 20 weeks of gestation.

The laws on the filing of certificates fall into the "administrative" category of law; that is, the form they take (with a great deal of interstate variation)<sup>31</sup> is primarily directed at achieving the greatest convenience for state record-keeping functions, although they may have the collateral purpose of helping to enforce the criminal laws.<sup>32</sup> Thus, they may say something, but probably not a great deal, about the state's judgment of the emerging "personhood" and consequent need for legal protection of the developing embryo and fetus. As was suggested above, they may even be employed by courts which are seeking guidance in determining whether a dead fetus is a "human body" within the meaning of a criminal statute on grave robbing. But their significance for our present concern is basically that they set forth some procedures with which researchers using dead fetuses should be careful to comply.

Beyond this, three broader conclusions can be reached. First, that most legislatures appear to have recognized that distinctions exist among (1) fetuses emerging from (induced or spontaneous) abortions prior to the sixteenth or twentieth week of gestation, (2) older fetuses which are expelled or extracted and lack signs of life, and (3) other kinds of dead human bodies, including those of fetuses which at least temporarily show signs of life following complete separation from their mothers. Second, that in most jurisdictions birth and death certificates are appropriate only when there has been complete expulsion of a fetus which shows some signs of life at the time of separation, although some states require both certificates for "stillbirths."

Finally, the general confusion of this area and the need to proceed with caution argue strongly that a "dead fetus," for purposes of research pursuant to the UAGA should be one which is "lifeless," in the sense of lacking all signs of life. The use of the term "lifeless" has the advantage of avoiding the question of whether the fetus to be "dead" had once to be "alive" in the sense of being a human being. It speaks instead to the absence in the fetus of the signs of life which are basically indicators of functioning organs (pulsation, respiration, etc.); it is apparent that from an early point in pregnancy the fetus has "life" in terms of such developing, rudimentary systems. On the other hand, the term "lifeless" does not suggest, at least to the lay mind, that there has been cessation of all intracellular life, which begins in "human" form with the fertilization of the egg and which persists after the point at which the fetus would appear "dead" to any naked eye.

# D. The Dead Fetus In Utero

The foregoing discussion has assumed that the "dead fetus" which might be a subject of research was ex utero. This might not always be the case, however. Consider, for example, a physician-investigator who wished to experiment with a new method for extracting (aborting) dead fetuses. For reasons which appear

more fully in later sections, the investigator in this case would have to obtain consent from the pregnant woman and only from her. The UAGA, under which the father of a dead fetus might attempt to have some say over its disposition, clearly was intended to apply only to independent dead bodies. Indeed, notwithstanding the clear language of the UAGA it would seem dubious that a spouse (class 1 under the Act) of a Siamese twin who died would be authorized to donate the body to research without the consent of the other twin (only in class 4 as a brother or sister), if the twins were still attached to each other! This conclusion is reinforced (if more than common sense is needed) by the preceding discussion on the death certification laws; they indicate that until the fetus is separated from its mother it is not regarded as a separate being for whom a "fetal death" or ordinary death certificate needs to be filed.

#### III. LIVE AND VIABLE FETUSES

A second category of research would be that done on living, viable fetuses, either ex utero, as for example development of means of supporting premature infants and of methods to prevent or treat disorders which affect only these infants, or in utero, as in experimental means of preventing prematurity, improving the means of monitoring the fetus during labor, or trying out new methods of prenatal diagnosis (like fetoscopy) and treatment (intrauterine transfusions). In addition, viable fetuses might be the indirect subjects of research carried out on the treatment of various conditions in pregnant women.

The fetal subjects of such research are clearly at the opposite pole from those discussed in the preceding section. Rather than being dead, they are presently functioning and have a reasonable chance of surviving with proper care-that is, they are "viable." In some ways, then, one would expect research of this type to be the most controversial, and it probably would be if such fetuses were used simply as experimental subjects. But, as the examples of research given above indicate, the intent of investigators is usually to treat the fetuses as patient-subjects who stand to benefit from the experiment. Not only in the investigator's conscience but in the law as well this difference in intent makes a substantial difference in the permissibility of the research. There may, however, be times when this rationale is not open because a live, viable fetus has become involved in research which will not benefit him, as for example, in a controlled experiment where some of the subjects will be assigned to a procedure (perhaps a placebo) which will not benefit them. Experimental techniques of abortion may also occasionally be employed with live, viable fetuses in utero and may even on occasion produce such a fetus alive outside the womb. Hence, it is not possible to cover all experiments on viable fetuses with the comforting blanket of "beneficial research."

### A. Ex Utero

As was shown in Section II, the statutes on fetal experimentation and on the registration of births do not regard viability as a necessary element in "live birth." Rather, the separation of the fetus from the mother, usually through complete expulsion or extraction, and the existence of some signs of life are the customary indicia of birth, and hence of the creation of a new

human being with full claim on society's concern and protection through the law.<sup>34</sup> Nevertheless, the fact that a particular fetus is "viable" (a prediction based on prior experience with fetuses of similar weight, size and gestational age) may heighten society's concern, as is manifest in the attitudes of the parents and the attending medical personnel.

1. Fetal Interests. Once birth has occurred, the law places definite limitations on the extent to which a viable fetus can be involved in research; these would be the same as those which apply to any neonate. The law recognizes the neonate's interests in survival, in dignity, and in avoiding pain and suffering. Consequently, the criminal law defines as homicide the failure of parents or attending medical personnel to take reasonable steps to care for the neonate or the taking of steps that endanger health or life if their conduct led to the infant's death, and the civil law provides remedies if these persons intentionally or negligently harm the neonate or neglect or otherwise fail properly to perform their duty to it. 6

These legal rules would obviously be relevant to proposed experiments with viable fetuses ex utero in a number of ways. First, neither criminal nor civil law would seem to stand in the way of the parents of such a fetus agreeing with a researcher to undertake an experimental mode of therapy, provided that such treatment (although new and perhaps even of unproven value) can be said on reasonable grounds to offer some advantages for the infant over modes of treatment that are presently available and that are foregone by the choice to use the experimental means instead. Even were it to be provable that the infant's death resulted from the experimental treatment (rather than from other causes, such as its prematurity) and that death would not have occurred had the conventional treatment been used--both obviously very difficult of proof--criminal liability for murder or manslaughter would not exist. To constitute a defense, however, the experimental modality must have been used in good faith and must be reasonable. For the physician-investigator this would probably mean that he or she can satisfy professional peers that the new treatment was as good as, or better than, existing treatments, based on theoretical reasoning, animal testing, and prior experience with the new treatment or others like it. For the parents the standard of reasonableness would turn on their care in selecting the physicianinvestigator and in weighing the relative risks and benefits of the alternatives. Their choice would also have to fall within the range of community-accepted values; despite the protection given by our constitution to individual beliefs and the wide scope allowed for behavior which may be harmful to oneself, the law limits a person's freedom to make choices which are harmful to others who are under the person's care. 37 The paucity of cases on point, however, makes a more precise statement about parental discretion to choose one treatment over another difficult. The most germane cases involve parents who were prosecuted for failing to provide any treatment or for delaying treatment; these cases suggest that parents will be liable if their choice fell far outside what the general community regards as reasonable.38

These observations also have relevance for a second situation. Suppose that rather than enrolling the viable "born" fetus in research a parent or physician-investigator were to decline to permit the meanate to be given an experimental treatment although no other means exist to keep the child alive.

Although the distinction between "ordinary" and "extraordinary" procedures has not been formally adopted into the law, 39 these concepts are closely related to the standard of "reasonable efforts" and so may be useful in this analysis. All experimental modalities would seem by definition not to be "ordinary"-rather than being customary, common or part of normal practice they are to some degree unusual and outside normal practice. But this is clearly a matter of degree, and some interventions that are classified as "experimental" for purposes of funding or institutional review procedures might involve such a slight deviation from the usual mode of treatment as not to be "extraordinary." Yet the smaller the innovation the greater the likelihood that there is an acceptable "ordinary" mode of treatment which would be offered as an alternative; hence, the less likely that the meonate would be left without any treatment whatsoever by the refusal to permit it to participate in the experiment. When such refusal is based on a reasonable effort to compare the risks of the experiment with the benefits to be derived by their neonate-subject, including in the calculation the pain and discomfort involved as well as the degree of recovery expected, it is highly dubious that the parents or physicians would be liable for homicide or criminal neglect.

The third point about ex utero research with viable fetuses on which the law may shed some light arises when the research proposed is not intended to benefit the fetus directly.<sup>40</sup> As an initial matter, it is obvious that, under the rules just articulated, there would be no grounds for holding criminally or civilly liable a parent or physician-investigator who declined to involve the fetus in such an experiment even were it later to appear that the experimental procedure would fortuitously have been beneficial or that its absence was in some unexpected way harmful to the fetus. But what of enrolling a viable fetus in a nonbeneficial experiment?

Since the viable fetus ex utero is in a position like that of the premature infant, it ought to be given the same protection accorded an infant. The difficulty is in knowing just what that protection is. At one extreme, it is well settled that an infant, or other nonconsenting person, may not be used in nonbeneficial research which exposes it to death or serious injury. Were death to follow, the persons responsible (parents, investigators, and so forth) would be guilty of murder if they acted intentionally, knowing that the experiment placed the life or health of the fetus at risk, or of manslaughter if they proceed in a grossly negligent fashion without regard to the potential adverse consequences for the fetal subject. If the fetus were injured but did not die, the conduct would amount to assault and child abuse, and even before injury occurs there would appear to be a violation of statutes prohibiting "neglect," which would seem to occur not only in the failure to provide adequate medical care, 41 but also in the doing of anything which in effect negates medical care and thereby imperils the infant's life or health.

The more difficult questions really arise when one begins with research which falls at the opposite extreme. Although no one would appear to have the authority to volunteer another, nonconsenting person for nonbeneficial research, there are probably some studies that involve so little risk (while still providing information which may be useful to medical science and perhaps to society) that it is hard to know on what grounds they should be prohibited. By definition,

such research would not interfere with the viable fetus' interests in survival or in being free of pain. What, then, of its interest in human dignity, in not being used as a thing for the objectives of others? This is a genuine interest, and one which is certainly recognized by the law. 42 In the case of risk-free research of scientific worth it is hard, however, to see that this interest is being denied; indeed, it may even be promoted. If a person, at no risk to himself, can aid others, is that not the proper thing to do? Would one not complain of an assault on one's dignity if he were prevented from doing such an act? Obviously, in the case of a neonate this argument should not be pressed too hard--the neonate is unaware of when a choice is made that it should pass up a chance to help others, so its sense of dignity is not likely to be much harmed. But, while there is danger that the rationale of "helping others" could become an excuse for using viable fetuses improperly in nonbeneficial but risky research, in the case of nonrisky research the rationale really gives voice to the common sense perception that such research is not offensive. Moreover, there is the utilitarian argument that society will be better off for such research, which in turn suggests that it may even be beneficial for the fetal subject, for it is only through the collective enterprise of research that the members of society, including the viable fetus ex utero, mutually bestow the benefits of new biomedical knowledge on one another.

As one moves away from this polar case--involving research along the lines of taking measurements of the neonate--and adds increments of risk or of pain it is hard to know where the line should be drawn. Professors Henry Beecher and William Curran have argued that minors may be used in experiments of no direct--and in some instances, no indirect--benefit to the child, without specifying a limit to the amount of danger which such experiments should be allowed to pose. Most commentators read the case law as providing no warrant for such a sweeping conclusion, and the unsettled nature of the law is indicated by a lawsuit brought by a member of the Human Studies Committee at the University of California Medical School to obtain a declaratory judgment on the legal rights and authority involved.

As a practical matter it should be borne in mind that unless the law is clarified through a declaratory judgment or through the promulgation of authoritative regulations, it is most likely to evolve in cases brought against parents and/or physician-investigators after injury to a viable fetus has occurred. The defendants in such a setting are at the disadvantage of having to insist that the experiment was not risky or involved only very minimum risk in the face of the fact that the subject actually was injured in the course of the procedure. This does not mean that they are sure to lose in such cases, since the burden of proof rests with the plaintiff-fetus or the public prosecutor as the case may be. But it does suggest that great caution be used in the design, approval or execution of experiments on the viable fetus. The overriding responsibility on all parties is to promote the health and well-being of the fetus by all reasonable steps and to take no actions which jeopardize that health or life unless they are necessary to secure some benefit to the fetus.

Although the recently enacted statutes in 14 states 46 which contain restrictions on experimentation with live fetuses from induced (but not spontaneous)

abortions might seem to alter the definition of the interests involved or the way in which they are usually balanced, only six of the statutes even appear to change the law. In seven of the other states, the statute, like the common law, explicitly permits research which is intended to preserve the life or health of the fetus, 47 and in the remaining state (South Dakota) the statute merely prohibits experimentation with a fetus to which the mother has not given "written consent."

The six states which have adopted "tough" anti-fetal experimentation laws probably did not intend to prevent physicians from employing experimental techniques in an attempt to save the lives of aborted fetuses. Were the language of these statutes taken literally, the legislators would seem to have decreased the weight accorded to the interests of a viable abortus which parents and physician want to save by using novel and extraordinary means; at the very least they seem to have reached the judgment that all experimental interventions are more dangerous than helpful for such abortuses. Yet this reading of the statutes is at odds with their other provisions 48 and with a more careful search for their intent. Thus, it seems fair to conclude that none of these statutes should be taken as having brought about a change in the common law.

When Do the Interests Attach? As will be discussed below, the fetus in utero is not without protection from the criminal and civil law. But the protection described in the preceding subsection revolved around the fetus being a "person" in the eyes of the law. When do the interests associated with this status attach? The general rule, already stated, is that they are owed once "live birth" has taken place, which is in turn defined as the separation of the fetus from the mother with heartbeat, respiration, or other signs of life. A somewhat clouded question is presented, however, whether "separation" occurs only upon "the complete expulsion or extraction from its mother of a product of human conception, "50 as is generally stated in the statutes on birth certification, or whether it can occur at an earlier point in the process of birth. This issue could be of real importance to a researcher engaged in the study of methods of abortion or other procedures which presented the undesired possibility of the live-born fetus. The generally accepted common law view, 51 which accords with the statutes, provided the basis in the recent trial of Dr. Kenneth Edelin in Boston for the instruction given by Superior Court Judge James P. McGuire to the jury that "for the defendant to be found guilty in this case, you must be satisfied beyond a reasonable doubt that the defendant caused the death of a person who had been alive outside the body of his or her mother."52 There was conflicting evidence on whether the aborted fetus in that case breathed or showed other signs of life after it was removed from the uterus; the jury's guilty verdict may have been based on its conclusion that the fetus was alive outside its mother's body. The jury may have concluded, however, as the prosecution urged, that even before this point the fetus was a person, based on the stage of its development and upon testimony by another doctor that while the fetus was still in the womb Dr. Edelin held onto its umbilical cord after separating the placenta from the uterus.

It is difficult to derive much from a jury verdict under such circumstances, and even the appeal may not clarify the matter, since the trial judge's instructions seem to have been in accord with the accepted legal view. At least one state has in effect moved back the point at which fetal "personhood" commences; Louisiana has created "the crime of killing a child during delivery" which is punishable by life imprisonment in the penitentiary at hard labor. 53

The question is further confused by the oft-cited dictum of an intermediate appellate court in California in People v. Chavez<sup>54</sup> that a viable child killed during, but prior to the completion of, the birth process is a person under the law of homicide. The Court concluded, in light of modern medical understanding and the availability of means of caring for premature infants, that a "viable" fetus should be regarded as a human being even though not yet removed from its mother. It was, however, able to affirm Miss Chavez's conviction on the simpler ground that the medical evidence was sufficient, beyond a reasonable doubt, to support jury findings that her child was "actually born" after it was "completely removed from its mother" and that it died because she failed in her duty to use reasonable care in protecting its life.<sup>55</sup>

Similarly, the Wyoming Supreme Court rejected the theory that a woman could be convicted of manslaughter for failing to take the necessary steps in advance to have care available for her newborn infant who died as a result; although a parent's failure to fulfill his or her duty of care is grounds for liability, the Court reversed her conviction because the duty does not commence until the child is born alive.<sup>56</sup>

Both the criminal and civil law recognize a greater burden on a physician who is actually attending a woman in labor as compared with the duty of the woman herself. If a fetus died after birth because of the physician's failure to be adequately prepared, the physician could be convicted of criminal homicide and held liable civilly for the wrongul death of the fetus. Although a physician has not contracted with the parents to care for the fetus following an abortion, he is under a duty to it having brought about the peril in which it finds itself.<sup>57</sup>

In sum, in the absence of a special statute the protection of the viable fetus which has been described here is that which is given once the fetus is in fact ex utero.

3. <u>Consent</u>: No differences appear to exist so far as the interests of the fetus based on the manner in which the viable fetus came to be alive *ex utero*, but this might provide a reason for differentiating in the way in which consent is sought for its involvement in research. For the fetus that emerges from the uterus as a premature neonate because of a spontaneous abortion there would appear to be no a *priori* reasons for interfering with the parental control over medical decisions which is established by the law. Thus, decisions about whether participation in research is consistent with the fetus' interests would be left with its mother and father (if the latter is available) within the limits set out above.

During the congressional debates on the bill to establish the National Commission, it was suggested that a woman who permits her fetus to be aborted has thereby disqualified herself from having any further say over it, should it emerge from the abortion process alive. There are other examples in the law of a person rendering him or herself unable to exercise powers otherwise possessed because of his or her attitude or conduct. For example, a judge who has an interest in the outcome of a case, who is biased for or prejudiced against a party, who has previously represented a party or was associated in the recent past with the attorneys for one of the parties, who is a material witness in the case in litigation, and so forth, should either recuse him or

herself or may be disqualified upon motion of one of the parties. Yet the analogy to judicial disqualification is not very persuasive for two reasons. First, there is a long and well articulated history of such disqualification, with statutory and common law which spells out the circumstances that require or permit a judge not to hear a case. This is in contrast to the vaguely based presumption behind the disqualification of parents in the abortion context. More important, the underlying principle for judicial decision making is that a judge should be completely objective and disinterested. In contrast, a parent is not disqualified from making choices for his or her minor children because he or she is not wholly impartial. Indeed, parents' concern for their children makes them highly subjective decision makers, and the need to balance the competing claims of family members renders it unlikely that parents have the sort of independent detachment desired for decision making on the bench. Thus, while the general illustration of conflicts of interest may be of some value, judicial disqualification does not supply solid ground from which to launch rules about fetal experimentation.

A closer parallel may be provided by the rules on the removal of guardians. The major reason for removal of a guardian is the finding of a conflict between the pecuniary or property interests of the guardian and the ward. In the case of a "natural guardian," such as a parent, conduct which is clearly illegal or immoral would warrant removal. A parent may also forfeit or waive his or her right of guardianship by knowingly and willfully abandoning the child, or, having the ability to do so, failing to maintain it. 59

The question thus arises whether the decision to abort ought, by analogy, to disqualify the parents (or at least the mother)<sup>60</sup> from exercising further control over the fetus once it is alive ex utero on the ground that they have behaved immorally and illegally regarding its interests or have abandoned it. An affirmative answer to this question has much to recommend it since it is plain that the parents have certainly exposed the fetus to greater burdens than it would have experienced had its gestation in utero not been disturbed. Nevertheless, it is hard if not impossible to conclude that the decision to abort provides simpliciter the basis for disqualifying the parents as the natural guardians.

The argument for disqualification faces at least three problems. First, since the Supreme Court has declared that women have a constitutional right to abortion, basing maternal disqualification on the exercise of that right smacks of an unconstitutional penalty or burden. It would appear likely that automatic revocation of parental decision-making authority could chill the exercise of the abortion option because it would face women with the prospect of an infant to whom they are psychologically attached and whom they have an obligation (morally if not legally) to support without the concommitant power of decision which usually accompanies such obligations.

Second, it must be assumed that the abortion itself was legal and hence did not deprive the fetus of any rights which the parents were obliged to protect; moreover, there is no basis for assuming that it was immoral as to the fetus because it may have represented the result of a very conscientious weighing of the relative advantages to the fetus of being born or being aborted.

Third, the rule of disqualification seems to be based on a misperception of the significance of the parental choice. Even when a woman has opted for an abortion on the grounds of her own interests and not because she believes this to be best for her fetus, she has not necessarily cast herself as being irrevocably opposed to the fetus' interests. The decision to abort what is believed to be a nonviable fetus has two parts: (1) that the woman will relieve herself of the burden of pregnancy, and (2) that there will be no live issue from the pregnancy. If, however, a live, viable fetus does result, then only the first of the maternal desires has been accomplished because the second one was based on an erroneous assumption. At this point, there is nothing in the law which says the woman should be regarded any differently than a woman who decided, for legally sufficient reasons, to abort a live viable fetus, i.e., to deliver prematurely. Such a woman is bound by the duties already spelled out which are intended to safeguard fetal well-being, and she would be assumed qualified to exercise choice about how best to carry out her duties unless and until her conduct demonstrated that she was not able or willing to do so 61 and was consequently exposing the infant to unreasonable risks.

As subject as they are to misuse, neglect proceedings at least provide a forum for the balancing of parental rights against those of the child and the state according to some principles and with an eye to the facts of the case. 62 This seems preferable to an absolute presumption for all cases. Moreover, it may provide greater protection for fetal interests. Parents who are operating within the scope permitted by the law are probably better situated than a judge or other state official to do what is best for the particular neonate, so far as medical care and participation in an experiment are concerned.

Nevertheless, a number of states have written some form of parental for-feiture of rights into their abortion statutes. Louisiana, which goes the furthest, places a live fetus which survives an abortion within its definition of a neglected or dependent child, and gives jurisdiction over it to the juve-nile court.<sup>63</sup>

Missouri also considers such product of an abortion "an abandoned ward of the state under the jurisdiction of the juvenile court" over which the mother, and the father if he consented to the abortion, "have no parental rights or obligations."64 These strictures apply, however, only if the abortion was not performed to save the life or health of the mother--a limitation of some practical as well as theoretical significance. As a practical matter, a live fetus is likely to survive only abortions performed in the third trimester; at this point the fetus is likely to be (or nearly be) "viable," which means under Missouri law that such an abortion could only be performed if necessary to preserve the life or health of the mother. Hence, the forfeiture of parental rights is made inapplicable to the situation in which it most likely would Furthermore, the Missouri statute serves to undercut the whole analogy to the disqualification or removal of "biased" decision makers, because it indicates that where the mother's interest is the greatest (i.e., to preserve her life or health) she does not lose her authority over the fetus by acting adversely to its interests.

The Montana statute also excepts abortions performed to preserve the woman's life, but goes further by providing that the parents can retain their authority if they agree prior to the abortion, or within 72 hours thereafter, to accept parental responsibility for the living fetus ex utero.66 Similarly, Kentucky allows the parents to object within 10 days to the child becoming "an abandoned ward of the state."67 Indiana puts the shoe on the other foot; an aborted fetus becomes a ward of the state if its mother (and father, if they are married) signs a custody release and does not retract it prior to the abortion. 68 Finally, the South Dakota statute provides that facts about the abortion are relevant evidence in any proceedings to terminate parental rights or to adjudicate a live-born fetus a dependent or neglected child; 69 the usual procedural rules and burden of proof are not short-circuited, and neglect proceedings would probably only be brought, and would largely be decided, on the basis of conduct after the abortion which showed that the parents--by submitting the fetus to dangerous experiments or otherwise failing to provide it ordinary care--were not the proper guardians of its interests. All these statutes, except perhaps those of South Dakota and Indiana, appear to be constitutionally suspect. 70 It seems better, as a matter of policy as well as constitutional law, to presume that parents retain control over their live, viable fetuses ex utero, and that the experimenter and the state would look first to the parents to protect the rights of any fetal subject of research.

#### B. In Utero

Although "viability" was seen not to be an important factor in considering the interests of the fetus ex utero it has played some role in differentiating fetal rights in utero. This is perhaps ironic since an accurate judgment about the viability of a fetus once it has emerged from the uterus is usually much easier to make than about the fetus while it is still en ventre sa mere. Nevertheless, the concept of viability has been employed by both the criminal and civil law.

1. Fetal Interests. As must be abundantly clear by now, the viable fetus has traditionally been said to achieve the interests of a full person only upon live birth. Thus, in utero even its interest in life is not protected by a homicide statute. A recognition of this principle underlies the Supreme Court's abortion opinions, since they permit a pregnant woman to take steps, in order to preserve her own health, which could extinguish the life of her viable fetus. This does not mean, however, that the viable fetus in utero is without protection of the law; there are two ways relevant to drawing up rules on fetal research that its interests are recognized by the criminal law, upon which the civil law has further expanded.

First, in the wake of the abortion decisions some states have sought to safeguard the fetus *in utero* against intentional injury which threatens its life. Such statutes, like the Louisiana law on "killing a child during delivery" set forth above, must be drawn narrowly so as not to favor the interests of the fetus over those of the mother, since the Supreme Court has determined that the state's interest in protecting the potential but not yet fully matured life of the fetus must give way to the mother's interests in life and physical and mental health. An older type of statute--prohibiting "feticide"--departed from the

common law rule by making it murder or manslaughter to kill an unborn child that is "quick."<sup>74</sup> Although these statutes have not yet been reevaluated by the courts in the light of *Roe*, it is unlikely that they would come into play in fetal experimentation. Conviction of feticide, the courts have held, requires proof that the injury inflicted upon the mother of the unborn child which caused her to miscarry was done with malice<sup>75</sup> and with an intent to kill or do great bodily harm to the mother.<sup>76</sup> Thus, an investigator studying, for example, a new means of fetoscopy who accidentally killed a fetus and provoked a miscarriage would not be guilty of feticide, since he would lack the requisite intent.<sup>77</sup>

The second way in which the law recognizes some interests of the fetus is by protecting it against injuries which occur <u>before</u> its separation from its mother and which then cause its death or impairment <u>after</u> it is born alive. The most dire consequences for the parents or physician would come under the criminal law, which regards it as murder or manslaughter if prenatal injuries bring about postnatal death. Thus, a researcher who gave a drug to a woman which caused a lethal deformity to occur in her fetus could be convicted if the fetus is born and then dies from the deformity; the mother could be regarded as an accessory or conspirator if she acted with the requisite knowledge. The effect of the law is therefore to put pressure on people to make sure that a complete and "effective" abortion is undertaken.

Suppose that, instead of investigating the effects of a drug, the research project was trying to develop a better means for late-term abortions, and that in the course of it a fetus was injured, emerged alive from the abortion, but then died of the injuries inflicted by the investigator. Under the law, this would seem to amount to homicide, but a number of defenses might be raised. First, the physician might argue that he injured the fetus at a time when its death was imminent (from the abortion) and thus his action should not be viewed as significant. This defense (which is complicated because the researcher was responsible for both the particular injuring act and the abortion as a whole) will avail him naught; it is well settled that a person is guilty of homicide for merely accelerating the demise of a dying person. 79 Second, the physician may defend on the basis that the method he was using was necessary to preserve the mother's life or health; if true, this should probably be a good defense, because under Roe v. Wade the woman has a right to abort even a viable fetus to protect herself against the "distressful life and future" and the psychological, social and medical harm that "additional offspring" may impose.80 viable fetus' interests, which may be seen as being strong enough to resist the claims of science presented by the first hypothetical experiment, may have to yield to the mother's claims in this hypothetical abortion experiment.

What understanding can be derived from these two examples of fetal research? They may suggest that no nonbeneficial research should be permitted on viable fetuses (or even earlier, on "quick" ones) because the law recognizes that an injury done to such a fetus will make the investigator (and probably the mother) culpable of homicide if the fetus is born and then dies of the injury. Yet the fact that culpability does not attach if the fetus dies--naturally or otherwise--in utero seems to suggest that the law's real concern is that no one be born with a serious injury; this is a recognition, in other words, not of fetal interests but of the interests of human beings, after birth, not to suffer and be at risk

of dying because of the culpable acts of another person. Although this latter reading of the criminal law almost seems compelled given the law on abortion, easy resolution of the issue is made impossible once one takes the civil law into account.

The civil law, which was for a time congruent with the criminal, has now developed some theories which would seem to recognize a broader fetal interest in protection against harm in utero. As Justice Blackmun wrote:

"[T]he traditional rule of tort law had denied recovery for prenatal injuries even though the child was born alive. That rule has been changed in almost every jurisdiction. In most States recovery is said to be permitted only if the fetus was viable, or at least quick, when the injuries were sustained, though few courts have squarely so held."82

Having overcome its fear that it is too difficult to prove that injuries in utero are the cause of defects or even of death, and having rejected the concept that the mother and fetus are a single entity so that there can be no separate injury to the fetus, 83 the majority of courts are satisfied to draw the line at viability.

"If the mother can die and the fetus live, or the fetus die and the mother live, how can it be said that there is only one life? If tortious conduct can injure one and not the other, how can it be said that there is not a duty owing to each?" 84

Not all courts have been willing to follow this reasoning to its logical conclusion, however. About half (thirteen) of the jurisdictions which have considered the issue hold that although the fetus may be a separate entity capable of being acted upon at viability, there has been no harm to a person until the fetus is born alive and undergoes the suffering and medical expenses which were caused by the defendant's act.<sup>85</sup> In the language of the New York Court, the wrongful conduct creates only "conditional prospective liability" prior to the fetus' live birth.<sup>86</sup> But an increasing number of courts (21 at last count) are willing to recognize a cause of action for injuries to a viable fetus which leads to its stillbirth.<sup>87</sup>

It is these rulings which appear to depart from the law established in the criminal context, as glossed by Roe v. Wade. Justice Blackmun attempts in that case to distinguish recovery for the wrongful death of still-born fetuses on the ground that this really vindicates the right of the parents to recover for their loss. Yet some jurisdictions allow the estate of the fetus, as well as the statutory beneficiaries, to recover for the actual pain and suffering prior to death. Before concluding that such rulings would (or should) be reversed under the Supreme Court's articulated rule that the unborn are not "persons" under the fourteenth amendment, one must remember that "unborn children have been recognized as acquiring rights or interests by way of inheritance or other devolution of property and have been represented by guardians ad litem. \*\*8\*\* Once the fetus is viable, so that the state's interest in it becomes "compelling" since the fetus "has the capability of meaningful life outside the mother's womb, \*\*8\*\* Roe does not appear to be an absolute bar to holding that the fetus (as well as its

parents) has an interest in its own "potentiality for life" and that actions which interfere with that interest injure the fetus in a present sense. Thus, the fetus may be represented by a guardian who would attempt to enjoin the injuries before they occur, and its estate may collect if the injuries nevertheless occur and cause the fetus' death *in utero*.

Consent. This resolution of the question of the interests of the viable fetus in utero brings us squarely to the issue of "consent," or "who speaks for the fetus?" Actually, this issue may be less perplexing than it might at first appear. From the viewpoint of the criminal law, the fetus is not a person until it is born, yet the state is still free to protect its interest in this potential person by penalizing conduct which endangers its life except the exercise by a woman of her right of privacy which "is broad enough to encompass [her] decision whether or not to terminate her pregnancy."90 In the exercise of that right, she is given the power of consent--both for herself, since the intervention is one into her own body, and on behalf of the fetus as parent and custodian. Actions taken by others pursuant to her consent are permissible, but otherwise may be culpable. Similarly, the civil law recognizes the parental interest in the developing fetal life and it may also recognize the fetus' own interest in health and life. These interests must bow to those of the mother if in making a medical decision for herself (including participation in experimental treatment for her own needs) she must trespass upon them, but otherwise they are paramount. Thus, there would appear to be no warrant for parents or others to expose the viable fetus to any other kind of experiment which poses genuine risk to its well-being, unless those risks were the necessary price for some countervailing benefit to the fetus. This resolution of the question of consent thus places the viable fetus in utero in approximately the same position as a fetus that has been born, though it should be recognized that both as to criminal and civil protection at the moment, not all jurisdictions accord such a broad scope to the fetus unless and until its injuries are manifest after it is born alive. 91

#### IV. LIVE BUT NONVIABLE FETUSES

Research on fetuses that are nonviable but possess some vital functions is the most troublesome area of fetal experimentation. On the one hand, apparently important studies have been proposed which are intended to yield information not otherwise available about normal fetal metabolism and drug safety during pregnancy among other things. On the other hand, the treatment of a nonviable fetus differently than one would treat a viable one is problematic since the judgment on viability is only a statistical one and may be altered by changes in the diagnosis or in the condition of the fetus. Furthermore, the vulnerability of the fetus and the perception, at least by some people, that it is "human" in significant ways, makes the prospect of such research a highly charged emotional issue and a matter of legitimate social concern. Much of the law which relates to this subject has already been discussed in the previous sections in examining what the law has to say about research in the viable and the dead fetus, but new strands will enter the analysis which follows.

#### A. The Meanings of "Nonviable"

An initial question is what is meant by "nonviable"? In the context used here, it may appear to be equivalent to "previable." But the previable fetus in utero obviously has the potential to become viable if left to continue its gestation; for it, previability is merely a stage toward eventual life. The same is not, of course, the case with the previable fetus ex utero. If the concept of viability is to have any meaning, it must be that when it does not exist the fetus is incapable—in its present locale (be it a uterus or a hospital unit) and with the present level of medical technology—of surviving more than a short period. Thus, for the fetus ex utero there may be no distinction between being previable and being nonviable for other reasons; that is, both categories suggest that a presently "living" fetus (i.e., one possessing some vital functions) is actually "dying" either from prematurity or from other conditions inconsistent with normal development and survival.

In the context of research ex utero, then, should there be any distinction drawn between a previable fetus and one which is dying? If the sole concern of the law were with preventing any significant injury that could diminish the likelihood of survival, the answer should be "no." Neither type of fetus has any real prospect of continued life. The significance of this response is that research with the nonviable fetus would then be treated the same as research with the viable fetus, and any nonbeneficial research which accelerated the complete cessation of vital functions ("death") would be forbidden.<sup>92</sup>

But there are other interests beside survival that the law is concerned to protect, prime among them the avoidance of pain. In the case of the fetus ex utero a focus on pain might prompt a distinction between the previable fetus and other nonviable fetuses, premised on the differences in their physical and mental development. Up until the point at which the fetus is able to feel pain in the sense that term is used with other persons, the concern of the law with protecting it may be less; after that point (which may perhaps be before viability) the fetus' increasing perception of pain would suggest that it be treated like a "dying" subject. Thus, for the purpose of deciding about fetal research, viability may be less important than other factors.

The law's further concern, which is to promote dignity and autonomy, has less relevance to the fetus. The concepts are premised upon the present or future capacity of the subject to perceive him or herself as a person. In the previable fetus it seems doubtful that such capacity exists or will ever exist. Indeed, it may even be questioned whether the interest in avoiding pain and suffering does not itself require that the fetus eventually become a self-perceptive person. Are we concerned to avoid pain in the sense of the absence from the world of certain electrical impulses in nerve cells? Or is that preference based on keeping people from being aware that they are suffering or that they have suffered in the past? If it is the latter, pain experienced by a fetus that will never be viable may not derogate from our objective since the fetus will never have such a perception. Perhaps, instead, the societal choice is based on some intermediate view about why injuries should be guarded against or upon other interests.<sup>93</sup>

In sum, while the term "nonviable" can be used to include a fetus that is far enough along in gestation to survive but will be unable to do so because of particular defects, there are good reasons for limiting the meaning of the term to those fetuses which are not sufficiently developed ever to become capable of maintaining heartbeat and respiration on their own. It may turn out, however, that for purposes of society exercising its protection over the fetus, viability is less relevant than the point at which the fetus develops a nervous system which can perceive "pain."

#### B. Ex Utero

1. Balancing the Interests. As we have seen, nonviable fetuses ex utero have been regarded as persons under the common law of crimes, protected against murder and assault; 4 under statutory law a still greater burden of care (than might be warranted by its "nonviability") may be imposed, as in some abortion laws, and restrictions may be placed on what can be done with it, as in the statutes governing what Louisiana vividly denominates "the crime of human experimentation." The common law of torts and property, and the rules of equity, also regard the nonviable fetus ex utero as a "person" to be accorded the full protection of the law. Although its small size and weight and general lack of development preclude such a fetus from having any true independent existence, the fact of its physical separation from its mother is sufficient to confer upon it the presumption of such independence.

Whether this is a wise result is another matter. The law's protection is conferred upon the fetus in part because of society's skepticism about the accuracy of determinations that a particular "nonviable" fetus has no prospect whatsoever of surviving; when a life is at stake, great scrupulosity is demanded. Against this must be weighed the possibilities foregone. It is a matter for policy determination, not derivable from the law, whether a particular incursion on the interest of the fetus is justified. If one is speaking of very young fetuses (say, 12 to 18 weeks), in which the diagnosis of nonviability (by size, weight, etc.) can be made with great certainty, thereby eliminating the possibility of survival to a point where the concerns of suffering and autonomy would come into play, it is for society to say whether there are persuasive reasons for exposing the fetus to some risk for the benefit of society, as through participation in an experiment. If the fetus is sufficiently immature that concern over any present awareness of pain can be eliminated, the horizon of permissible experiments might be expanded accordingly.

Would a law which permitted experimentation, under specified limits and controls, with nonviable fetuses ex utero run afoul of any legal standards? The claim might be made, on behalf of such fetuses, that they would be denied the equal protection of the laws if they could be subjected to experiments without their consent but other persons could not be and if investigators would escape criminal and civil liability for injuries done them but not other persons. It might also be said that any legislative redefinition of personhood which excluded them would amount to an arbitrary deprivation of due process, just as if all

children under twelve or all women were declared not to be "persons." But both of these arguments beg the real question, which is whether actual differences between nonviable fetuses and other beings are great enough to justify a distinction drawn for the purpose of permitting a certain class of research. That is the sort of judgment on which the National Commission has been asked to give an opinion. Ultimately, legal rules drawn for other purposes do not appear to offer very good pegs on which to hang one's hat. The choice of "birth" (i.e., emergence from the mother with some signs of life) as the pivot point for "personhood," regardless of viability, was made in the context of different competing interests (such as a person's hypothetical interest in being free to kill a newborn baby, or to behave negligently toward it) than those interests (such as the advancement of biomedical knowledge and the provision of new therapy) which present themselves in the present context. Obviously, the balancing of different sets of interest may lead to different conclusions; moreover, the interests themselves may be subject to redefinition. The point of birth (independent of viability) provided a standard which was easily administered in all sorts of settings--from spontaneous abortion at 24 weeks in a taxicab to premature delivery in a hospital. It is open to question whether some other line, dependent upon a more precise and thorough determination of viability, might not lead to a different description of the rights of the beings falling on either side of the line.

2. Consent. If it is concluded that the nonviable fetus ex utero is to be regarded like any other incompetent person, and thus available only for beneficial research or for research which poses absolutely no risks, then consent should be fairly straightforward. The same rules would apply as governed the giving of consent for the viable fetus ex utero. There is no need to repeat here the reasoning which concluded that the decision-making power should remain with the parents, subject to revocation if their decisions viz-à-viz care or participation in an experiment show them to be at odds with the established rules of civil and criminal law which are designed to protect all persons against harm.

Were a wider range of experimentation to be allowed, more difficult issues of consent are presented. The law's recognition of the parents' rights as "natural guardians" to give or withhold consent for the use by others of their dead as well as living offspring 98 would seem to argue that they should at least have the authority to refuse to permit their nonviable fetus to be used in an experiment. There appears at this time at least to be no convincing argument made that the state needs, in order to secure collective benefits, to intervene and conscript fetal subjects.99

In any case, it must be asked whether the parents' consent is sufficient to permit participation in experiments which are no longer limited to those that involve no risk or may be beneficial. The fact that such an experiment would have to be justified on the basis of its collective benefit (via scientific knowledge) might suggest that the decision on participation should be made by a representative of society, but it might equally argue that such a person should be kept at arms length since he represents an interested party. The decision might, therefore, be left in the hands of the parents, with some review by a disinterested person, like a judge, concerning either (1) broadly, whether all the relevant factors have been taken into account in the parental decision making

and whether there is any affirmative evidence that the parents are acting irresponsibly or maliciously in their choice, or (2) more narrowly, whether certain specified, minimal criteria, about the certainty of the diagnosis of "nonviability" and the degree of risk involved, have been met. In the organ transplant field, the advance approval of the courts has on occasion been sought for the removal of an organ or tissue from a minor; the parents' approval was not regarded as sufficient because there was thought to be no benefit to the donor, and because the parents were perceived to have a conflict of loyalties between protecting their well and healing their sick children. The entire cast of these cases suggests that they were intended more to benefit the adults involved (by protecting them against liability for battery once the donor came of age) than to protect the donors from harm. The early cases on kidney transplants between identical twins $^{100}$  were decided on the dubious basis that the donor obtained a psychological benefit, and this rationale has been repeated in cases to which it has increasingly attenuated application; now courts have, without explanation, approved the transplants (of bone marrow) in cases where the donor was too young to receive any psychological benefit. 101 While the experience with judicial review of parental choice in this area is thus not encouraging, this does not mean that a judge or other special decisionmaker could not play a useful role in reviewing parental decisions about fetal experimentation. 102 "Broad" review (as described above) would be most likely to protect the fetus against the illmotivated or ill-informed parent, but would involve a large administrative expense and perhaps impossible delay. "Narrow" review might be nothing more than an extension of the approval necessary to be obtained from the institutional review committee prior to any research; it would not be concerned with the basis of parental choice, but merely with assuring that each fetus came within the diagnostic criteria of eligibility for the project.

## C. <u>In Utero</u>

Not surprisingly, the law has generally regarded the nonviable fetus in utero as having the least well developed set of interests. Not yet visible to the naked eye as a being separate from its mother (like a fetus ex utero) nor even capable biologically of having a separate existence (like a viable fetus), a fetus of this class still enjoys many forms of legal protection though far fewer than the others we have discussed.

1. Balancing the Interests. Live birth following an injury is the sine qua non of liability, either for homicide or assault. For crimes not requiring live birth, quickening is the touchstone, since it provides the necessary assurance that there is a life which might be endangered. The common law of abortion is a tangled web, but the best historical view is that bringing about an abortion was no crime at all before quickening; 103 the feticide statutes are to a similar effect. But as abortion statutes were first adopted and then revised the quickening distinction disappeared. There is good reason to believe that this reflected a social desire to protect women from the dangers of abortion, 105 rather than a belief that the fetus was an entity deserving full legal protection from the moment of conception. At any event, the Supreme Court plainly adopted a view of history and of the interests derived therefrom which accepts that an unborn fetus does not receive full recognition and protection prior to birth and certainly not prior to viability. 106

The civil law has not spoken with one voice on the question of the previable fetus' rights. The law of property for a long time gave the greatest recognition, since a child from the point of conception was able to acquire property interests and was treated as being "'born' and 'alive' for all purposes for his benefit." Professor David Louisell has suggested that the presence of live-born children before the courts in all the cases was merely a happenstance of litigation timing, and that judicial observations that the child must be born alive for its property interests to vest are "really gratuitous and superfluous" and "only dictum." Cases have said otherwise and the language of many statutes is explicitly contrary to this view. Thus, the cases may signify nothing more than a recognition that it would be unfair to exclude a posthumous child from its share of an estate rather than demonstrating any strongly held common law belief that the previable fetus is a person.

As already shown, the law of torts has recently moved from a niggardly view of the fetus' interests to a very expansive one. For the child born alive, it seems to be of no importance to most courts which have addressed the question whether the injury which causes impairment or death occurred before or after viability. Again, the significance of these cases is unclear. Certainly, a research project should not expose even a nonviable fetus to injury if it is later to be born—the law attempts to protect people against injury, even when the harmful conduct occurred before the time of personhood. Allowing recovery for injuries occurring prior to viability simply recognizes the reality of biological cause—and—effect: although not yet an independent being, the early—term fetus is capable of being injured, and indeed is highly susceptible to certain kinds of injuries.

No jurisdiction seems, however, actually to have allowed recovery for the wrongful death of a fetus that was injured and died before it was viable, 115 and some have expressly disapproved it, 116 apparently on the view that until the fetus reaches a stage when it is capable of independent existence, (1) it cannot be considered a "person" under the wrongful death statutes, (2) there is no assurance that it would ever have attained this state in development had the defendant not injured it, and (3) as a matter of proof, it is difficult even to be sure (at least prior to quickening) that there was a "live" being at all which was caused to die by the defendant's act and not otherwise. 117

Courts of equity will act to protect at least some of the interests of the fetus, apparently without regard to the stage of gestation, for example, the conservation of property to which it is entitled upon its birth. A father's statutory obligation to support his children has been read to entitle an unborn child to be represented by a guardian appointed to bring an action against the father to compel support prior to birth. The cases on the appointment of a guardian to consent to a transfusion for a pregnant women to save her life and that of her child all involve fetuses that were viable and indeed near term, but if a well-defined right of a previable fetus (to be protected against physical or financial injury) can be indentified, it is probable that the courts would be willing to appoint a guardian to conserve and protect that interest on behalf of the fetus.

2. Consent. This presents the question of consent since the balancing of the nonviable fetus' interests will depend on whose interests are being asserted on the other side. Even more than with the viable fetus in utero, the mother's right to take steps which will lead to the destruction of the fetus suggests that its interests are only weak ones; whether they are viewed as being outweighed by the mother's or whether they should be seen instead as being non-existent in the face of hers is a moot question. State intervention to promote the well-being of a nonviable fetus ex utero raises policy issues but is probably constitutional, but dictation to the mother and physician of medical decisions on the grounds of protection of the nonviable fetus in utero has been found unconstitutional.

There are, however, two difficult consent issues which remain regarding fetal research. The first is whether the woman's control over her own body, which allows her to participate or refuse experimental interventions which affect her as the subject of research and may incidentally affect her fetus, should be balanced by any separate consent from someone else in the case of research which is intended primarily to affect the fetus as a subject. The physical relationship of mother and fetus makes it plain that her consent must be required for all experiments on her fetus, except perhaps for a lifesaving procedure which is experimental but nevertheless likely to give needed benefit to the fetus. When the woman is willing to consent, there may be two grounds on which no further consent need be sought. One would be that the nonviable fetus, lacking a legal personality, need not be represented. The teaching of the civil law, however, would seem to be that the state may recognize a potential person and protect it in certain ways. The second ground for not requiring "fetal consent" as such is that the mother's right of decision, recognized in Roe v. Wade, to destroy the fetus for her own, possibly selfish reasons, is broad enough to permit her to permit it to be used in research that is less harmful than total destruction and is supported by legitimate scientific reasons.

Yet this points to the second consent issue: whether the consent to participate in research can be tied to an agreement to abort. Without such agreement, the law's concern that harm not be done to a person has not been met; furthermore other parties, such as the father and officials of state welfare agencies, who have an interest in the potential child's health and life after birth and obligations to provide it with necessary care, would seem to have legitimate grounds for insisting that their interests be protected. Yet an agreement to abort would probably be unenforceable, as against public policy and in violation of the pregnant woman's rights of self-decision under Roe v. Wade.

There is no easy way out of the conundrum created once one recognizes the nonviable fetus in utero as a being of some sort (though not yet a person) for whom permission must be given for use in an experiment. To locate the authority with the pregnant woman will not satisfy some because of her potential conflict of interest; yet to locate it with another person not only creates problems of great substantive and procedural complexity but would in all probability be found to be unconstitutional in the event that the other person were to try and keep the woman from acting in the way she wanted to. One partial "solution" to the dilemma is suggested by the Massachusetts statute; it provides that research may take place on a fetus which is "not the subject of a planned abortion" and

that a statement signed by the women "that she was not planning an abortion" supplies conclusive evidence on the point. While this might permit a fetus that was to be carried to term to be exposed to risk, and thus contradict the law's solicitude for a sound mind and body at birth, it can be seen instead as asking the pregnant woman (as well as the physician-investigator): "Are you willing to experiment in this way and with these risks on a fetus which will be born?" Thus, it attempts to use maternal concern as a protection against exploitation and unwarranted risks, without precluding the subsequent performance of an abortion if there is a change of mind or if experience (with other fetuses that were carried to term) shows that the risks were greater than had reasonably been anticipated. In some cases this arrangement might be just a charade by women who intended all along to abort, but it might prompt caution and greater protection of the fetus as a research subject in other cases and it would provide a very valuable safeguard in those cases in which a woman did actually change her mind and not have an abortion.

Unfortunately, if such a statute were actually used to keep a woman who declared that she was planning an abortion from volunteering for an experiment it would probably be held to exceed the state's legitimate authority to intervene in the private decisions of women and their physicians. The great deference which the Supreme Court showed to women's right to decide about what medical steps are in their own best interests would probably extend to a desire not to "waste" a pregnancy if it could help medical science. Of course, it is just this factor which may amount to the conflict of interest that is argued to disqualify maternal decisionmaking about fetal participation in research. A Massachusettstype limitation would raise fewer questions (although it would not be immune from attack) if it were part of the conditions governing the award of government grants and contracts. Neither women nor their physicians can insist that the government fund certain types of research, or permit everyone who wants to participate to do so.

Nothing is included here on the elements of the consenting process itself, whether the person giving permission is the mother or someone else. These matters are taken up in another recent publication. $^{125}$ 

3. Compensation. Although the scope of this memorandum was limited to the question of what the law says about the interests implicated in fetal experimentation, one comment should be made about another function of the law. The rules of the criminal and civil law have been described largely in terms of the interests they articulate and the means by which they attempt to affect behavior, through deterrence of conduct which is harmful to those interests or through active intervention (as by a court-appointed guardian). Once harm occurs, however, the law also determines how the burdens imposed by that harm are to be borne. It would therefore seem imperative for the National Commission to define the types of conduct which would cause the harm suffered by fetal subjects to be shifted from them and their parents to the persons or agencies sponsoring the research or perhaps to society at large, if we are all the beneficiaries of the research. Since there is no way that the fetus can itself consent to the research, the usual standard—that the losses are shifted only if they are attributable to the investigator's negligence—does not provide adequate compensation

or take fair account of who it was who decided to run the risks in the first place. On the other hand, the adoption of a strict liability standard makes more crucial the problem of determining whether the handicaps of the fetus were the product of the research (and hence compensable) rather than of other causes (not compensable), and it also highlights the inequity of fully compensating an injured fetal subject while other fetuses who suffer from naturally occurring handicaps of the same or great degree are often not provided with adequate medical care, much less "compensation."

#### REFERENCES

- For example, any official attempt to limit the publication of the results of fetal experiments conducted in violation of the law would run into first amendment problems.
- 2. 410 U.S. 113 (1973).
- 3. Such disciplinary action may become a matter of legal interest if, for example, question is raised whether it comports with the procedural requirements imposed on bodies which impose penalties, particularly with state sanction.
- 4. See, e.g., Philipson, Sabath, and Charles, "Transplacental Passage of Erythromycin and Clindamycin," New England Journal of Medicine 288:1219, 1973, the legal sequelae of which are discussed more fully below.
- 5. If it is thought that such things as the amniotic fluid and placenta relate to the woman's body, rather than being "tissues . . . fluids and other portions of [the fetus'] body," then these would be regarded like any other anatomical specimen and her consent would be necessary for their use in a research procedure. See The Institutional Guide to DHEW Policy on Protection of Human Subjects 3, 1971.

- 6. "Availability" is not further defined, but would seem to be subject to the "good faith" requirement of §7(c).
- 7. Ky. Gen. Ann. Acts, ch. 255, §13 (1974); La. Rev. Stat. Ann. §14:87.2 (Supp. 1974); Me. Rev. Stat. Ann., tit. 22, §§1574-76 (Supp. 1974); Minn. Sess. Laws, ch. 562, §2 (1973); Mo. 77th Gen. Ass., 2d Reg. Sess., Act 76, §6(3) (1974); Mont. Rev. Codes Ann. §94-5-617 (Supp. 1974); Neb. Rev. Stat. §28-4, 161 (Supp. 1973); and Pa. Sess. Laws 1974, Act 209, §5 (1974). The Louisiana, Maine and Pennsylvania statutes make fetuses "live born" or "born alive" impermissible subjects of human experimentation, but it seems probable that the statutes would be construed not to prohibit research with a live born fetus which subsequently died and was given for research pursuant to the UAGA.
- 8. "Fetal remains" is defined as "a lifeless product of conception regardless of the duration of pregnancy." Cal. Health & Safety Code §25956 (Supp. 1974).
- 9. In criminal, although not in civil, actions, a written statement authorizing the use of the fetus in research from the mother (at least 18 years old) is "conclusively presumed" to constitute the necessary consent. The consent also permits the "transfer of the dead fetus" to the site of the experiment. Although the sale of a fetus "for a use which is in violation of the provisions of" the statute is illegal, and the cost of an abortion may not be

#### REFERENCES (Continued)

- 9. (cont.) reduced in whole or in part because the woman has agreed to give "the fetal remains" for research, the statute does not appear to prohibit outright payment to a woman for a dead fetus to be used consonant with the statutory provisions. Mass. 1974 Reg. Sess. Laws, ch. 421 (adding §12J to Ch. 112 of the General Laws).
- 10. S.D. Compiled Laws Ann. §34-23A-17 (Supp. 1974).
- 11. The Illinois statute requires an "analysis and tissue report" by a pathologist on "all tissue removed at the time of abortion" as a "matter of record in all cases," while prohibiting "exploitation of or experimentation with" such tissue. Ill. 1973 Laws, Pub. Act 78-225, §8. In Indiana, pathological examinations are permitted but not required; no experimentation is permitted "nor shall any fetus so aborted be transported out of this state for experimental purposes." Ind. Ann. Stat. §10-112 (Burns Supp. 1974).
- 12. Ohio Rev. Code Ann. §2919.14 (Page's Legis. Supp. 1974).
- 13. Mo. 77th Gen. Ass., 2d Reg. Sess., Act 76, §2(1) (1974).
- 14. This follows for two reasons. First, the statutes typically permit persons to make use of a body if they are "lawfully authorized" to do so. Second, the UAGA, which is a recent enactment, would appear to supersede any inconsistent prior legislation. It specifically provides, in section 7(c), that a person acting in good faith accord with the Act is not subject to prosecution in any criminal proceeding.
- 15. See note 4 supra. Despite the women's consent to undergo the experiments themselves, permission was not asked nor given to study the aborted fetuses. Culliton, "Grave Robbing: The Charge Against Four from Boston City Hospital," Science 186:420, 1974.
- 16. The Massachusetts Violation of Sepulture Statute provides:

Whoever, not being lawfully authorized by the proper authorities, wilfully digs up, disinters, removes or conveys away a human body, or the remains thereof, or knowingly aids in such disinterment, removal or conveying away, and whoever is accessory thereto either before or after the fact, shall be punished by imprisonment in the state prison for not more than 3 years or in jail for not more than 2-1/2 years or by a fine of not more than two thousand dollars.

Mass. Gen. Laws Ann., ch. 272, §71 (1968).

17. 36 Mass. (19 Pick.) 304 (1837).

- 18. One case suggests that "human body or remains" will be narrowly construed. In State v. Glass, 27 Ohio App.2d 214, 273 N.E.2d 893 (1971), a real estate developer who had purchased a tract of approximately 60 acres, the deed to which excepted a cemetery about 1/7 of an acre in size containing 4 graves about 125 years old, nevertheless ordered the leveling of the cemetery and employed a licensed undertaker to move the bodies. Defendant was arrested and convicted under a statute providing for the removal of gravestones and under the Ohio grave robbing statute. His conviction was affirmed as to the removal of the gravestones, but reversed under the grave robbing statute, the court holding that excavation ceases to be a grave under the statute when the human remains originally placed therein have decomposed to such a degree that they no longer meet the definition of a corpse or a dead body. The court also said the statute only applied to grave robbers, ghouls and like persons who have a nefarious purpose in disturbing the excavation.
- 19. Fla. Stat. Ann. §872.01 (Supp. 1974).
- 20. See, e.g., Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death, "A Definition of Irreversible Coma," Journal of the American Medical Association 205:337, 1968; "When Is A Patient Dead?" Journal of the American Medical Association 204:1000, 1968 (editorial); Curran, "Legal and Medical Death--Kansas Takes the First Step," New England Journal of Medicine 284:260, 1971.
- 21. See Cal. Health & Safety Code §§7180-82 (Supp. 1975); Kan. Stat. Ann. §77-202 (Supp. 1974); Maryland Sess. Laws ch. 693 (1972). The American Bar Association recently adopted a policy statement, defining death as "irreversible total cessation of brain function," which they recommended for consideration by states adopting definitions and by the National Conference on Uniform State Laws. See 43 U.S.L.W. 2362 (1975). At the time the UAGA was drafted, its authors did not believe that a definition of death need be included; under section 7(b) the "time of death" was left to the "physician who attends the donor at his death or, if none, the physician who certifies death."
- 22. See, e.g., Capron and Kass, "A Statutory Definition of the Standards for Determining Human Death: An Appraisal and a Proposal," University of Pennsylvania Law Review 121:87, 1972. See also note 32 infra.
- 23. See, e.g., Colo. Rev. Stat. Ann. §66-8-2(6) (Cum. Supp. 1967); Conn. Gen. Stat. Ann. §7-60 (1958); Fla. Stat. Ann. §382.071 (1973); Ga. Code Ann. §88-1702(f) (1971); Ill. Ann. Stat. ch. 111-1/2, §73-1 (Smith-Hurd Supp. 1974); Mass. Ann. Laws ch. 46, §94 (1973); N.Y. Pub. Health Law §4160 (McKinney 1971); Pa. Stat. Ann. tit. 35, §450.105 (Supp. 1975); Wash. Rev. Code Ann. §70.58.150 (1961).
- 24. See, e.g., Colo. Rev. Stat. Ann. §66-8-10 (Cum. Supp. 1967).

- 25. See, e.g., N.J. Stat. Ann. §26:6-11 (Supp. 1974) and Pa. Stat. Ann. tit. 35, §450.501 (Supp. 1975) (after 16 weeks gestation).
- 26. See, e.g., Cal. Health & Safety Code §10175 (1964); Conn. Gen. Stat. Ann. §7-60 (1972); Fla. Stat. Ann. §382.071 (1973); Mass. Ann. Laws ch. 46 §9A (1973); Mich. Comp. Laws Ann. §326.15 (1967); Wash. Rev. Code Ann. §70.58.160 (1961). Illinois, in addition to the certificate of fetal death for post-20 week fetuses, Ill. Ann. Stat. ch. 111-1/2, §73-20 (Smith-Hurd Supp. 1974), also provides for a special report of each abortion performed prior to 20 weeks, Ill. Ann. Stat. ch. 38, §81-15 (Smith-Hurd Supp. 1974).
- 27. See, e.g., Ga. Code Ann. §88-1716 (1971) and N.Y. Pub. Health Law §4160 (McKinney 1971).
- 28. Examples of birth certificate related statutes defining "live birth" are Ill. Ann. Stat. ch. 111-1/2, §73-1(5) (Smith-Hurd Supp. 1974); Minn. Stat. Ann. §144.151 (1970); N.Y. Pub. Health Law §4130 (McKinney Supp. 1974); Pa. Stat. Ann. tit. 35, §450.105(3) (1964). In addition, a number of the anti-fetal research statutes passed in the last two years also include a definition of "live born," which adopts the usual indicia of life. See, La. Rev. Stat. Ann. §14:87.2 (Supp. 1974) and Me. Rev. Stat. Ann., tit. 22, §1576 (Supp. 1974); see also note 7 supra. Statutes in a number of states, such as California, Connecticut and Florida, use the term "live birth" without definition.
- 29. See, e.g., Mass. Ann. Laws ch. 46, §9 (1973) and S.D. Compiled Laws Ann. §34-23A-16 (Supp. 1974).
- 30. See e.g., Colo. Rev. Stat. Ann. §66-8-5 (1963, repealed and reenacted, Sess. L. 1967, pp. 1056-63, §§1, 4; "stillborn" is not defined. The District of Columbia provision on reporting stillbirths after 20 weeks of gestation as a form of death certification is typical. D.C. Code Ann. §6-301 (Supp. III, 1970). Florida, which provides for a "fetal death" certificate, as discussed in the text above, also requires that certificates be filed for all "births, deaths, and stillbirths"; in the absence of a statutory definition it is not clear whether a "stillbirth" is the same as a fetus born dead or is meant to include a broader category, such as fetuses born with minimal signs of life who survive only a very brief period because of their young gestational age. Fla. Stat. Ann. §§382.19 382.20 (1967).
- 31. There is no uniform act proposed for death certification.
- 32. The investigation of abortions at Boston City Hospital, begun by anti-abortion furor over the fetal research cited in note 4 supra, was spurred on when the district attorney's office learned of two dead fetuses in the pathology department for whom no death certificate had been filed. This led to the

- 32. (cont.) indictment of Dr. Kenneth Edelin for manslaughter. Culliton, "Manslaughter: The Charge against Edelin of Boston City Hospital," Science 186:327 (1974).
- 33. This is the term used in the California statute prohibiting fetal experimentation except research with "fetal remains," which are defined as "a lifeless product of conception regardless of the duration of pregnancy." In explaining this term the statute states that a fetus "shall not be deemed lifeless" unless "there is an absence of a discernible heartbeat." Cal. Health & Safety Code §25956 (Supp. 1974).
- 34. This issue of "When Do the Interests Attach?" is explored more fully at pp. 13-16 to 13-17 infra.
- 35. Williams, G., Criminal Law: The General Part, 2d ed., 1968.
- 36. The doctrine of intrafamilial immunity, which although criticized still prevails in most states, would protect the parents from liability to the fetus for negligent or intentional injuries.
- 37. The leading case is Regina v. Senior, [1899] 1 Q.B. 283, in which a father was convicted of manslaughter for declining to provide medical care for his 8- or 9-month-old infant based on his religious beliefs. It has been followed in this country. See, e.g., Craig v. State, 220 Md. 590, 155 A.2d 684 (1959). See also Stehr v. State, 92 Neb. 755, 139 N.W. 676, aff'd on rehearing, 142 N.W. 670 (1913) (upholding manslaughter convictions of father who attempted to excuse his negligent failure to care for his 2-year-old stepson on the grounds that as a poor immigrant he was unable to procure medical assistance). But see Regina v. Knights, 175 Eng. Rep. 952 (1860), which involved the failure of a woman in labor to obtain the necessary assistance, wherefore her child died; the trial judge's dismissal suggests that there are circumstances in which conduct though unreasonable as a general rule is excused by the actor's condition.
- 38. When the harm threatened is great the state may not wait for it to occur but instead may intervene to override a parental choice that falls outside the bounds of "reasonableness" in the society at large. See, e.g., Johovah's Witnesses v. Kings County Hosp., 278 F.Supp. 488 (W.D. Wash. 1967), aff'd, 390 U.S. 598 (1968).
- 39. See Robertson, "Involuntary Euthanasia of Defective Newborns: A Legal Analysis," Stanford Law Review 27:213,235-37, 1975.
- 40. The term "nonbeneficial experiment," which is used here for this category, may be somewhat confusing since it might suggest that no good will come to anyone from the research. The term is meant, on the contrary, to suggest that despite the potential benefits to others (which may be great or small, but if lacking entirely would mean that the research should not be done) the subject does not stand to gain anything (such as an improvement in

- 40. (cont.) diagnosis or therapy) as a result of participating. It is assumed that there is another, complementary category of experiments which can be said to be "beneficial" to their patient-subjects. Since experimentation is involved, the risks and benefits are uncertain (to a greater degree than the uncertainty which is said to attend each use of even well established medical techniques), but the experiment may still be termed "beneficial" in the intent of the investigator, a factor which the law regards seriously provided that he is operating within the bounds of reason and good faith.
- 41. See Paulsen, "The Legal Framework for Child Protection," Columbia Law Review 66:679, 1956; Robertson, note 39 supra, at 222-24. Neglect statutes tend to be broadly and vaguely worded and loosely interpreted; while they have been held to cover parents who do not provide proper medical care, see, e.g., Matthews v. State, 240 Miss. 189, 126 So.2d 245 (1961) (neglecting to provide digitalis for child left in nursery), and while some specifically punish the failure to furnish medical assistance, see, e.g., N.J. Stats. \$9:6-3 (West 1960), they are certainly open to due process objections and many are probably unconstitutional.
- 42. The doctrine of "informed consent," which grew out of the law of assault and battery, is the most important example of this concern in the tort rules applicable to medical experimentation. It proceeds from the premise that a person's interests in autonomy, self-determination and privacy are such that he or she has suffered a compensable dignitary harm if a physician does (or threatens to do) anything to them without permission, even if no physical harm is caused thereby. See generally, Katz, J. with assistance of Capron, A., and Glass, E., Experimentation with Human Beings 521-724, 1972.
- 43. Curran and Beecher, "Experimentation in Children," Journal of the American Medical Association 210:77, 1969.
- 44. See generally Capron, "Legal Considerations Affecting Clinical Pharmaco-logical Studies in Children," Clinical Research 21:141,143-44, 1972.
- 45. Nielsen v. Regents of the Univ. of California, No. 665-049 (Super. Ct. S.F. Co., filed Sept. 11, 1973).
- 46. See notes 7-13 supra for citations.
- 47. California, Louisiana, Massachusetts, Minnesota, Missouri, Montana and Pennsylvania. The Minnesota statute contains the additional proviso, congruent with the common law view but not otherwise spelled out, that research is also permissible if "verifiable scientific evidence has shown [it] to be harmless to the conceptus." Minn. Sess. Laws, ch. 562, §2(1973).

48. The Ohio statute, for example, flatly declares that "No person shall experiment upon . . . the product of human conception which is aborted." Ohio Rev. Code Ann. §2919.14 (Page's Legis. Supp. 1974). But this comes immediately after a section (§2919.13) creating the crime of "abortion manslaughter" which consists of failing "to take the measures required by the exercise of medical judgment in light of the attending circumstances to preserve the life of a child who is alive when removed from the uterus of the pregnant woman." The Illinois, Indiana, Kentucky, Maine and Nebraska statutes also require measures be taken to save viable abortuses.

- 49. The Maine statute, which would appear to ban all experimental interventions with a living aborted fetus, was plainly directed only at nonbeneficial research since it punishes anyone who "shall use, transfer, distribute or give away" a fetus "for scientific experimentation or for any form of experimentation." Me. Rev. Stat. Ann. tit. 22, §157 (Supp. 1974). The Illinois ("exploitation of or experimentation with"), Indiana ("transported out of this state"), Kentucky ("sell, transfer, distribute or give away any live or viable child or permits such child to be used for any form of experimentation"), Nebraska ("sell, transfer, distribute, or give away"), and Ohio ("experiment upon or sell") statutes are subject to a similar construction.
- 50. III. Ann. Stat. ch. 111-1/2, §73-1(5) (Smith-Hurd Supp. 1974). See note 28 supra for additional statutes.
- 51. Harris v. State, 28 Tex. App. 308, 12 S.W. 1102 (1889); Evans v. People, 49 N.Y. 86 (1872) (dictum); but it is not necessary that the umbilical cord be severed, Jackson v. Comm., 265 Ky. 295, 96 S.W.2d 1014 (1936), nor that the fetus should have breathed, Rex v. Brain, 172 Eng. Rep. 1272 (1834), provided there are other signs of life.
- 52. Boston Globe, Feb. 15, 1975, at 3, col. 3.
- parturition of the mother, of the vitality of life of a child in a state of being born and before actual birth, which child would otherwise have been born alive; provided, however, that the crime of killing a child during delivery shall not be construed to include any case in which the death of a child results from the use by a physician of a procedure during delivery which is necessary to save the life of the child or of the mother and is used for the express purpose of and with the specific intent of saving the life of the child or of the mother. La. Rev. Stat. Ann. §14:87.1 (Supp. 1974). In the absence of the "defense" of "best care for the mother," such a statute would be unconstitutional on its face. Hodgson v. Anderson, 378 F.Supp. 1008 (D. Minn. 1974), appeal dismissed and remanded sub nom. Spannaus v. Hodgson, 43 U.S.L.W. 3415 (Jan. 27, 1975). Further extensions of this line of protection of fetal interests are considered in the discussions of the fetus in utero, at pp. 13-20 to 13-21 infra.

- 54. 77 Cal. App.2d 621, 176 P.2d 92 (1947). Contra State v. Cooper 22 N.J.L. 52 (1849) (not murder to kill a child before it is born, "even though it be killed in the very process of delivery").
- 55. 77 Cal. App.2d at 627, 176 P.2d at 95. In a more recent opinion, Keeler v. Superior Court of Amador County, 2 Cal.3d 619, 87 Cal. Rptr. 481, 470 P.2d 617 (1970), the California Supreme Court reiterated the common law rule that an infant cannot be the subject of homicide unless it has been born alive. It recognized the Chavez dictum that homicide could encompass a living baby "where in the natural course of events a birth which is already started would naturally be successfully completed," id., at 637, 87 Cal. Rptr. 492, 470 P.2d at 628 (italics in original), quoting 77 Cal. App.2d at 626, 176 P.2d at 94, but found that this limited rule had no application to the case before it, in which an estranged husband had caused the death in utero of a viable 35-week fetus by "stomping" on his ex-wife's abdomen. In apparent reaction to this decision, the California legislature amended the murder statute to include the killing of a fetus, unless it occurred (a) during a therapeutic abortion, (b) as a result of medical intervention where childbirth threatened the mother's life, or (c) with the mother's consent. Cal. Pen. Code §187 (West Supp. 1975), as amended by Stats. 1970, c. 1311, p. 2440, \$1. The failure of the legislature to amend the manslaughter statute means that the common law rule of "live birth" continues to apply to that offense. People v. Carlson, 37 Cal. App. 3d 349, 112 Cal. Rptr. 321 (1974).
- 56. State v. Osmus, 73 Wyo. 183, 276 P.2d 469 (1954). Professor John A. Robertson argues that where the need for medical care is clear, "failure to obtain care that leads to the infant's death should be culpable," and cites State v. Shepherd, 255 Iowa 1218, 124 N.W.2d 712 (1963), as embodying a "better approach" to the question of whether liability flows from an unreasonable railure to seek medical care when birth is imminent. Robertson, supra note 39, at 218 n. 34.
- 57. This duty is recognized in both the criminal law, see LaFave, W., and Scott, A., Handbook of Criminal Law 186, 1972; Holmes, O., The Common Law 278, 1881 ("If a surgeon from benevolence cuts the umbilical cord of a new-born child he cannot stop there and watch the patient bleed to death. It would be murder wilfully to allow death to come to pass in that way."); and in the civil, cf. Depue v. Flateau, 100 Minn. 299, 111 N.W. 1 (1907).
- 58. See, e.g., in re Kershaw, 5 Rob. 488 (La. 1843).
- 59. See, e.g., in re Principal's Guardianship, 101 Cal. App. 669, 282 P. 26 (1929); Succession of Simkin, 164 La. 223, 113 So. 825 (1927).
- 60. The father, by explicitly agreeing to the abortion, may place himself in the same category as the mother, but since he cannot under *Roe* v. *Wade* forbid her from undertaking the abortion his mere acquiescence should not be taken

as sufficient to deny him the rights he would otherwise enjoy concerning the fetus. See, e.g., Coe v. Gerstein, 373 F.Supp. 695 (S.D. Fla. 1973) appeal dismissed, 417 U.S. 279 (1974) (requiring spousal consent held unconstitutional).

- 61. The neglect laws typically provide for a means for a parent voluntarily to give his or her rights and obligations over to the public welfare authorities.
- 62. That is not to say that the process of decisionmaking, including the involvement of the judiciary in determining neglect, is easy or painless. The situation in which this issue has arisen has thus far not involved proposed experimentation on a neonate but parental refusal of "ordinary" surgery needed by a defective infant to survive. The parents in one recent case, Maine Medical Center v. Houle, Civil No. 74-145 (Super. Ct., Cumberland Co. Feb. 14, 1974) (parents' refusal constituted neglect), expressed great anguish at being brought into the legal system and having the decision taken away from them (the baby died following the surgery). Auerback, "Court-Ruled Surgery Fails to Save Baby," Washington Post, Feb. 25, 1974, §A at 1, col. 1.
- 63. La. Rev. Stat. Ann. §§13:1569, :1570 (Supp. 1974).
- 64. Mo. 77th Gen. Ass., 2d Reg. Sess., Act 76, §7 (1974).
- 65. It would, of course, apply to the rarer case of the abortion of a previable fetus who lived for a short time; this is discussed below.
- 66. Mont. Rev. Codes Ann. §94-5-617(2)(b) (Supp. 1974).
- 67. Ky. Rev. Stats. \$199.600 (Supp. 1974).
- 68. Ind. Ann. Stat. §10-113 (Burn's Supp. 1974).
- 69. S.D. Compiled Laws Ann. §34-24A-18 (Supp. 1974).
- 70. The Minnesota abortion statute, which is similar to the Montana law described in the text, provided that a live born child resulting from an abortion shall become a ward of the state unless the abortion was performed to save the life of the woman or the child or one or both parents agree within 30 days to accept the parental rights and responsibilities; it has been held unconstitutional and enjoined. Hodgson v. Anderson, 378 F.Supp. 1008 (D. Minn. 1974), appeal dismissed and remanded sub nom. Spannaus v. Hodgson, 43 U.S.L.W. 3415 (Jan. 27, 1975). The Missouri provision described in the text (accompanying note 64) was upheld by a three judge district court but stayed pending appeal by the Supreme Court, F.Supp. (E.D. Mo. 1974), 43 U.S.L.W. 3451 (Feb. 18, 1975).

The problems with the revocation of parental rights over an area as fundamental as control and custody of a child, see Wisconsin v. Yoder, 406 U.S.

205 (1972); Eisenstadt v. Baird, 405 U.S. 438 (1972); Pierce v. Society of Sisters, 268 U.S. 510 (1925), are exacerbated when the revocation is made automatic; it would seem to be a violation of due process to act without a clear showing of actual or impending neglect and only on the basis of a presumption. See Cleveland Board of Education v. LaFleur, 414 U.S. 632 (1974) (conclusive presumption that school teacher is physically unable to work after fifth or sixth month of pregnancy held unconstitutional). As the Court, in holding unconstitutional an irrebutable presumption that unmarried fathers are incompetent to raise their children, stated in Stanley v. Illinois, 405 U.S. 645, 654 (1972):

It may be, as the State insists, that most unmarried fathers are unsuitable and neglectful parents. It may also be that Stanley is such a parent and that his children should be placed in other hands. But all unmarried fathers are not in this category; some are wholly suited to have custody of their children. (Footnotes omitted.)

Similarly, some mothers who abort fetuses that then survive may be unsuitable and neglectful, so that their infants should be placed into the state's hands. But it violates due process so to presume for all such mothers. As Stanley also holds, the speed and efficiency of a presumption are not sufficient to redeem it. Idem, at 656.

- 71. Keeler v. Superior Court of Amado Co., 2 Cal. 3d 619, 87 Cal. Rptr. 481, 470 P.2d 617 (1970) (unborn, viable fetus not a person within meaning of murder statute); State v. Dickinson, 23 Ohio App.2d 259, 52 Ohio Ops.2d 414, 263 N.E.2d 253 (1970) (unborn, viable fetus not a person within meaning of vehicular homicide statute). See also note 54 supra.
- 72. See note 53 supra.
- 73. Of course, Roe v. Wade, 410 U.S. 113 (1973), is always subject to revision or even reversal, either through a constitutional amendment or through subsequent decisions of the Court (which approved it by an 7-2 majority). For the moment, however, it must be regarded by the National Commission, in any recommendations it makes to the Secretary, or by the national and state legislatures, in any laws they pass, as setting forth the constitutional limits within which fetal experimentation may be regulated.
- 74. There have been various definitions of "quickening" used by the common law over the years, both in abortion law (since causing an abortion before quickening was not regarded as a punishable offense, but after quickening it was a misdemeanor) and under the feticide statutes. Whenever it is assumed to occur (from 6 weeks to 18 weeks, depending on the authority), quickening means that the fetus is felt to move; this was significant because (1) it showed that a live being, capable of being killed, was in existence, and (2) it was associated with the theological concept of the soul entering the body. In any case, this point of development almost certainly occurs before the fetus is "viable" given present medical technology.

- 75. "Malice" as used in the law of homicide is a term of art, not used in its usual sense of "ill will," but meaning that the actor has manifested the specific intent to cause death or grievous bodily harm or otherwise to commit a felony.
- 76. See, e.g., Passley v. State, 194 Ga. 327, 21 S.E.2d 230 (1942) (feticide conviction reversed because indictment was defective in failing to allege necessary intent); State v. Harness, 280 S.W.2d 11 (Mo. 1955) (manslaughter conviction reversed because evidence that defendant had killed unborn child was insufficient to prove that he acted with malicious intent to kill the pregnant woman). Cf. Williams v. State, 34 Fla. 217, 15 So. 760 (1894) (affirming manslaughter conviction under feticide statute on grounds that defendant's unprovoked and cruel assault upon his wife with a club and his threats to kill her were sufficient evidence of premeditation of murder; statute deemed it manslaughter if fetus died from injury which would have been murder if it had resulted in death of the mother).
- 77. Were he to bring about the miscarriage of the fetus intentionally he would probably still not be liable under the feticide statute unless he also assaulted the woman and tried to kill her; he would, however, probably be guilty of criminal abortion, which is defined in many states to include the performance of an abortion without the consent of the woman.
- 78. See Clark v. State, 117 Ala. 1, 23 So. 671 (1898); Morgan v. State, 148 Tenn. 417, 256 S.W. 433 (1923); Abrams v. Foshee, 3 Iowa 274 (1856) (dictum).
- 79. Anderson, Wharton's Criminal Law and Procedure 435, 1957.
- 80. Roe v. Wade 410 U.S. 113, 153 (1973).
- 81. The British Abortion Act of 1967 and the pre-Roe Uniform Abortion Act (proposed by the Conference of Commissioners on Uniform State Laws and endorsed by the American Bar Association) both permitted abortion when there was substantial risk that the child if born would suffer from a serious defect. See also Smith v. Brennan, 31 N.J. 353, 364, 157 A.2d 497, 503 (1960) ("a legal right to begin life with a sound mind and body"). But see Gleitman v. Cosgrove, 49 N.J. 22, 237 A.2d 689 (1967) (holding no cognizable claim for physician's failure to warn parents of prenatal injuries which would have led them to abort the child), criticized in Capron, "Informed Decisionmaking in Genetic Counseling: A Dissent to the 'Wrongful Life' Debate," Ind. L.J. 48:581,594-602, 1973.
- 82. Roe v. Wade, 410 U.S. 113, 161-62 (1973).
- 83. This view was established by Justice Holmes in Dietrich v. Northampton, 138 Mass. 14 (1884).
- 84. O'Neill v. Morse, 385 Mich. 130, 135, 188 N.W.2d 785 (1971).

- 85. Norman v. Murphy, 124 Cal. App.2d 95, 268 P.2d 178 (1954); Stokes v. Liberty Mut. Ins. Co., 213 So.2d 695 (Fla. 1968); McKillip v. Zimmerman, 191 N.W. 2d 706 (Iowa 1971); Leccese v. McDonough, 279 N.E.2d 339 (Mass. 1972); Action v. Shields, 386 S.W.2d 363 (Mo. 1965); Drabbels v. Skelly Oil Co., 155 Neb. 17, 50 N.W.2d 229 (1951); Graf v. Taggert, 43 N.J. 303, 204 A.2d 140 (1964); Endresz v. Friedburg, 24 N.Y.2d 478, 248 N.E.2d 901, 301 N.Y.S. 2d 65 (1969); Gay v. Thompson, 266 N.C. 394, 146 S.E.2d 425 (1966); Padillo v. Zirod, 424 P.2d 16 (Okla. 1967); Caroll v. Skloff, 415 Pa. 47, 202 A.2d 9 (1964); Durrett v. Owens, 212 Tenn. 614, 371 S.W.2d 433 (1963); Lawrence v. Craven Tire Co., 210 Va. 138, 169 S.E.2d 440 (1969). Cf. Mace v. Jung, 210 F.Supp. 706 (D. Alas. 1962) (recovery for nonviable fetus denied).
- 86. Endresz v. Friedburg, 24 N.Y.2d 478, 486, 248 N.E.2d 901, 905, 301 N.Y.S.2d 65, 70 (1969), quoting Keyes v. Construction Service, 340 Mass. 633, 636, 165 N.E.2d 912, 915 (1960).
- Eich v. Town of Gulf Shores, 300 So.2d 354 (Ala. 1974); Hatala v. Markiewicz, 87. 20 Conn.Supp. 358, 224 A.2d 406 (1966); Worgan v. Greggo and Ferrara, Inc., 50 Del. 258, 128 A.2d 557 (1956); Simmons v. Howard Univ., 323 F.Supp. 256 (D.D.C. 1971); Porter v. Lassiter, 91 Ga.App. 712, 87 S.E.2d 100 (1955); Christafogeorgis v. Brandenburg, 55 Ill. 368, 304 N.E.2d 88 (1974); Britt v. Sears, 277 N.E.2d 20 (Ind. ct. App. 1971); Hale v. Marrion, 189 Kan. 134, 368 P.2d 1 (1962); Mitchell v. Couch, 285 S.W.2d 901 (1955); Valence v. Louisiana Power and Light Co., 50 So.2d 847 (La. Ct. App. 1951); State ex rel. Odham v. Sherman, 234 Md. 179, 198 A.2d 71 (1964); O'Neill v. Morse, 385 Mich. 130, 188 N.W.2d 785 (1971); Verkennes v. Corniea, 229 Minn. 365, 38 N.W.2d 838 (1949); Rainey v. Horn, 221 Miss. 269, 72 So.2d 434 (1954); White v. Yup, 458 P.2d 617 (Nev. 1969); Poliquin v. MacDonald, 101 N.H. 104, 135 A.2d 249 (1957); Stidam v. Ashmore, 109 Ohio App. 431, 167 N.E.2d 106 (1959); Libbee v. Permanente Clinic, 518 P.2d 636 (Ore. 1974); Fowler v. Woodward, 244 S.C. 608, 138 S.E.2d 42 (1964); Baldwin v. Butcher, 184 S.E.2d 428 (W. Va. 1971); Kwaterski v. State Farm Mut. Auto. Ins. Co., 34 Wis.2d 14, 148 N.W.2d 107 (1967).
- 88. Roe v. Wade, 410 U.S. 113, 162 (1973), citing Louisell, "Abortion, The Practice of Medicine, and the Due Process of Law," U.C.L.A. Law Review 16:233,235-38 (1969); Note, Iowa Law Review 56:994,999-1000, 1971; Note, "The Law and the Unborn Child," Notre Dame Law 46:349,351-53, 1971.
- 89. Roe v. Wade, 410 U.S. 113, 163 (1973).
- 90. Idem, at 153.
- 91. Since the unborn fetus is not a "person" legally, there can be no question of depriving it of the equal protection of the laws in those jurisdictions that do not impose criminal or civil liability on persons who injure a viable fetus which dies in utero while imposing such liability if the same acts caused death in a live born person.

- 92. The criminal law is sterner on this point than the civil. It is murder intentionally to extinguish the last spark of life even in a person who has been mortally wounded by someone else. The civil law takes a wider view of causation. An action is said to be a legal cause of harm to another if it is a substantial factor in bringing about the harm; it may be a substantial factor even if the harm would have been sustained without it, so long as both the action in question and the other causes are actively operating to the same result. See Restatement, Torts 2d, §§431-32. Because it enjoys greater flexibility than the criminal law (judgments from 1¢ on up rather than simply "guilty" or "not guilty"), tort law can say that a person's conduct caused the death of a dying man and still award only a small damage award because the amount of life left was very short.
- 93. It may be, for example, that society wishes to prevent what it sees as harm to fetuses because of the pain that the perception of such harm brings to its viewers. While the protection of such interests is a dubious rationale for preventing people from doing things which may hurt themselves but not harm others physically (e.g., "victimless" crimes), it does provide the justification for other kinds of legal constraints on people's conduct toward other people or things (e.g., statutes on humane treatment of animals.
- 94. See notes 35-41 supra and accompanying text.
- 95. The Missouri statute makes it manslaughter if the fetus died because the physician (or others) failed to use the same "degree of professional skill, care and diligence" to keep alive any abortus "as would be required . . . in order to preserve the life and health of any fetus intended to be born." Mo. 77th Gen. Ass., 2d Reg. Sess., Act 76, §6(1) (1974). The Ohio statute likewise provides that a person performing an abortion must attempt to "preserve the life of a child who is alive" and makes no distinction between viable and nonviable fetuses, although it does leave the steps to "medical judgment." In light of the felony penalties, a physician's judgment is likely to be very constricted, however. Ohio Rev. Code Ann. §2919.13 (B) (Page's Legis. Supp. 1974).
- 96. La. Rev. Stat. Ann. §14:87.2 (Supp. 1974). Of the fourteen statutes on experimentation with aborted fetuses, see notes 47-49 and accompanying text, only the California provision might not apply to some previable fetuses ex utero, namely those which are "lifeless" because they lack a "discernible heartbeat." Cal. Health & Safety Code §25956 (Supp. 1974).
- 97. See pp. 13-17 to 13-20 supra.
- 98. See pp. 13-4 to 13-6 supra.
- 99. Cf. Note, "Compulsory Removal of Cadaver Organs," Columbia Law Review 69:693, 1969.
- 100. See Curran, "A Problem of Consent--Kidney Transplantation in Minors,"

  New York University Law Review 34:891, 1959.

- 101. See, e.g., In re Martin, Eq. No. 44602 (Cir. Ct. Montgomery Co., Md., Oct. 20, 1972).
- 102. One problem with the transplant cases was that the actual facts and role relations had to be forced into the adversary process—although it was only recently that vigorous independent advocacy for the minor donor became part of the process (in the bone marrow transplant cases in Boston). The resolution of questions like this may better be handled under the aegis of a European-type judge who plays the active role of inquisitor rather than a neutral arbiter between litigious adversaries. See generally Damaska, "Evidentiary Barriers to Conviction and Two Models of Criminal Procedure," University of Pennsylvania Law Review 121:506,554-86, 1973.
- 103. See Roe v. Wade, 410 U.S. 113, 132-35 (1973) ("usually from the 16th to the 18th week of pregnancy").
- 104. See notes 74-76 supra and accompanying text.
- 105. See Means, "The Law of New York Concerning Abortion and the Status of the Foetus, 1664-1968: A Case for Cessation of Constitutionality," N.Y.L.F. 14:411 (1968); Means, "The Phoenix of Abortional Freedom: Is a Penumbral or Ninth Amendment Right About to Arise from the Nineteenth-Century Legislative Ashes of a Fourteenth-Century Common-Law Liberty?" N.Y.L.F. 17:335, 1971; Roe v. Wade, 410 U.S. 113, 148-52 and cases cited idem, nn. 48 and
- 106. Roe v. Wade, 410 U.S. 113, 162 (1973).
- 107. In re Holthausen's Will, 175 Misc. 1022, 1024, 26 N.Y.S.2d 140, 143 (Sur. Ct. 1941). The requirement that the decision benefit the fetus is not always adhered to. See In re Sankey's Estate, 199 Cal. 391, 249 P.517 (1926) (posthumous child bound by decree entered against living heirs). Cf. Barnett v. Pinkston, 238 Ala. 327, 191 So. 371 (1939) (posthumous child died a few hours after birth, followed in a few days by its mother who was its sole heir; her heirs held entitled to remainder of father's estate which passed through child to mother's estate).
- 108. Louisell, "Abortion, the Practice of Medicine and the Due Process of Law," U.C.L.A. Law Review 16:233,237, 1969.
- 109. See, e.g., Swain v. Bowers, 91 Ind. App. 307, 158 N.E. 598 (1927); Wehrman v. Farmers' Sav. Bank of Durant, 221 Iowa 249, 259 N.W. 564, rehearing overruled, 221 Iowa 249, 266 N.W. 290 (1935); Mackie v. Mackie, 230 N.C. 152, 52 S.E.2d 352 (1949). Cf. Roe v. Wade, 410 U.S. 113, 162 (1973) (perfection of interests of fetus contingent upon live birth).

- 110. Cal. Civ. Code §29 (West 1954) ("in the event of its subsequent birth");
  Mich. Stat. Ann. §27.3178 (155) (1962) ("posthumous children"); N.Y. Est.
  Powers & Trusts Law §2-1.3, §6-5.7 (McKinney 1967) ("posthumous children");
  Okla. Stat. Ann. tit. 15, §15 (1972) ("in the event of its subsequent birth"); Tex. Prob. Code §66 (1956) ("posthumous children"). Cf. Kimbro v. Harper, 113 Okl. 46, 238 P.840 (1925) (statutory construction).
- It is also worth noting that there is no recorded case of the heir of a stillborn child claiming rights that had accrued to the child; such a case would settle the question of whether the fetus is fully "a child" for estate purposes. Professor Louisell attempts to dismiss the absence of any such case as a result of "practicalities," Louisell, supra note 108, at 238, n. 24, but the absence only serves to spotlight the repeated view that children must be born to acquire their contingent property rights.
- 112. See notes 82-87 supra and accompanying text.
- See, e.g., Scott v. McPheeters, 33 Cal. App.2d 629, 92 P.2d 678, reh. denied 33 Cal. App.2d 629, 93 P.2d 562 (1939) (statutory construction); Hornbuckle v. Plantation Pipe Co., 212 Ga. 504, 93 S.E.2d 727 (1956) (fetus six weeks old at time of injury); Daley v. Meier, 33 Ill. App.2d 218, 178 N.E.2d 691 (1961); Cooper v. Blanck, 39 So.2d 352 (La. App. 1923) (statutory construction); Torigian v. Watertown News Co., 352 Mass. 446, 225 N.E. 2d 926 (1957) (3-1/2 month fetus injured and born at 5-3/4 months can recover although it died 2-1/2 hours after birth); Womack v. Buckhorn, 187 N.W.2d 218 (Mich. 1971) (injury to fetus at four months); Bennett v. Hymers, 101 N.H. 483, 147 A.2d 108 (1958); Smith v. Brennan, 31 N.J. 353 157 A.2d 497 (1960); Kelly v. Gregory, 282 App. Div. 542, 125 N.Y.S.2d 696 (1953), app. granted, 283 App. Div. 914, 129 N.Y.S.2d 194 (1954) (fetus 3 months at time of injury); Sinkler v. Kneale, 401 Pa. 267, 164 A.2d 93 (1960); Sylvia v. Gobeille, 220 A.2d 222 (R.I. 1966); Yandell v. Delgado, 471 S.W.2d 569 (Texas 1971). There are dicta in other jurisdictions, see Panagopoulos v. Martin, 295 F.Supp. 220 (D.W. Va. 1969); West v. McCoy, 233 S.C. 369, 105 S.E.2d 88 (1958), that a fetus must have been viable when injured to recover after birth, but these are only dicta, and some of the jurisdictions now permitting recovery formerly said that such an action did not lie, until presented with a case, e.g., Poliquin v. MacDonald, 101 N.H. 104, 135 A.2d 249 (1957); Leal v. C.C. Pitts Sand & Gravel, Inc., 419 S.W.2d 820 (Tex. 1971), overriden respectively by Bennett and Yandell, supra.

- 114. See, e.g., Bennett, "The Liability of Manufacturers of Thalidomide to the Affected Children," Austral. L.J. 39:256,263, 1965.
- 115. But see Porter v. Lassiter, 91 Ga. App. 712, 87 S.E.2d 100 (1955) (draws no distinction between viable and quick fetuses under wrongful death statute).
- 116. See, e.g., Mace v. Jung, 210 F.Supp. 706 (D. Alas. 1962).

- 117. The mother may have a cause of action for her miscarriage, however. Cf. Graf v. Taggert, 43 N.J. 303, 204 A.2d 140 (1964). Some courts have also said, as regards stillborn viable fetuses as well, that there is no way to prove the pecuniary loss to the beneficiaries under the wrongful death statutes.
- 118. See, e.g., Utah Copper Co. v. Industrial Commission, 57 Utah 118, 193 P. 24 (1920); Morrow v. Scott, 7 Ga. 537 (1849) (dictum, quoting Blackstone). The protection afforded to the unborn child does not rest on any theory that he is already a person, however, since a trust which provides for possible unborn beneficiaries may not be set aside without their representation before the court, including representation for those not yet conceived, who are certainly not "persons." See, e.g., Hatch v. Riggs Nat. Bank, 361 F.2d 559 (D.C. Cir. 1966); Gunnell v. Palmer, 18 N.E.2d 202, 370 III. 206 (1938); McPherson v. First & Citizens Nat. Bk. of Elizabeth City, 81 S.E.2d 386, 240 N.C. 1 (1954) (reformation refused on grounds that guardian ad litem could not adequately represent the interests of the children not yet in existence); Caine v. Griffin, 103 S.E.2d 37, 232, S.C. 562 (1958).
- 119. Kyne v. Kyne, 38 Cal. App.2d 122, 100 P.2d 806 (1940); Metzger v. People, 98 Colo. 133, 53 P.2d 1189 (1936). Yet in Burns v. Alcala, 43 U.S.L.W. 4374 (1975), the Supreme Court held that Congress, in using the term "dependent child" in the Social Security Act, 42 U.S.C. \$606(a), intended the ordinary meaning of a child already born, so that states which deny pregnant women AFDC benefits for unborn children are not in violation of federal requirements.
- 120. See, e.g., Raleigh-Fitkin-Paul Morgan Memorial Hosp. v. Anderson, 42 N.J. 421, 201 A.2d 537, cert. denied, 377 U.S. 985 (1964) Cf. In re Matter of Bentley, 102 Wash. L. Rptr. 1221 (D.C. Super 1974) (declining to order transfusion for pregnant woman where it was not necessary for safe delivery of child, although a two percent chance existed that it would be needed to keep the mother alive); Hoener v. Bertinato, 67 N.J. Sup. 517, 171 A.2d 140 (1961) (order granted for blood transfusion of child, over parents' religious objections, to be carried out immediately after the child was born). A guardian cannot have a legal abortion enjoined, however, on the grounds of protecting a person. McGarvey v. Magee-Womens Hospital, 340 F.Supp. 751 (W.D. Pa. 1972); Byrn v. New York City Health and Hospitals Corp., 329 N.Y.S.2d 722 (1972).
- 121. See note 96 supra and accompanying text.
- 122. See, e.g., Hodgson v. Anderson, 378 F.Supp. 1008 (D. Minn. 1974), appeal dismissed and remanded sub nom. Spannaus v. Hodgson, 43 U.S.L.W. 3415 (Jan. 27, 1975); Planned Parenthood of S.E. Penna. v. Fitzpatrick, No. 74-1220 (E.D. Pa. Oct. 10, 1974).
- 123. Mass. 1974 Reg. Sess. Laws, ch. 421 (1974).

- 124. The Massachusetts law also requires that the experiment "not substantially jeopardize the life or health of the fetus," but this limitation is probably unconstitutional and is, in any case, not necessary if the hypothesis in the test is correct.
- 125. Capron, "Informed Consent in Catastrophic Disease Research and Treatment,"

  University of Pennsylvania Law Review 123:340, 1974.



# A REPORT ON LEGAL ISSUES INVOLVED IN RESEARCH ON THE FETUS

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## A Report on Legal Issues Involved in Research on the Fetus

### I. INTRODUCTION

The subject of fetal experimentation, until now largely unheeded by the general public, is likely to become a new topic of national controversy. It is linked inextricably with abortion, and like abortion it poses a complex clash of values and public policy considerations.

The outlines of the dilemma are easy to discern--perhaps the most easy in a city such as Boston which is host to over eighty hospitals in its forty-three square miles. In Boston are some of the most presitigious hospitals in the world. Much of the research which takes place in them is dependent on fetal tissue, and the Massachusetts medical community has strongly supported such research in the interest of eliminating many of the ills which afflict mankind. Arrayed against the doctor-researchers is a strong "pro-life" movement which, believing that human life commences at conception but having suffered a defeat on abortion, is determined to limit the implications of this defeat.

And one should not underestimate the fury of the conflict. Nearly 900,000 abortions were performed in the United States last year, an increase of 30 percent in two years; in New England there were 51,700 legal abortions last year, compared to 6,200 in 1972. The products of these abortions are a rich source for research. The doctors are seen by some as callous, impersonal investigators who place scientific inquiry over "human" suffering. Those who believe a fetus is a child draw on more than conservative doctrine or religious belief to sustain their position. They can point out that in the nineteenth century, a not-so-long-ago but less sensitive time, children from orphanages and foundlings were used for research. Our sense of protection is a relatively recent phenomenon and must be zealously nurtured. Even now hundreds of children are killed every year by their parents or parent surrogates, the very ones who should be most concerned with their welfare. And potential children are put at risk, e.g., women intending to have abortions have agreed to be injected first with rubella vaccine to determine whether the vaccine would harm the fetus.

The research community disputes the assertion that a fetus is human, or at least protectible in the fully human sense, and its spokesmen point to the substantial benefits which have resulted from fetal research. Across the country doctors and researchers studying the diseases of very young children, both before and after birth, contend that prohibitions on their work will needlessly condemn countless future babies to illness and death. In fact fetal research has resulted in saving babies from abortion; recently the use of a new technique for examining the fetus in utero and removing a sample of its blood from the

placenta convinced five women with sickle cell trait or Cooley's anemia trait not to have abortions. In a letter to the New England Journal of Medicine, John F. Enders of Children's Hospital Medical Center in Boston said:

"Most physicians and biomedical scientists will agree, I believe, that the legal prohibition of the investigative use of embryonic and fetal tissues derived from dead human embryos or fetuses will gravely retard the advancement of medical knowledge in many areas. Examples of such areas are: (1) the further understanding of the causes and development of means for the prevention of fetal abnormalities; (2) the alterations in cellular mechanisms underlying transformation of normal human cells to cancer cells and the immunologic factors involved in resistance to cancer; and (3) the development of vaccines not now available against viral and other infectious micro-organisms such as varicella virus, cytomegalovirus and the agents of hepatitis and mycoplasma. Regarding the last mentioned area of investigation, it should be realized that the development of the prophylactics now generally employed in the prevention of poliomyelitis, measles and German measles stemmed from the results of original studies with human embryonic tissues."9

### II. ABORTION

In terms of legal and factual analysis, fetal experimentation cannot be fully understood without a corollary understanding of abortion and the law relating to it. Both topics are fueled by emotional energy from the same source. As the facts and law are reasonably well known, however, the information presented here will be limited.

### 1. Abortion Procedures

During the first 12 weeks, or first trimester, of pregnancy, dilation and curettage (a "D and C") or suction curettage are employed. The former involves widening the mouth of the cervix and scraping and emptying the uterus manually. The latter involves the use of a vacuum-powered device to scrape the fetus, placenta and amniotic sac from the uterine wall, homogenize them and suck them out of the uterus. 11

Abortions are generally not performed after 12 weeks until the sixteenth week of pregnancy, 12 but between 16 and 20 weeks two methods are used: injection of a saline solution into the uterus or intravenous injection of the drug prostaglandin. In almost all cases a saline solution kills the fetus, 13 often deforming it hideously 14 and burning the first layer of flesh from its body. 15 Prostaglandin may not kill the fetus, 16 but at least 90 percent of the fetuses aborted by this method are delivered dead. 17 If they show some signs of life—a determination made by the delivering physician—they generally "die" within minutes or at most a few hours. 18

If other methods do not produce an abortion, a hysterotomy, or little Ceasarian, is performed. This is a surgical procedure in which the fetus is removed intact from the uterus, and it may be the procedure of choice for pregnancies between 20 and 24 weeks. This method poses the least risk to the fetus and the greatest risk to the mother. 20

Maternal deaths from complications arising from suction curettage are 0.4 per 100,000 cases; from saline infusion, 16.3 per 100,000 cases; from hyserotomy, 222.8 per 100,000 cases. The overall maternal mortality rate, including deaths from abortion and from childbirth at full term, is 25 per 100,000 cases. <sup>21</sup>

At the Boston Hospital for Women, fetal remains are regarded as pathological specimens for any abortion when the gestational term is under 20 weeks. According to hospital policy, if the gestational term is over 20 weeks a birth or stillborn certificate is filled out. A death certificate is required by law for any fetus over 20 weeks gestation if born dead. In the past two years, the hospital has performed only two or three abortions in the last trimester of pregnancy. A premature infant weighing approximately 1 pound 13 ounces was delivered at 28 weeks of pregnancy and was kept alive through heroic effort. After two and one-half months, the baby, then weighing 6 pounds 15 ounces, was sent home. The cost of hospitalization and medical treatment was \$30,000.<sup>23</sup>

### 2. Roe v. Wade 24

Although Roe v. Wade was a decision about abortion, its holding and dicta have direct relevance to fetal experimentation. In this latter regard, it is important to state precisely what the opinion said and did not say. I start with the Court's own summary of its now well known trimester scheme:

- (a) For the stage prior to approximately the end of the first trimester, the abortion decision and its effectuation must be left to the medical judgment of the pregnant woman's attending physician.
- (b) For the stage subsequent to approximately the end of the first trimester, the State, in promoting its interest in the health of the mother, may, if it chooses, regulate the abortion procedure in ways that are reasonably related to maternal health.
- (c) For the stage subsequent to viability, the State in promoting its interest in the potentiality of human life may, if it chooses, regulate, and even proscribe, abortion, except where it is necessary, in appropriate medical judgment, for the preservation of the life or health of the mother. 25

In arriving at this formulation, the Court determined that a woman's right of privacy is protected by the Fourteenth Amendment, 26 that the decision to have

an abortion falls within this right,<sup>27</sup> and that the right to abortion is fundamental and can only be subject to regulation when there is a compelling state interest.<sup>28</sup> The State has two legitimate interests—maternal health and the protection of the potentiality of human life.<sup>29</sup> Each acquires greater significance throughout the duration of pregnancy; this maturing of significance permits limited state regulation during the second trimester and provides the state with a compelling interest in limiting abortion, if it chooses, during the third trimester.<sup>30</sup>

In terms of fetal rights, what did Roe decide? The Court held that "the word 'person,' as used in the Fourteenth Amendment, does not include the unborn."31 A fetus in utero therefore enjoys no Fourteenth Amendment rights and, in all probability, since the Courts' constitutional analysis was not limited to the Fourteenth Amendment, 32 no other constitutional rights until after birth. A state may choose not to restrict abortions at any time during pregnancy, and a fetus has no constitutional right to object, despite the harm that might occur. On the other hand, a state's "important and legitimate interest in protecting the potentiality of human life"33 becomes "compelling" at viability, or during the third trimester. "If the State is interested in protecting fetal life after viability, it may go so far as to proscribe abortion during that period except when it is necessary to preserve the life or health of the mother."34 The Court described "viable" as the point at which the fetus is "potentially able to live outside the mother's womb, albeit with artificial aid." 35 It went on to say that "[v]iability is usually placed at about seven months (28 weeks) but may occur earlier, even at 24 weeks." 36

What of an abortus or premature infant outside the womb? Roe v. Wade dealt (perhaps badly, as I shall point out in the next section) with a woman's rights vis-à-vis the unborn being within her. The word "person," said the Court, does not include the unborn. The word "person," and the Court, does not include the unborn. The word "person," At one point the majority opinion rather offhandedly remarks that the law has been reluctant to endorse any theory that life begins before live birth. The North Archive birth is not explained, and at another point the Court states "We need not resolve the difficult question of when life begins. When those trained in the respective disciplines of medicine, philosophy and theology are unable to arrive at any consensus, the judiciary, at this point in the development of man's knowledge, is not in a position to speculate as to the answer.

Roe v. Wade leaves many questions unanswered. It does not define "birth" 40 (partial or total emergence? 41 severance of the umbilical? 42), "viable" (no precise gestational age; a medical judgment?), "artificial aid" for sustaining premature but "viable" infants (equipment available at the most advanced, average, or least advanced hospital? equipment available at the site of the abortion?), the point at which "life begins," and, perhaps most importantly, the extent of legitimate state interests in protecting previable fetuses and the previable "born."

### 3. The Massachusetts Cases

Because Roe v. Wade left unanswered questions, because Boston has a substantial antiabortionist population, because it was an election year, and because fetal experimentation is linked to abortion, it is hardly surprising that the

issues of experimentation and abortion have surfaced in two criminal cases in Massachusetts which have captured national attention. It all began with a brief article in the New England Journal of Medicine authored by three doctors at the Boston City Hospital. Briefly summarized, their article described tests to determine which of two drugs reached a fetus in sufficient concentrations to prevent congenital syphilis where the mothers were allergic to penicillin. Thirty-three women, all of whom had requested abortions and had given written consent to the experiment, participated in the study. Following the abortions, fetal tissues were obtained, and an assay for antibiotic content was performed. A valuable finding, that the drug clindamycin passed the placental barrier more readily, was obtained.

Following a hearing by the Boston City Council, the Suffolk County District Attorney's Office began an eight-month investigation culminating in the issuance of indictments in April 1974, against the three doctors who wrote the article and against a pathologist who assisted them. The indictments charged each with "wilful and unauthorized removal of body for purpose of dissection" and "knowingly aiding in the wilful and unauthorized removal of body for purpose of dissection" in violation of M.G.I.A. Ch. 272 §71. The statute speaks in terms of "a human body," and the indictments allege that the dissections were performed on fetuses more than twenty weeks old. Trial of the doctors is tentatively scheduled for June 1975.

In the process of the investigation of the research doctors, a representative of the Suffolk County District Attorney's Office found two dead fetuses at the Suffolk County Mortuary. One was allegedly 24 weeks old, and a certificate listing cause of death for it could not be found. Kenneth Edelin, the doctor who performed the abortion (a hysterotomy following several unsuccessful attempts to use saline solution), was charged in an indictment with assaulting and beating "a certain person, to wit, a male child . . . and by such assault and beating did kill said person." <sup>47</sup>

At the trial the age of the fetus was disputed by several witnesses. The prosecution maintained that it was between 24 and 28 weeks in gestation and viable. Although the prosecution also contended that the "child" was born when Dr. Edelin detached the placenta from the uterine wall and that Dr. Edelin suffocated the fetus in the uterus after detachment, the judge charged the jury that a fetus is not a person, that birth is defined as "the process which causes the emergence of a new individual from the body of its mother," and that a person is one who is born, that is, outside the body of the mother. The only eyewitness for the state testified that the fetus showed no sign of life when it was removed from the mother.

The jury convicted Dr. Edelin of manslaughter. In an interview, several of the jurors said their guilty finding was based on the belief that Dr. Edelin was negligent in not attempting to save the life of a premature infant while performing an abortion. A picture of the "premature infant" had a powerful effect in moving the jury toward conviction. According to Dr. Mary Ellen Avery, chief physician at Children's Hospital Medical Center in Boston: "This judgment could lead to extraordinary efforts to sustain life against all odds of a successful outcome of an intact human being." 53

### III. SHOULD THERE BE FETAL EXPERIMENTATION? WHAT KIND? IN UTERO OR EX UTERO? PREVIABLE OR VIABLE? WHO DECIDES?

A few terms must be clarified at the outset. It seems sensible to adopt the definitions in the Proposed Rules of the Department of Health, Education, and Welfare pertaining to the Protection of Human Subjects. 54

"...(b) "Biomedical research, development, and related activities" means research, development, or related activities involving biological study (including but not limited to medical or surgical procedures, withdrawal or removal of body tissue or fluid, administration of chemical substances or input of energy, deviation from normal diet or hygiene, and manipulation or observation of bodily processes).

- (c) "Pregnancy" encompasses the period of time from confirmation of implantation to the time of delivery.
- (d) "Fetus" means the product of conception from the time of implantation to the time of delivery.
- (e) "Viability of the fetus" means the ability of the fetus, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. If the fetus has this ability, it is viable and therefore a premature infant.
- (f) "Abortus" means a fetus when it is expelled whole, prior to viability, whether spontaneously or as a result of medical or surgical intervention. The term does not apply to the placenta; fetal material which is macerated at the time of expulsion; or cells, tissue or organs excised from a dead fetus . . . "55

These definitions, of course, are no doubt the result of a complex balancing process. The period from conception to implantation is not explained. It is clearly tautological to define research as research, although the difficulties of definition here may require a connotative rather than denotative approach. Cells, tissue or organs excised from a dead fetus are not to be defined as an abortus, and cells, tissue or organs excised from an abortus are not defined at all.

As the definition is not clear, it should be pointed out that the objectives of research may vary substantially. An article in the *Stanford Law*Review 56 (with reference to human subjects) states:

"The objectives of experiments on human beings cover a wide spectrum, but may be classified roughly as therapeutic or nontherapeutic. Many experiments are intended to benefit the subject (therapeutic experimentation). Frequently a doctor must treat a patient with an untried method because no "accepted" treatment exists. A doctor may also use a new method of treatment where other procedures are regarded as "standard practice," thinking that the new method will prove more

These objections notwithstanding, Roe v. Wade is the law. And the decision makes some pragmatic sense, as even Professor Ely admits. El is my argument, however, that the opinion should be construed narrowly, particularly because it is questionable in terms of constitutional doctrine. It is a decision about the rights of the mother vis-à-vis the fetus in the context of abortion. Because the fetus may be killed in abortion, it does not necessarily follow that it has no rights in other contexts where the mother's right to privacy is nonexistant or less compelling. The right to abort does not infer a right to experiment any more than a state's right to execute a felon confers a right to inflict cruel and unusual punishment.

It is unlikely, however, that the Court would be so inconsistent as to define the fetus as a person in terms of the Fourteenth Amendment for one purpose and as a nonperson for another purpose. It has spoken in *Roe* that the fetus is not a person; 69 the Court has the power to define the terms of the Constitution, 70 and this interpretation should be taken as definitive. Several questions, therefore, must be answered.

- 1. Does the fetus, even though not a person, possess rights inferrable from areas of the law unrelated to abortion sufficient to enable the state or federal government to compel, prohibit, or limit experimentation?
- 2. Is an abortus, or premature infant ex utero, a person? What rights to compel, prohibit, or limit experimentation would either have as a person?
- 3. May federal or state lawmaking bodies compel, prohibit, or limit experimentation on an abortus, or premature infant ex utero, if not a person?

In the context of experimentation, I assume that any being, if defined as a person for purposes of the Fourteenth Amendment, is entitled to an array of protections under that amendment which may prohibit a state from infringing on its "life" or "liberty." In the absence of a definition of personhood, or in the event that a being is declared not to be a person by the Supreme Court, state legislative enactments or court decisions would be controlling in terms of defining fetal rights, unless Congress preempted the field, although a person protected by the Fourteenth Amendment—the mother, perhaps—might assert a constitutionally protected property interest in it. Regulations promulgated by the Department of Health, Education, and Welfare would be controlling in the disposition of its funds in the absence of state law, but a researcher would be required to conform to state law if it imposed higher standards than were imposed by federal regulations.

### 1. The Rights of the Fetus in Areas of the Law Other Than Abortion

States have long exercised the right to grant a fetus--or the parents of one--certain rights. This exercise has an honored, historical heritage, because Judeo-Christian civilizations have long looked upon fetuses, in at least some contexts, as human beings. "When men strive together, and hurt a woman with

child, so that there is a miscarriage . . . the one who hurt her shall be fined . . . " (Exodus XX1, 22, emphasis added). "And Joseph also went from Galilee . . . to . . . Bethlehem . . . to register, together with Mary his espoused wife, who was with child." (Luke 2, 1-5, emphasis added).

recognition and protection in several fields. The law of property, for example, recognizes rights of the unborn child from the moment of conception. In the 1834 case, Hall v. Hancock, 11 where the issue was whether a grandchild born almost nine months after the death of the testator was entitled to share with his four brothers in the testator's bequest to such grandchildren "as may be living at my death," the court held that a child en ventre sa mere 12 is within the description of "children living." Most states followed this Massachusetts opinion. In other property situations, as well, "the law regards an infant en ventre as in being. It may take a legacy; have a guardian; an estate may be limited to its use, etc." However, the property rights of a child in utero are not perfected until and unless the child is born alive. 15

The liberal construction of fetal property interests apparently stems from an attempt to carry out testator intent, the presumption being that the testator would not wish to exclude any of his issue. Because the interest of the fetus derives largely from testator intent, the competing interests of other siblings are usually regarded as insufficient to divest the fetus of its rights.

(b) Homicide Law. "It is undisputed that at the common law, abortion [including killing of the fetus] performed before 'quickening'--the first recognizable movement of the fetus in utero, appearing usually between the tenth and eighteenth weeks of pregnancy--was not an indictable offense." To Some legal scholars maintain that the common law refused to recognize any feticide as homicide, demanding that a child be fully born (i.e., entirely separated from its mother, with an entirely independent life with the umbilical cord cut and with its own breathing and heart action) in order to be treated as the victim of homicide. To

This is disputed by others who believe that the early common law required not birth, but only quickening, or animation, for a fetus to be protected by the laws against homicide. Whatever the early English law, it is generally agreed that by the mid-seventeenth century the common law had adopted the "born alive" theory. The seventeenth century the common law had adopted the "born alive" theory.

Most American jurisdictions have followed the "born alive" theory and apply the law of homicide only in cases of infants born alive. Some state courts, however, have held that a fetus shall be regarded as a human being for the purpose of homicide statutes when it has reached viability. Several have required only a showing of "quickening" in fetal manslaughter cases. And a number of others have pushed the definition of a human being for purposes of manslaughter back to the "moment" of conception.

(c) <u>Tort Law</u>. Early American tort law, as exemplified by the language of a Massachusetts opinion, *Dietrich* v. *Northampton*, 85 denied recovery for fetal injury on the ground that "the unborn child was a part of the mother at the time

of the injury . . . . " The *Dietrich* decision was followed universally for a number of years, but its basic premise was challenged in 1900 by J. Boggs, dissenting in *Allaire* v. *St. Luke's Hospital* 87 who argued that a fetus must be regarded as constituting a life distinct from that of its mother when it reaches the prenatal stage of viability.

"The logic of Justice Boggs met with increasing approval in subsequent decisions, and a few jurisdictions began to recognize the surviving infant's right of action for prenatal injuries." Beginning with a decision in the District of Columbia in 1946, a series of more than thirty cases, many of them expressly overruling prior holdings, have brought about the most spectacular abrupt reversal of a well settled rule in the whole history of the law of torts." Today there are few, if any, American jurisdictions in which recovery is not permitted for wrongful fetal injury. To

Of significance when considering fetal experimentation, "[m]ost of the cases allowing recovery have involved a foetus which was then viable . . . . Many of them have said, by way of dictum, that recovery must be limited to such cases, and two or three have said that the child, if not viable, must at least be quick. But when actually faced with the issue for decision, there are [approximately thirteen] jurisdictions which . . have allowed recovery even though the injury occurred during the early weeks of pregnancy, when the child was neither viable nor quick." 91

However, to maintain a suit upholding fetal rights in tort law, courts traditionally have required that the fetus be born alive. Thus the potential for human life is not sufficient to permit recovery in tort unless that potential is actualized by at least momentary life after birth. In jurisdictions where this rule survives, if a fetus is to be aborted, with no possibility of live birth, so that any property or tort rights which it theoretically possesses have no possibility of ever being exercised, it is at least arguable that the fetus possesses no such rights in the first instance. The rule requiring live birth has, however, been undergoing rather rapid change in wrongful death actions during the past 20 years. As of last fall, between 22 and 24 jurisdictions would permit an action for the wrongful death of a stillborn fetus who was fatally injured while viable; 12 jurisdictions would not. One state, Georgia, permits such an action for children injured when not yet viable but only "quick."

(d) Welfare Law. Another context in which the law recognizes fetuses as possessing some degree of "personhood" is that of welfare benefits. The meaning of "dependent child" in the Federal Aid to Families with Dependent Children (AFDC) program has caused much confusion in the courts. Nowhere in the statutory definition is there mention of the unborn. "The statute simply refers to needy children who are deprived of the care and support of a parent and who are 'under the age of eighteen.'97 HEW regulations refer to the unborn as a group for which federal matching funds are available, but the regulations are not phrased in mandatory terms. Accordingly, HEW has approved both state plans which exclude the unborn from coverage and plans which do not. At present, only 19 states include the unborn in the category of eligible dependent children."

Because there was no Congressional intent explicitly to exclude the unborn from these benefits,  $^{100}$  and because "in terms of need and dependency, many unborn

children are in far more severe circumstances than born children . . "101 five of the six federal appeals courts which have considered the matter during the past two years have ruled in favor of fetal eligibility. One of these cases is currently before the U.S. Supreme Court. 103 Its decision should clarify the status of fetuses for AFDC benefits and perhaps for other areas as well.

From the above, it can easily be seen that the extent of fetal rights is very much a function of the particular context in which they are asserted. These rights may even supersede the constitutional rights of the mother. In a pre-Roe New Jersey case 104 a mother, on religious grounds, had refused blood transfusions necessary to save her unborn child's life. The Court's opinion stated: "We are satisfied that the unborn child is entitled to the laws' protection and that an appropriate order should be made to ensure blood transfusions to the mother in the event that they are necessary in the opinion of the physician in charge at the time." 105

### 2. In Utero--The Viable Fetus

For fetal research, especially since the *Roe* decision, the clearest demarcation line (from a legal but not biological viewpoint) must be that of viability. It is at viability, the *Roe* court said, that a state's interest in protecting "the potentiality of human life" becomes so compelling that the state may protect that interest even over the constitutional right of the woman to abort. 106 It would appear that if a state may act to protect fetal interests over the very strong interest of the woman wishing to abort, it may surely protect fetal interests over less compelling interests such as nontherapeutic research which is conducted on the mother or fetus for the benefit of medical science or society at large. In so doing, it may ban all nontherapeutic research or limit such research to procedures involving minimal risk or study and diagnosis. 107

When therapeutic (including diagnostic) research is involved, however, two questions arise. May a state proscribe therapeutic research on the mother when there may be potential harm to the fetus? May the state compel therapeutic research on the fetus when there may be potential harm to the mother?

In my view, before a mother undertakes therapeutic research, there should be a careful weighing of potential risk of harm to the fetus and the potential benefit to the mother. If the mother's need is not serious, the research should be delayed until after she gives birth, first considering any additional risk to the mother such a delay would entail.

If her situation is relatively serious, however, and if an abortion would not pose as great a risk to the mother and fetus as the risks of research, then every effort should be made to convince her to abort. We know, however, that a hysterotomy would be performed at this stage of pregnancy, and it is the most dangerous abortion procedure to the mother. Consequently, if the risks in abortion are great, or if she simply refuses an abortion (in all probability she cannot be compelled to have one 108), then the same weighing of the interest of mother and fetus should be performed before research is permitted.

If the situation is life-threatening to the mother or is potentially very deleterious to her health, I would weight the balance conclusively in her favor, regardless of the risk to the fetus. She is the life-in-being, quite possibly with a husband and other children. Roe does not permit a state to proscribe the abortion of a viable fetus "when it is necessary to preserve the life or health of the mother." While a right of privacy covering therapeutic experimentation is no more apparent than was such a right covering abortion in Roe, the public policy justification of preserving maternal life or health is sound in both contexts. Roe does not define health, but I would limit it in the research context to the possibility of grave impairment of the mother's physical or psychological well-being.

A somewhat similar weighing of interests should apply with respect to therapeutic research solely for the benefit of the fetus. If the research can be delayed until after birth, it should be. If it is necessary but poses a risk to the mother's health, she should be urged to obtain an abortion first, if possible, so that the experimentation on the fetus will be outside her womb. However, if she objects to an abortion but consents to the research, her consent must be honored if she is an adult and legally competent. If the mother is an adolescent or not otherwise competent, the risks and benefits to each party must be weighed, but the mother's interest should take precedence as she is the life-in-being.

Because judgments in this area will be based on a complex set of variables, statutes or regulations can probably do little more than proscribe "unnecessary" research, list guidelines incorporating the considerations discussed above, and leave the decision in specific cases to the women and her physician with, perhaps, the concurrence of another consulting physician or of a medical research board. A major difficulty for these parties may occur in determining whether research provides a "benefit." If research may sustain the life of a fetus regardless of a possibly impaired condition and the impossibility of it ever enjoying a "full" human life, some would argue that such research is not beneficial. But the law generally endorses efforts to sustain life, however impaired that life may be. Thus some recent state statutes which attempt to ban all research on live fetuses probably go further than their authors intended by presumably including within their proscription even research for the benefit of the fetus.

### 3. *In Utero--*The Previable Fetus

Living, previable fetuses, like viable fetuses, enjoy no constitutional rights. Some older judicial opinions, e.g., Dietrich v. Northampton, 113 go farther than Roe v. Wade and hold that fetuses are merely part of the woman bearing them and thus have no independent rights whatsoever. Under this theory the woman enjoys unrestricted authority over the fetus.

But, unlike the woman's appendix, the fetus (as well as the placenta, amniotic sac, and umbilical cord) is composed of chromosomes from her male partner as well as herself. It therefore has a separate biological identity. The Roe v. Wade decision did not, by its terms, give the woman absolute control over the fetus. The Court held that the mother had a constitutional right to abort it,

that is, to remove it from her body. Death may be the natural and usual consequence of abortion, but the Court did not explicitly grant the mother a right to terminate fetal existence, nor did the Court grant her any right to experiment with the fetus and possibly harm its future development.

It is therefore my opinion that there should be no difference in the rights accorded to a previable or viable fetus. If the mother intends to carry a fetus to full term, it should be protected against all but the most innocuous forms of nontherapeutic research, whatever its stage of development. If therapeutic research is required for either the mother or previable fetus, the same weighing of interests should occur as in the case of the viable fetus. The mother's interest should prevail conclusively only when there would be substantial danger to her life or health.

What of the situation, however, where the woman has decided to have an abortion? The fetus will die anyway. Indeed, it may suffer a violent death. These fetuses, no longer possessing the potential to develop into full human beings, represent a class for which a "potential life" rationale may be inapplicable.

Nevertheless, I do not favor research in this situation either, at least until the moment of the abortion procedure. In the first place, a potential life remains a potentially full and useful life until death. Its interests should be protected as much as—and perhaps more than—those of a dying, adult person. Another basis for my opinion is that the mother may change her mind. And the mother has a right to freedom of choice in this area, in the form of her voluntary consent to a surgical or medical procedure. Her power to revoke her consent to an abortion procedure would be compromised if the fetus were subjected to experimentation in utero with the possibility of harm to it, thereby reducing her desire to carry it to full term. 114

A similar withdrawal-of-consent problem exists in adoptions of newborn children. Frequently a mother who, before giving birth, has consented to surrendering her child for adoption, wishes to withdraw that consent upon or shortly after birth. To cope with this problem, "[a] number of states have statutes which declare invalid any consent executed by a mother before the birth of the child . . . [T]he British Adoption Act of 1958 . . . absolutely voids any consent unless the infant is at least six weeks old on the date of the execution of the document." 115

An equally difficult case involves the possibility of research on the fetus during the abortion procedure. Here, if previable, the possibility of it being "saved" to develop into a full human being no longer exists, and the mother can no longer withdraw her consent. Some might contend that birth is a process, whether spontaneous or induced, and the fetus, if intact, is "born" and a person immediately following separation from the uterus. The jury in the Edelin trial apparently adopted this position, although the charge to the jury differed, and no case has so held. However, if complete separation from the mother is the standard, I would permit nontherapeutic research during the abortion procedure (see my discussion of reasons in the section on the abortus, infra).

Federal or state law could also proscribe nontherapeutic research, even if the previable fetus is not a person for purposes of the Fourteenth Amendment. If a state lawmaking body decided to protect the rights of the previable fetus, either before or during abortion, it could do so on the grounds that research on the fetus has a brutalizing effect on society as a whole. To arrive at this conclusion, the lawmaking body could find that the fetus experiences pain and that such pain is not outweighed by a more weighty societal interest. To pursue this analysis, we should inquire whether the fetus, like any sentient creature, does in fact suffer pain and whether research is permitted on nonhuman, i.e., animal, subjects regardless of pain.

No one knows whether a fetus feels pain. The ability to perceive pain is apparently a function of the degree of development of the nervous system, and previable fetuses may not have developed to the sentient point. Also, pain causes living creatures to avoid or withdraw from contacts, environments, and situations which may injure them; in the previable state the fetus has no need of such a physiological warning function, and it may therefore not have one.

However, fetuses react to stimuli at a gestational age of only a few weeks. This may be a reflex action not indicative of pain, 117 but there is no clear evidence proving the validity of this assumption, nor is it apparent that conclusive evidence can be obtained in the near future. As many capacities which serve no functional purpose until after viability and birth are acquired and develop during the previable stage, 118 there is no reason to believe that the ability to experience pain does not also begin to develop early in gestation.

In any event, it would not be necessary to demonstrate conclusively the presence of pain in order to regulate research. Statutes governing wrongful death actions typically require that in order for damages to be awarded for the decedent's pain resulting from a fatal injury, the pain and suffering must be "consciously" experienced. The formidable obstacles in determining whether a fetus' experiences conscious pain are apparent. But in the case of cruelty to animals, where difficulties of defining and determining mental state also exist, legislatures have not required any showing of "consciousness." They make an assumption that an animal experiences pain as we know it.

Animals, like the fetus, enjoy no constitutional rights. 120 A rational basis for the statutes banning cruelty to animals in most, if not all, states 121 can be found in the dehumanizing and brutalizing effect on society of needless cruelty inflicted on helpless creatures. 122 However, the rights which states assign to animals are generally quite limited in the area of research, barring only "unnecessary" infliction of pain, but permitting the use of animals for "the purpose of scientific investigation, experiment . . . or for the testing of drugs or medicines." 123 In the case of animals, any pain necessarily associated with research is considered acceptable in the interest of a greater societal good. 124 An institution performing such research is generally licensed by states only after an investigation of its standards, facilities, and practices shows that it is "a fit and proper agency to receive such license" 125 and that the issuance of a license is "in the public interest." 126 Also, some states provide that such institutions may be periodically inspected by interested organizations such as the Society for the Prevention of Cruelty to Animals. 127

If the state restrictions described above are justified in the case of animal research, it is clear that a state may impose even greater controls in the case of human fetal research. In fact, in my opinion a state (and possibly Congress) may go so far as to ban such research, even though this restraint impinges on the constitutionally protected activity of another. 128

### 4. Ex Utero--The Premature Infant

Research on the premature infant who has been born presents the easiest case. As its name implies, it is not a fetus at all. Roe v. Wade, by necessary implication, accords the infant the rights of a person. 129 If the viable fetus has rights against nontherapeutic research, a fortiori so must the infant. In the case of therapeutic research, while its interests may conflict with those of the mother, the allocation of rights is much easier than when it resides within her womb. Efforts should be devoted to insure its health and survival, even if its needs conflict with a constitutional right of a parent. Any experimental procedure should be for the child's direct benefit. 131

### 5. Ex Utero--The Abortus

If research on the premature infant ex utero presents the easiest case, the question of research on an abortus is in many ways the hardest. To be sure, the critical problem evident with the fetus—that to "get at" it one must also "get at" the mother—is missing. The abortus is "on its own." But it is also, at the present state of technological knowledge, a being consigned to death, if it is not dead already. There is no longer the potential for human life in any meaningful sense.

Having been "born," however, if one may refer to a spontaneous or induced abortion as birth, it may have rights as a person. The cases, including Roe v. Wade, are, to put it charitably, highly ambiguous on this issue. The first matter to consider, therefore, is whether the abortus possess qualities sufficient to give it standing as a person.

The amicus curiae brief of Dr. Bart Heffernan, guardian ad litem for the class of unborn children in the state of Illinois, to the Supreme Court in the case of United States v. Vuitch, contains a summary of the development of the fetus. It points out that "[h]uman life is a continuum—all of it, fetal, infant, adolescent, mature or aged, is in the process of becoming." While the brief refers to the fetus, not an abortus, it is useful in its description of the stages of development during gestation. Excerpts are presented below:

"From conception the child is a complex dynamic rapidly growing organism. By the end of the first month, the child completes the period of relatively greatest size increase and the greatest physical change of a lifetime. The month old child is 10,000 times larger than the fertilized egg and will increase its weight six billion times by birth.

"By the end of the seventh week, we see a well proportioned small scale baby. In its seventh week, it bears the familiar external features and all the internal organs of the adult, even though it is less than an inch long and weighs only 1/30th of an ounce. The body has become nicely rounded, padded with muscles and covered by a thin skin. The arms are only as long as printed exclamations marks, and have hands with fingers and thumbs. The slower growing legs have recognizable knees, ankles and toes.

"The new body not only exists, it also functions. The brain in configuration is already like the adult brain and sends out impulses that coordinates [sic] the function of the other organs. The brain waves have been noted at 43 days. The heart beats sturdily. The stomach produces digestive juices. The liver manufactures blood cells and the kidney begins to function by extracting uric acid from the child's blood. The muscles of the arms and body can already be set in motion."

\* \* \*

"The primitive skeletal system has completely developed by the end of six weeks. This marks the end of the child's embryonic (from Greek, to swell or teem within) period. From this point, the child will be called a fetus (Latin, young one or offspring).

"In the third month, the child becomes very active. By the end of the month he can kick his legs, turn his feet, curl and fan his toes, make a fist, move his thumb, bend his wrist, turn his head, squint, frown, open his mouth, press his lips tightly together. He can swallow and drinks the amniotic fluid that surrounds him. Thumb sucking is first noted at this age. The first respiratory motions move fluid in and out of his lungs with inhaling and exhaling respiratory movements."

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". . . By the beginning of the ninth week, the baby moves spontaneously without being touched. Sometimes his whole body swings back and forth for a few moments. By eight and a half weeks the eyelids and the palms of the hands become sensitive to touch. If the eyelid is stroked, the child squints. On stroking the palm, the fingers close into a small fist.

"In the ninth and tenth weeks, the child's activity leaps ahead. Now if the forehead is touched, he may turn his head away and pucker up his brow and frown. He now has full use of his arms and can bend the elbow and wrist independently. In the same week, the entire body becomes sensitive to touch."

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"Dr. Arnold Gesell states that: 'By the end of the first trimester (12th week) the fetus is a sentient moving being. We need not pause to speculate as to the nature of his psychic attirbutes but we may assert that the organization of his psycho-somatic self is now well under way.'

"Further refinements are noted in the third month. The fingernails appear. The child's face becomes much prettier. His eyes, previously far apart, now move closer together. The eyelids close over the eyes. Sexual differentiation is apparent in both internal and external sex organs, and primitive eggs and sperm are formed. The vocal cords are completed. In the absence of air they cannot produce sound: the child cannot cry aloud until birth, although he is capable of crying long before."

\* \* \*

"From the twelfth to the sixteenth week, the child grows very rapidly. His weight increases six times, and he grows to eight to ten inches in height."

\* \* \*

"In the fifth month, the baby gains two inches in height and ten ounces in weight. By the end of the month he will be about one foot tall and will weigh one pound. Fine baby hair begins to grow on his eyebrows and on his head and a fringe of eyelashes appear. Most of the skeleton hardens. The baby's muscles become much stronger, and as the child becomes larger, his mother finally perceives his many activities."

\* \* \*

"In the sixth month, the child develops a strong muscular grip with his hands. He also starts to breathe regularly and can maintain respiratory response for twenty-four hours if born prematurely. He may even have a slim chance of surviving in an incubator. The youngest children known to survive were between twenty to twenty-five weeks old. The concept of viability is not a static one . . . " 134

Where is the point of discontinuity? Is it viability, a line which has moved back in the spectrum of fetal development with technological advances, which may differ from child to child and which may vary with race? Is it "quickening"? Is it implantation? Conception? As Professor Tribe has said:

". . . [T]he advance of embryology and medicine over the past century and a half rendered untenable any notion that the fetus suddenly 'came to life' in a physiological sense at a definable point during pregnancy. Once the embryo's growth had been traced in a

continuous line from a single unfertilized ovum through the unbroken processes of fertilization, cell division, segmentation (in the case of identical twins), implantation of the blastocyst in the uterine wall, and gradual fetal development to the point of birth, those who believed in the sanctity of the fetus from the 'moment' of quickening, or from some other 'moment,' were deprived of the ability to link their belief to any distinct physical or biological event other than perhaps 'conception,' which was itself later revealed as a complex and continuous process." 136

As a response to this dilemma, Professor Tribe has suggested that "the question when human life truly begins asks not for a discovery of the point at which the fetus possesses an agreed-upon set of characteristics which make it human, but rather for a decision as to what characteristics should be regarded as defining a human being." The Supreme Court declined to make this decision. And Sissela Bok, in an article addressed to the problem of abortion, has suggested that "[w]e must abandon . . . a definition of humanity capable of showing us who has a right to live." Instead, she argues for an examination of the reasons for protecting life, stating that we cannot "simply equate killing an embryo with murder . . For it is important that most of the reasons why we protect lives are absent here. It does not matter that the group of cells cannot feel the anguish of pain connected with death, that it is not conscious of the interruption of its life, and that other humans do not mourn it or feel insecure in their lives if it dies." 140

I find this reasoning persuasive in the case of abortion, and applied analogically, I find it persuasive also in the case of experimentation on an abortus. It is probable that the product of an early abortion, most likely homogenized or mangled in any event through a "D and C" or vacuum curretage, does not feel pain; and I, at least, do not recoil at the thought that it be the subject of experimentation. Conversely, a premature infant struggling for life, or an abortus which is destined to live for only a few minutes, evokes a much different response. The chances of extrauterine survival of a 700 gram, 24 weeks old fetus are "extraordinarily remote," and only one in 250 of such infants will survive for any length of time. 142 Nevertheless, a sizable number of infants in the 600-800 gram range--or about 1-1/3 to 1-4/5 pounds--are capable of sustaining life for at least a few minutes, $^{143}$  sometimes hours, $^{144}$  and to me it is as disturbing to subject these beings to nontherapeutic experimentation as it would be to experiment on a terminally ill patient or a prisoner condemned to death. If I even suspect that the abortus might suffer pain, I am concerned about the brutalizing effect nontherapeutic experimentation would have on me.

Having said the above, I am caught in another dilemma. Instead of the continuum between less human and more human, I am confronted by another continuum of growing reasons for protecting an abortus the further along it is in the process of development. And here it is equally difficult to draw a line. The best, but not entirely satisfactory, way to resolve this problem is to attempt to draw lines at points which allow a substantial margin for error. Thus I suggest that nontherapeutic research for minimally justifiable reasons be permitted on an abortus before brain-wave activity can be measured, or until about six to

eight weeks.<sup>146</sup> After that point, until approximately 18 weeks, I recommend that such research be permitted only after greater justification of its purposes—such as the development of vaccines to combat serious diseases. Beyond 18 weeks,<sup>147</sup> I suggest that only therapeutic research be permitted on a living abortus, as I would then regard it as a person.

Needless to say, state legislatures have not adopted this approach. Most legislation prohibits experimentation on "live" fetuses; "live" is usually associated with heartbeat, and heartbeat can occur as early as the first month of gestation. The statutes, however, are very confusing (a brief analysis of them is set forth in the Appendix). They occasionally make no distinction between an adult, a premature infant (where the potential for life is present), and an abortus (where heartbeat, in most instances, is only a momentary flicker before death). In Louisiana and Maine, life is defined as "beating of the heart, pulsation of the umbilical cord, or movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached." Maine adds the word "definite," as if it were significant, to further define movement of voluntary muscles.

In this confusing morass, perhaps the one truly essential point to bear in mind is that for purposes of assigning legal rights, the real question is: Who decides? At the moment, in the absence of federal legislation and a definitive interpretation of the personhood of an abortus under the Fourteenth Amendment by the Supreme Court, it appears that a state legislature or court may decide. If a state lawmaking body determines that an abortus is not a person, it may permit research, but it equally is not precluded from imposing restrictions. The previous analysis of laws regulating cruelty to animals is applicable here. I doubt that any person could raise a constitutional objection to state action in these circumstances.

If, on the other hand, a lawmaking body concludes that an abortus is a person, then it stands in the same capacity as a premature infant. Nontherapeutic research should not be performed on it unless, in the opinion of the attending physician, it is dead. However, if the abortus is dead, one must still inquire into the authority physicians have to perform research on dead human beings, or on the tissue of dead human beings.

The first problem to be confronted is that there is no uniformly accepted definition of death. Black's Law Dictionary defines death as "the cessation of life; ceasing to exist; defined by physicians as a total stoppage of the circulation of the blood, and a cessation of the animal and vital functions consequent thereon, such as respiration, pulsation, etc." This definition is not especially useful in this age of artificial respirators and hearts.

The Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death has proposed a definition which would require a flat EEG for 24 hours or longer and the absence of spontaneous responses and certain reflexes. Such an elaborate definition and test is probably not warranted in the case of a newly delivered fetus. (Incidentally, such tests are at present not possible for fetuses in utero, and even if they could be performed, they would fail to indicate the presence or absence of life during the first few weeks of pregnancy.)

The Uniform Anatomical Gift Act was adopted by the Commission on Uniform State Laws in 1968 and has now been adopted, with minor variations, by all fifty states. <sup>152</sup> In the Massachusetts statute (which is believed to be typical of such laws generally) determination of time of death is explicitly left to the attending physician. <sup>153</sup> Some safeguards in the transplantation context are provided by forbidding that physician from participating in the removal or transplantation of any organ. <sup>154</sup> A comment by the commissioners specifically notes that "no attempt is made to define the uncertain point in time when life terminates." <sup>155</sup> They suggest that "the real question is when have irreversible changes taken place that preclude return to normal brain activity and self-sustaining bodily functions." <sup>156</sup> By its terms, this definition may be irrelevant to an abortus.

A New York statute provides that "[F]etal death is defined as death prior to the complete expulsion or extraction from its mother of a product of conception; death is indicated by the fact that after such separation, the fetus does not breathe or show any other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movement of the voluntary muscles." 157 It is the death of a child, not a fetus, if death occurs after expulsion or extraction from the mother. The New York statute further provides that when an abortion is performed after the twentieth week of pregnancy, a physician other than the physician performing the abortion must be present to provide immediate care in case of live birth. 158 If live birth occurs, the child is accorded immediate legal protection by the laws of New York. 159 Idaho and Utah have similar provisions requiring lifesaving efforts for a "viable" fetus. 160

If, by whatever definition established by a state, the death of an abortus or a premature infant is established, two questions remain: Who may validly consent to the use of the remains for research? Who may perform such research?

Generally, if a decedent has expressed no preference as to the disposition of his remains, his closest surviving relative's wishes in this regard will be honored. If the father is present, it would probably be wise to require his consent as well as the consent of the mother. "As in the case of the mother, the period of gestation is for the father one of anxiety, anticipation, and growth in feeling for the unborn child . . . The modern trend is for fathers to take a more active role in pregnancy and, indeed, to participate during the mother's labor and delivery of the child." 162

Under the Massachusetts' Anatomical Gift Act, which is part of the chapter on Promotion of Anatomical Science, unless the decedent has indicated otherwise, a relative or guardian may donate<sup>163</sup> all or part of his body to donees specified by the statute. A body should include disorganized, homogenized fetal tissue and an intact abortus or infant, as the distinction between them is only in the manner of expulsion or extraction.<sup>164</sup> Permissible donees include "any hospital, surgeon, or physician for medical or dental education, research, advancement of medical or dental science, therapy or transplantation . . . or any accredited medical or dental science, therapy or university for education, research, advancement of medical or dental science or therapy . . . ."<sup>165</sup> I would also include private, nonprofit research organizations. Under the Massachusetts statute, a guardian may not give permission if the parent is "available" at the time of

death, 166 and the act specifically states that the term "decedent" includes a fetus or stillborn infant. 167 Both the Massachusetts statute on Promotion of Anatomical Science and the statute on fetal experimentation 168 permit a mother of any age to consent to the research use of a dead fetus under specified limitations, but the latter statute states that consent is not required in the case of a routine pathological study and that, in a criminal proceeding, there shall be a conclusive presumption of consent if it is in a written statement signed by a mother at least eighteen years of age. 169

#### IV. PROTECTIVE OR REGULATORY MECHANISMS

To recapitulate briefly, it is my recommendation that only innocuous, non-therapeutic experimentation be allowed on beings with a potential for life, i.e., the previable fetus and the viable fetus. Where therapeutic research is necessary for the health of either the fetus in utero or the mother, with a chance of harm to the other, I suggest, in general, a careful balancing of the risks and benefits to each party, with ultimate preference being given to the mother's health and life, as she is the life in being. For the premature infant ex utero, I recommend only therapeutic research. For the abortus, where in all but the rarest instances death must ensue, I suggest that any reasonable nontherapeutic research be permitted in the first six to eight weeks of gestation, that only "justifiable" nontherapeutic research be permitted between six to eight and eighteen weeks, and that only therapeutic research be permitted thereafter. In my (admittedly untutored) view, the fetus becomes an abortus or premature infant for purposes of determining the appropriateness of research when it is entirely separated from the mother.

#### 1. Child Protection Statutes

In the above scheme, the mother may consent to research on the fetus *in utero*, and both parents—if the father is available—or a guardian may consent to research on an abortus or premature infant. This society grants substantial authority to parents to care for their children, <sup>170</sup> and it would be surprising and inconsistent if this grant of authority did not extend to the fetus as well.

Therefore, the first mechanism to consider which may protect fetal interests is the general legal requirement that parents provide adequate care for their children. The criminal codes of every jurisdiction in the United States contain provisions prohibiting desertion or nonsupport of minor children, and these statutes impose a duty upon parents or guardians to provide medical care. The typical nonsupport statute ". . . lays the foundation for a manslaughter charge based on criminally negligent omissions should a child's death result from inaction or neglect . . . "172 Thus parents conceivably may be subject to criminal penalties if they do not seek at least "ordinary" therapeutic experimentation when all conventional measures to preserve the life or health of a child have failed. The possibility of prosecution for failure to provide such care is certainly no more unlikely than the pending "graverobbing" case in Massachusetts.

"Cruelty to children" statutes may achieve the same result. Inaction as well as action is frequently covered, 174 and their terms frequently include deprivation of the necessities of life (such as medical care) and endangerment of life, limb or health. 175 The Model Penal Code states: "A parent, guardian, or other person supervising the welfare of a child under 18 commits a misdemeanor if he knowingly endangers the child's welfare by violating a duty of care, protection or support." 176

In cruelty to children statutes, many states limit punishment to parents or those standing in loco parentis. 177 Many states, on the other hand, say "any person" may be punished, 178 and presumably, therefore, an attending physician at an abortion procedure or normal birth might be covered. In any event, physicians, and even hospitals, may be liable under statutes requiring them to report "child abuse," if they remain silent. 179

#### 2. Consent

The most commonly employed and the most commonly discussed protective device is, of course, consent. Nevertheless, the issue of who is capable of consenting to experimentation on a fetus is one of great difficulty. It is similar to the question concerning who can consent to experimentation on children or individuals who are mentally incompetent. Both classes of individuals are incapable of consenting on their own behalf, and therefore proxy consent must be obtained. 180

In the case of children, there are no clear guidelines as to who may consent for them. For purely therapeutic procedures it is the child's natural guardians, his parents, who are given this power, <sup>181</sup> and the consent of one parent is sufficient. Where a procedure is therapeutic but experimental or innovative in nature, it again appears that a single parent may consent. But problems arise in the area of nontherapeutic experimentation.

In the leading case on the subject, Bonner v. Moran, 182 a 15 year old boy consented to be the donor in a skin transplantation procedure that was necessary to save the life of his cousin. Although his aunt, the mother of the recipient, was aware of his participation, his mother (at least at the outset) knew nothing of the arrangement. The donor brought an action for assault and battery claiming that his consent was insufficient to permit the physician to operate on him. The trial court, following section 59 of the Restatement of Torts, instructed the jury that if the plaintiff was capable of appreciating, and did appreciate, the nature and consequences of the procedures and actually consented, then their verdict must be for the defendant doctor. The jury returned a verdict for the doctor.

After questioning the soundness of the general rule, the appeals court pointed out that this procedure was not for the benefit of the plaintiff and that it subjected him to substantial risk. The court then stated that in such circumstances the consent of the parent (not parents) is required. It thus appears from this case that the consent of one parent is sufficient to enable a physician to perform a procedure on a minor that is not for the benefit of that minor.

In the late 1950s the issue of parental consent for a nontherapeutic procedure performed on a minor gained significance as a result of advances in kidney transplantation. At that time several transplantation procedures had been performed on adults but not minors. In 1957 three cases<sup>183</sup> arose in Massachusetts in which minors were to be used as donors in kidney transplant cases. Counsel for the Peter Bent Brigham Hospital in Boston informed the hospital that parental consent for the healthy minor was probably insufficient to permit the surgery. This advice was based on two judicial opinions<sup>184</sup> which stated that a parent could not recover money paid to an infant upon his voluntary enlistment in the Armed Forces, in part because a parent could not require a son to enlist in the Army against his wishes. On this basis, counsel reached the conclusion that:

"If a parent has no power to make an effective decision regarding his child's enlistment because of the hazardous nature of the service, the conclusion seems inescapable that the parent likewise has no power to give effective consent to an operation which is both hazardous and personally detrimental to the child." 185

In the kidney cases the minors had all given their consent, and it does not appear that the parents were forcing them to undergo operations. However, as a result of counsel's advice, the hospital felt obliged to petition a single justice of the Supreme Judicial Court to ratify the parents' consent. The Court decided that each donor would receive a psychological benefit, and therefore the parents could consent to the operations. 186

In a similar case, the Supreme Court of Kentucky allowed the transplantation of a kidney from an incompetent adult to his brother. <sup>187</sup> This Court also relied on the fact that the donor would receive a psychological benefit from the donation; it also employed the doctrine of "substituted judgment" in which the chancellor has the power to make decisions for an incompetent in the same manner as the incompetent would, if he were competent. A dissenting opinion stated that psychological benefit is not sufficient to allow a procedure that puts an incompetent at peril.

Another recently developed transplantation procedure involves taking bone marrow from a healthy sibling and transplanting it to a terminally ill sibling in an attempt to cure the sick sibling. In earlier cases courts again utilized the concept of psychological benefit, but recently a court specifically rejected this test. <sup>188</sup> The Court found that "the evidence does not permit a finding that the procedure will be of any benefit to [the donor]." Pointing out that any belief that the donor will receive a psychological benefit is mere speculation, the Court said:

"If the sanctioning of a bone marrow transplant were to depend on the finding of some benefit to the donor arising from it [sic], allowance or of some detriment to him or her if the sanction were denied, this court would have to enter a judgment that the transplant proposed in this case could not legally be performed since there is no such finding

with respect to [the donor]. This court does not believe that a finding of benefit to the donor is essential . . . To require a finding of benefit to the donor, and particularly to accept a psychological benefit as sufficient, often seems to invite testimony conjured to satisfy the requirement by words but not by substance." 190

The court discussed and refused to utilize the substituted judgment doctrine. The opinion clearly stated that parents have "the right and responsibility to make these decisions . . . "<sup>191</sup> with the safeguard of judicial review to guard against a conflict arising from their responsibility to care for both their children. The court must merely decide if the parents' decision to allow their child to be a donor is "fair and reasonable." <sup>192</sup>

These cases, and a number of similar cases, teach us several lessons. First, courts will allow parents to consent to the use of their children in nontherapeutic procedures, if the benefits of the particular procedure (even though not to the subject) outweigh the risks. In the bone marrow and kidney transplant cases, the benefit (the possibility of saving a life) outweighed the risk of possible physical harm to the donor. The risks are not insubstantial; in kidney transplant cases the donor is subject to the risk of general anesthesia (also true in the bone marrow cases) as well as the risk of living with only one kidney. But in all of the kidney and bone marrow cases, a court has refused to grant permission only once, and then on very narrow grounds. 193 Second, courts allow parents to place their children at serious risk where the child may derive a benefit from it. One of the striking things about these cases is that the courts never question the parents' right to consent to an experimental procedure on behalf of the donee child. As this portion of the experimental procedure is therapeutic (as opposed to the portion for the donor), and since without the procedure the child will die, the courts grant parents great latitude of choice. Third, courts are very reluctant to second-guess parents after they have made a decision concerning their child.

An unanswered question in these cases is whether both the mother and father must consent to an experimental procedure which is not for the benefit of their child. The question has not arisen because in all cases both parents have consented. Had they not, it would nevertheless make sense to require the consent of both, if both are available. Both run the risk of additional support if there is damage to the donor child. I assume, moreover, that as the number of individuals involved in protecting a child increases, the greater the protection will be. The consent of both parents offers greater protection than the consent of one, and an exception can be made in emergency situations.

For the most part the general principles stated above should be applicable to fetuses. As I have attempted to demonstrate, however, the rules governing fetal research should vary with the kind of research and the circumstances of the fetus, i.e., viable or previable, in utero or ex utero. I shall therefore discuss the doctrine of consent in these various situations.

## (a) The Previable Fetus

I have argued previously that the fetus, as a being with a potential life, should not be subjected to a nontherapeutic, experimental procedure. Even if the mother plans an abortion, such research should be prohibited on the ground that potential harm to the fetus may compromise her capacity to withdraw consent to the abortion procedure. The kidney and bone marrow transplant cases are in accordance with this position; in them a nontherapeutic procedure was permitted, but only when this procedure was directly related to a lifesaving benefit to another human being. I doubt that research on a fetus for the benefit of mankind in general falls within the spirit of these cases, but, as is the case under the Massachusetts statute on fetal experimentation, 195 it is my view that the mother should be permitted to consent to diagnostic procedures and to nontherapeutic studies which do not substantially jeopardize the fetus.

There are times when therapeutic research is necessary for the mother which may be detrimental to the fetus, and vice versa. Here we have a situation very similar to the kidney and bone marrow transplant cases. A human being, the mother, is intimately involved. She should be permitted to place the fetus at risk if necessary to avert a substantial danger to her life or health. Because the fetus is in utero, and her body is obviously involved in the most intimate way in the experimental procedure, I would grant to her alone the right to consent. It would be necessary to modify this rule in emergencies, where consent would be implied, and in cases such as unconsciousness where it might be necessary to obtain the consent of next of kin or a guardian.

#### (b) The Viable Fetus

The viable fetus should have at least the status of the previable fetus, and I recommend substantial protection for the latter. Here also, in my view the fact that the fetus is within the mother's body gives her an overwhelming interest which should not be subject to coercion from, or a veto by, the father.

#### (c) The Abortus

When the fetus is no longer inside the body of the mother, she has no greater interest in it than does the father. Therapeutic experimentation performed on a living abortus should, if possible, have the consent of both parents. While there is a near certitude that the "child" will not live to leave the hospital, if it survives for a few days, the expense may be great. Perhaps parents need consent to only "ordinary," not extraordinary, research techniques. But as "ordinary" techniques are perfected to increase the period of viability, the day may come when an (apparent) abortus will live to become an infant. Both parents should participate in a decision—even a decision made under legal compulsion—of such financial magnitude. 197

Of course if the abortus is dead it should be treated no differently than a dead child or adult. Under the Uniform Anatomical Gift  ${\rm Act}^{198}$  a parent may donate the body of his deceased child (including a fetus) for the purposes of research.  $^{199}$ 

## (d) The Premature Infant

The general rules of consent for the use of therapeutic and innovative procedures on a child should be followed here. However, in view of the precarious condition of these infants, special precautions should be taken.

As a parting comment on the topic of consent, I assume it must be competent, voluntary, and knowledgeable. This may pose a problem for a mother, or a mother and father, under 18. I am not insensitive to the fact that girls in their early teens may bear children, and the girl or young father may be confronted with decisions about research for which they have little mature judgment. In such circumstances, perhaps for children under 15 or 16, the concurring consent of an adult might be required for research on an abortus or premature infant; but I would not remove the power of consent altogether from the young mother and father. For research on a fetus, I would require the consent of a mother of any age. This recommendation may be easier for me to make because I am opposed to nontherapeutic research on a fetus. My basic feeling, however, is that even a young mother is entitled to safeguard the sanctity of her own body, except possibly in situations of grave peril to herself or the fetus.

#### 3. Review Committees

The proposed HEW regulations require an elaborate array of review committees. 201 No doubt review, by bringing many minds and different points of view to bear, is useful in exposing hidden biases and in discovering potential perils. It also may provide sufficient additional protection to permit consent by adolescent parents. 202

Those who have suggested review committees have recommended that they include physicians involved in research and those who are not, 203 and individuals from all walks of life. 204 It has been suggested that review committees not be associated in any way with the institution sponsoring research. My own experience on a committee to review grant applications involving research on human subjects makes me somewhat pessimistic about the efficacy of lay representation. To perform an effective evaluation, many projects require technical expertise, and too many proposals of this sort dull an outsider's interest. Having a technical review committee and a committee to review the ethical implications of different kinds of research is probably a good way to resolve the dilemma, as long as bureaucratic inefficiency is avoided.

## 4. Physician Advocate

Another protective device is to require two physicians to be present in any research situation, one to perform research and the other to be responsible for the patient.<sup>207</sup> The latter physician, who might be appointed to represent a fetus, an abortus or a premature infant, would be responsible for protecting his patient's best interest; he would communicate the progress of research faithfully to the parents or guardian, make sure that consent is truly informed,

and require that every precaution be taken; he could withdraw his patient from the research if the risk of harm became too great. 208 There would be a problem, however, in the case of therapeutic experimentation. There the doctor performing the research would also be clearly responsible for the patient's care, and the presence of an additional, independent physician might constitute an unwarranted interference with the first doctor's professional responsibility. 209

## 5. Compensation Fund

When fetal research is performed, parents or guardians may incur substantial financial hardships. If nontherapeutic research in utero is permitted, it may be very difficult to prove the chain of causation leading from the research to a deformed infant. In these cases, therefore, it might be useful to consider adopting a standard of liability without fault against the research investigator in order to ensure the highest standard of care.<sup>210</sup>

For therapeutic research, however, such a standard would be too stringent. The rules governing malpractice should apply, although they would have to be modified with regard to proof of customary practice in the locality, as therapeutic research, by definition, is not customary. Because an award of damages for a deformed child might be crushing or unobtainable, it might be useful to establish a compensation fund (perhaps through insurance) to protect doctors from excessive claims and parents or guardians from long-term financial burdens.

Experimental methods to keep an abortus or premature infant alive may be enormously expensive and impose a crushing economic hardship. Faced with this possibility, a doctor might be tempted to diminish his efforts, and parents might be tempted to demand less of him. This would be a cruel choice, in particular for poor, inner-city residents. Therefore, in addition to ensuring a fair distribution of costs in the case of malpractice, a compensation fund might be used to assist parents where no negligence is present. The promise of some assistance in paying for in-hospital expenses and postnatal care at home might help to stimulate the most vigorous yet responsible research efforts by members of the medical profession engaged in fetal research.

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- 32. Idem, at 157.
- 33. Idem, at 162.
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- 37. Idem, at 158.
- 38. Idem, at 160-61.
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- 40. Unlike Shakespeare's Second Apparition in Macbeth, the Court most certainly did not intend to exclude from the class of "born" persons those who from their mothers' wombs were "untimely ripped" (Act IV, Scene VIII) by Caesarian section.
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- 54. DHEW, "Proposed Rules, Protection of Human Subjects," Federal Register 39:30648, Aug. 23, 1974.
- 55. Idem, at 30653, \$46.303.
- 56. Note, "Experimentation on Human Beings," Stanford Law Review 20:99, 1967 [hereinafter cited as "Stanford Human Experimentation Note"].
- 57. Idem, at 101.
- 58. Ely, "The Wages of Crying Wolf: A Comment on Roe v. Wade," Yale L.J. 82:920, 1973 [hereinafter cited as "Ely"].

- 59. Idem, at 935-36 (footnotes omitted).
- 60. Idem, at 940. Lochner v. New York, 198 U.S. 45 (1905).
- 61. "Ely," note 58 supra, at 948.
- 62. Tribe, "The Supreme Court, 1972 Term, Foreword: Toward a Model of Roles in the Due Process of Life and Law," *Harvard Law Review* 87:1, 15-32, 1973 [hereinafter cited as "Tribe"].
- 63. Idem, at 21.
- 64. Idem, at 19.
- 65. Idem, at 23-25.
- 66. Idem, at 29.
- 67. McGowan v. Maryland, 366 U.S. 420 (1961); Two Guys from Harrison-Allentown, Inc. v. McGinley, 366 U.S. 582 (1961). See also Gallagher v. Crown Kosher Super Market of Mass., Inc., 366 U.S. 617 (1961) and Braunfeld v. Brown, 366 U.S. 599 (1961).
- 68. "Ely," note 58 supra, at 926.
- 69. 410 U.S. at 158.
- 70. Marbury v. Madison, 1 Cranch 137, 2 L. Ed. 60 (1803).
- 71. 32 Mass. (15 Pick.) 255 (1834).
- 72. "In its mother's womb," Black's Law Dictionary 619, rev. 4th ed. 1968.
- 73. E.g., Crowles v. Crowles, 56 Conn. 240, 13 A. 414 (1887); In re Laird, 85 Pa. 339 (1877).
- 74. Black's Law Dictionary 619, rev. 4th ed. 1968, citing 1 Bl. Comm. 130.
- 75. Paton, G., A Text-Book of Jurisprudence 354, 3d ed. 1964. See also Roe v. Wade, note 24 supra, at 162.
- 76. Roe v. Wade, 410 U.S. 113, at 132 (citation omitted).
- 77. Perkins, Criminal Law 27, 1957; American Jurisprudence 40, 2d, Homicide, §9, at 300-01; C.J.S. 40, Homicide, §2, at 825; Means, "The Law of New York Concerning Abortion and the Status of the Foetus, 1664-1968: A Case of Cessation of Constitutionality," N.Y.L. Forum 14:411, 1968; Annot., 159 ALR 523.

- 78. Bracton's The Laws and Customs of England, quoted by Means, "The Law of New York...," note 77 supra, at 419 represents a 13th century description of English law: "If there be anyone who strikes a pregnant woman or gives her a poison whereby he causes an abortion, if the foetus be already formed or animated, and especially if it be animated, he commits homicide."
- 79. "If a woman be quick with child, and by a potion or otherwise killeth it in her wombe, or if a man beateth her whereby the childe dyeth in her body, and she is delivered of a dead childe, this is a great misprision, and no murder; but if the childe be born alive and dyeth of the potion, battery, or other cause, this is murder; for in law it is accounted a reasonable creature, in rerum natura, when it is born alive." Sir Edward Coke, Institutes III \*50, 1648, as quoted by Means, "The Law of New York...," note 77 supra, at 420.
- 80. American Jurisprudence 40, 2d, Homicide, §9, at 300-01; Annot., ALR 40, 3d, 446, §2. See also People v. Harper, 300 N.Y. 171 (1949) and Singleton v. State, 33 Ala. App. 536, 35 So. 2d 375 (1948). "'Person,' when referring to the victim of a homicide, means a human being who has been born and is alive." New York Penal Law, §125.05 (1).
- 81. See People v. Chavez, 77 Cal. App. 621, 176 P.2d 92 (1947).
  - 82. Evans v. People, 49 N.Y. 86 (1872); Foster v. State, 182 Wis. 298, 196 N.W. 233 (1923).
  - 83. "'[M]oment of conception' is a figment of the imagination, since conception like everything else is a process which takes time." Williams, "The Legalization of Medical Abortion," The Eugenics Review 19, April 1964, at 21, as cited by Brodie, "The New Biology and the Prenatal Child," J. Fam. Law 9:391, 1970, at 391, n. 2. Also, conception is "a 'process' over time, rather than an event...," Roe v. Wade, note 24 supra, at 161, citing a number of "new biology" articles.
  - 84. State v. Atwood, 54 Ore. 526, 102 P. 295 (1909), reh. 54 Ore. 542, 104 P. 195 (1909); State v. Elliott, 207 Ore. 82, 289 P.2d 1075 (1955).
  - 85. 138 Mass. 14 (1884).
  - 86. Idem, at 17.
  - 87. 184 Ill. 359, 56 N.E. 638 (1900), overruled, Amann v. Faidy, 415 Ill. 422, 114 N.E. 2d 412 (1953).
  - 88. Annot., 15 ALR 3d 992, 994.
  - 89. Prosser, Handbook of the Law of Torts 355-6, 3d ed. 1964, [hereinafter cited as "Prosser"].

- 90. Prosser, in 1964, listed Alabama, Rhode Island, and Texas as the only jurisdictions not yet permitting recovery for prenatal injuries. Idem, at 356. Since 1964, Rhode Island (Sylvia v. Gobeille, 220 A.2d 222 (1966)) and Texas (Leal v. Pitts Sand and Gravel, 419 S.W.2d 820 (1967)) appear to have abandoned the old rule.
- 91. "Prosser," note 89 supra, lists only nine jurisdictions (Cal., Ga., Ill., La., Mich., N.H., N.J., Pa., and Wis.) as having discarded the "viability" and "quickening" requirements. It appears that New York (Kelly v. Gregory, 282 App. Div. 542, 125 N.Y.S.2d 696 (1953)) should have been included in his compilation. And, since Prosser's 1964 survey, Rhode Island (Sylvia v. Gobeille, 220 A.2d 222 (1966)), Texas (Delgado v. Yandel, 468 S.W.2d 475 (Tex. Civ. App. Tex.)), and possibly Massachusetts (Torigian v. Watertown News Co., 352 Mass. 446, 225 N.E.2d 926 (1967) (viability test discarded, no reference to quickening requirement)) have joined the list.
- 92. See, e.g., Leccese v. McDonough, 279 N.E.2d 339 (Mass. 1972); Henry v. Jones, 306 F.Supp. 726 (D. Mass. 1969).
- 93. 21 of the 22 jurisdictions permitting, the 12 jurisdictions denying, and the 2 jurisdictions which have recently permitted a wrongful death action where there has been a live birth but have expressly reserved decision on the stillbirth situation are listed in Note, "Damages for the Wrongful Death of a Fetus--Proof of Fetal Viability...," Chicago Kent Law Review 51:1 227, 1974, at 228-9, no. 17. The Note lists Alabama as a state reserving decision, but in September 1974, Alabama joined those states permitting such an action. Eich v. Town of Gulf Shores, 8 Ala. B. Rep. 2075 (Sept. 12, 1974), reviewed in Cumberland Samford Law Review 5:362, 1974.
- 94. Porter v. Lassiter, 91 Ga. App. 712, 87 S.E.2d 100 (1955).
- 95. Enacted as part of the Social Security Act of 1935, 42 U.S.C., secs. 601-10 (Supp. II, 1972).
- 96. Note, "Statutory and Constitutional Bases for Extending AFDC Benefits to Families with Unborn Children," Southern California Law Review 48:121, 130, 1974, [hereinafter cited as "AFDC Note"].
- 97. 42 U.S.C. sec. 607 (a) (1970).
- 98. 45 C.F.R. sec. 233.90 (c)(2)(ii) (1973).
- 99. "AFDC Note," note 96 supra, at 124-5 (several footnotes abbreviated or omitted).
- 100. Idem, at 137-9.
- 101. Parks v. Harden, 354 F.Supp. 620, 622 (N.D. Ga. 1973), as quoted in "AFDC Note," note 96 supra, at 151.

- 102. 43 U.S.L.W. 3409 (U.S. Jan. 28, 1975).
- 103. Alcala v. Burns, 326 F.Supp. 180 (S.D. Iowa 1973), aff'd 494 F.2d 743 (8th Cir. 1974) cert. granted, 43 U.S.L.W. 3187; oral arguments heard Jan. 22, 1975, 43 U.S.L.W. 3409 (U.S. Jan. 28, 1975). [The Supreme Court rendered a decision shortly after this paper was submitted. On the basis of statutory analysis, it held that the unborn are not dependent children.]
- 104. Raleigh Fitkin-Paul Memorial Hospital v. Anderson, 42 N.J. 421, 201 A.2d 537 (1964), cert. denied 377 U.S. 95 (1964).

- 106. 410 U.S. at 163-4.
- 107. Mass. G.L.A. ch. 112, §12J.
- 108. See In re Smith, 16 Md. App. 209, 295 A.2d 238 (1972). But see Application of President and Directors of Georgetown College, Inc., 118 D.C. App. 8, 331 F.2d 1000, 9 ALR3d 1367, reh en banc denied, 118 D.C. App. 8, 331 F.2d 1010, cert. denied, 377 U.S. 978 (1964) (blood transfusion).
- 109. 410 U.S. at 163-4.
- 110. "[G]eneral usage and modern understanding of the word 'health' ... includes psychological as well as physical well-being." U.S. v. Vuitch, 402 U.S. 62, 72 (1971).
- 111. Maine Medical Center v. House, Sup. Ct. Cumberland Cnty., Maine, No. 74-145 (Feb. 14, 1974) (unreported opinion, Judge David Roberts). Case noted in Knox, "Defective Newborns: Life or Death Issue," Boston Globe, Mar. 10, 1974, at A-1. See also Annas, G., The Rights of Hospital Patients, New York, New York: Discus, 79-87, 1975.
- 112. E.g., California Health and Safety Code, §25956.
- 113. 138 Mass. 14 (1884).
- 114. "Nathan Interview," note 14 supra.
- 115. Foote, C.; Levy, R.; and Sander, F.; Cases and Materials on Family Law, 480, 1966.
- 116. "Nathan Interview," note 14 supra.
- 117. Idem.

- 118. It has been reported that a team of doctors led by Dr. Geoffrey Dawes and Dr. Kenneth Boddy of Oxford, England has shown, through the use of ultrasound, that about thirteen weeks after conception fetuses being to "'breathe' in the womb. Not only that, [some] also gasp, sigh, cough, and hiccup as well." Johnson, Lawrence H., Science Editor #1112, at 3, University of California, April 9, 1974.
- 119. See, e.g., Mass. G.L.A. ch. 229, §6.
- 120. 8A C.J.S., Animals, §99; Mass. S.P.C.A. v. Comm. of Public Health, 339 Mass. 216, 228 (1957); N.J.S.P.C.A. v. Board of Education, 219 A.2d 200, aff'd 227 A.2d 506 (1966).
- 121. E.g., Ill. Rev. Stat. ch. 8, §221; Iowa Code Ann. §717.3; Mass. G.L.A. ch. 272, §75; Tenn. Code Ann. §39-404.
- 122. Comm. v. Turner, 145 Mass. 296 (1887); Comm. v. Higgins, 227 Mass. 191 (1931); 8A C.J.S., Animals, §99.
- 123. Mass. G.L.A. ch. 49A, §2. See also Mass. S.P.C.A. v. Comm. of Public Health, 339 Mass. 216, 228 (1957).
- 124. 8A C.J.S., Animals, §101. But see N.J.S.P.C.A. v. Board of Education, 219 A.2d 200, aff'd 227 A.2d 506 (1966).
- 125. Mass. G.L.A. ch. 49A, §2.
- 126. Idem.
- 127. See, e.g., Mass. G.L.A. ch. 49A, §8A.
- 128. "Ely," note 58 supra, at 926.
- 129. 410 U.S. at 157-58.
- 130. In re Sampson, 65 Misc. 2d 658, 317 N.Y.S.2d 641 (1970), aff'd 37 App. Div. 2d 668, 323 N.Y.S.2d 253, aff'd 29 N.Y.2d 900, 278 N.E.2d 918 (1972). See also the fetal research statutes of Ill., Ind., Ky., Me., Mass., Minn., Nebr., Ohio, Pa., and Utah, set forth in the Appendix.
- 131. But see American Medical Association, Ethical Guidelines for Clinical Investigation, Opinions and Reports of the Judicial Council, Chicago: A.M.A., 9-11, 1969; Editors, "Judgment Difficult," New England Journal of Medicine 269:479, 1962.
- 132. 402 U.S. 62 (1971).

- 133. Brief and Appendices of Dr. Bart Heffernan, Amicus Curiae in Support of Appellant, U.S. v. Vuitch, 402 U.S. 62 (1971), at 4.
- 134. Idem, at 27-33 (footnotes omitted).
- 135. Idem, at 15.
- 136. "Tribe," note 62 supra, at 19-20 (footnotes omitted).
- 137. Idem, at 21.
- 138. Roe v. Wade, 410 U.S. 113, at 159.
- 139. Bok, "Ethical Problems of Abortion," The Hastings Center Studies 2:33, 41, 1974, [hereinafter cited as "Bok"].
- 140. Idem, at 43.
- 141. Boston Globe, Feb. 11, 1975, at 10.
- 142. Boston Globe, Feb. 6, 1975, at 15.
- 143. Boston Globe, Feb. 12, 1975, at 8.
- 144. Boston Globe, note 142 supra.
- 145. "Bok," note 139 supra, at 44.
- 146. Idem, at 37.
- 147. Idem, at 51.
- 148. "Stanford Fetal Experimentation Note," note 6 supra, at 1199.
- 149. La. Rev. Stat., Title 14, Sec. 87.2 (Acts 1973, No. 77, Sec. 1); Maine Rev. Stat., Ann., Title 22, Sec. 1574-76 (Acts 1973, Chapt. 518, Sec. 3-5).

- 150. Black's Law Dictionary 488, rev. 4th ed. 1968. See also Thomas v. Anderson, 215 P.2d 478 (1950).
- 151. See "A Definition of Irreversible Coma: Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death,"

  Journal of the Americal Medical Association 255:337, Aug. 5, 1968.
- 152. Handbook of the National Conference of Commissioners on Uniform State Laws, 1968, Appendix 293 [hereinafter cited as "Handbook"]; Sadler and Sadler, "Providing Cadaver Organs: Three Legal Alternatives," The Hastings Center Studies 1:15, 1973, [hereinafter cited as "Sadler"].

- 153. Mass. G.L.A. ch. 113, §13(b). The Comment following Sect. 7 of the Uniform Anatomical Gift Act, "Handbook," note 152 supra, states: "Subsection (b) leaves the determination of the time of death to the attending or certifying physician. No attempt is made to define the uncertain point in time when life terminates. This point is not subject to clear cut definition and medical authorities are currently working toward a consensus on the matter. Modern methods of cardiac pacing, artificial respiration, artificial blood circulation and cardiac stimulation can continue certain bodily systems and metabolism far beyond spontaneous limits. The real question is when have irreversible changes taken place that preclude return to normal brain activity and self sustaining bodily functions. No reasonable statutory definition is possible. The answer depends upon many variables, differing from case to case. Reliance must be placed upon the judgment of the physician in attendance. The Uniform Act so provides.
- 154. Mass. G.L.A. ch. 113, §13(b).
- 155. "Handbook," note 152 supra, at 192.
- 156. Idem (emphasis added).
- 157. N.Y. Public Health Law, Title V, §4160 (effective Sept. 1974).
- 158. Idem, at §4164 (1).
- 159. Idem, at §4164 (2).
- 160. Idaho Code \$18-608 (3) (Supp. 1973); Utah Code Ann. \$76-7-309 (Supp. 1973).
- 161. See generally Annot., 54 ALR3d 1043-6.
- 162. Doe v. Doe, No. 1105-6 (Mass. Sup. Jud. Ct., July 3, 1974) (Hennessey dissent), citing Spock, Baby and Child Care, 28-31 (Rev. Pocket Book ed. 1968) and Wright, The New Childbirth, 158-90 (Pocket Book ed. 1971).
- 163. Mass. G.L.A. ch. 113, §§8 (a) and (b).
- 164. "Stanford Fetal Experimentation Note," note 6 supra, at 1203.
- 165. Mass. G.L.A. Ch. 113, §9.
- 166. Idem, at §8(a).
- 167. Idem, at §7(b).
- 168. Mass. G.L.A. ch. 112, §12J.
- 169. Idem.

- 170. See Kleinfeld, "The Balance of Power Among Infants, Their Parents, and the State," Part II, Parental Power, Family L. Q. 4:409, 1970.
- 171. Paulsen, "The Legal Framework for Child Protection," Columbia Law Review 66:679, 689-90, 1966 [hereinafter cited as "Paulsen"].
- 172. Idem, at 690.
- 173. Idem, at 684.
- 174. Idem.
- 175. Idem, at 682.
- 176. Uniform Laws Annotated, Model Penal Code, at 568, \$230.4, (West 1974).
- 177. "Paulsen," note 171 supra, at 683.
- 178. Idem.
- 179. Idem, at 712.
- 180. "Prosser," note 89 supra, at 103.
- 181. Zoski v. Gaines, 271 Mich. 1, 260 N.W. 99 (1939); Moss v. Rishworth, 222 S.W. 225 (Tex. 1920); "Prosser," note 89 supra, at 104.
- 182. 126 F.2d 121 (D.C. Cir. 1941).
- 183. Masden v. Harrison, 68651 Eq. Mass. Sup. Jud. Ct., June 12, 1957; Huskey v. Harrison, 68666 Eq. Mass. Sup. Jud. Ct., Aug. 30, 1957; Fostor v. Harrison, 68674 Eq. Mass. Sup. Jud. Ct., Nov. 20, 1957. See Curran, "A Problem of Consent: Kidney Transplantation in Minors," New York University Law Review 34:891, 1959.
- 184. Banks v. Conant, 14 Allan 497 (Mass. 1867); Taylor v. Mechanics Savings Bank, 97 Mass. 345 (1867).
- 185. Katz, J., Experimentation with Human Beings, 966, 1972 [hereinafter cited as "Katz"].
- 186. Idem, at 972.
- 187. Strunk v. Strunk, 445 S.W.2d 145 (Ky. 1969).
- 188. Nathan v. Farinelli, No. 74-87 Eq. Mass. Sup. Jud. Ct., July 3, 1974.
- 189. Idem, at 3.

- 190. Idem, at 7-8.
- 191. Idem, at 10.
- 192. Idem, at 11.
- 193. In re Richardson, 284 So. 2d 185 (La. 1973).
- 194. In his concurring opinion in Lacey v. Laird, 166 Ohio St. 40, 139 N.E.2d 25 (1956), Justice Hart states that the requirement of parental consent to medical procedures is "based upon the right of the parents whose liability for support and maintenance of their child may be greatly increased by an unfavorable result of the operational processes..."

  Idem, at 139 N.E.2d 30.
- 195. Mass. G.L.A., ch. 112, §12J.
- 196. "Staton Interview," note 10 supra, describing policy at Boston Hospital for Women.
- 197. See generally Robertson, "Involuntary Euthanasia of Defective Newborns: A Legal Analysis," Stanford Law Review 27:213, 1973.
- 198. "Handbook" and "Sadler," note 152 supra.
- 199. Idem. Interestingly, under a statute recently passed in Illinois, parental donation of a dead fetus may not be permitted. Ill. Crim. Law and Procedure 38 §81-18 states that all "tissue" removed at the time of the abortion must be examined by a pathologist. It goes on to say "There shall be no exploitation of or experimentation with the aborted tissue." As a matter of policy it makes no sense to treat a dead fetus differently from a dead adult.
- 200. Kaimowitz v. Dept. of Mental Health for the State of Michigan, Civ. Action No. 73-19434-AW (Cir. Ct. for Cnty. of Wayne 1973).
- 201. DHEW, "Proposed Rules, Protection of Human Subjects," Federal Register 39:30648, 30653-54, Aug. 23, 1974.
- 202. See Calabresi, "Reflections on Medical Experimentation in Humans," *Daedalus* 98:2:387, 403, Spring 1969 [hereinafter cited as "Calabresi"].
- 203. Lewis, McCollum, Schwartz, and Grunt, "Informed Consent in Pediatric Research," Children 16:143, 148, 1969, reprinted in "Katz," note 185 supra, at 994.
- 204. "Stanford Human Experimentation Note," note 56 supra, at 109.

- 205. Idem.
- 206. This view is voiced by others: "Nathan Interview," note 14 supra; "Stanford Human Experimentation Note," note 56 supra, at 109.
- 207. "Stanford Human Experimentation Note," note 56 supra, at 109; Wall Street Journal, April 14, 1971, at 1 and 17, reprinted in "Katz," note 185 supra, at 997-98.
- 208. Idem.
- 209. "Stanford Human Experimentation Note," note 56 supra, at 109.
- 210. Idem, at 115.
- 211. Karp v. Cooley, 349 F.Supp. 827 (S.D. Tex. 1972), aff'd 493 F.2d 408 (5th Cir. 1974).
- 212. Note, however, that at least thirteen states now have statutes requiring that measures be taken to save viable fetuses, Family Planning/Population Reporter 3:5:92, Oct. 1974. "The inability to distinguish postviability fetacide from infanticide, and hence the state's power to prohibit both, may entail serious hardships for the woman or family involved... But our society does not regard killing as an acceptable remedy." "Tribe," note 62 supra, at 28, n. 128. For discussions of the ethical problem of withholding treatment from children, see Duff and Campbell, "Moral and Ethical Dilemmas in the Special-Care Nursery," New England Journal of Medicine 289:890, 1973, and Shaw, "Dilemmas of the 'Informed Consent' in Children," New England Journal of Medicine 289:885, 1973.
- 213. See "Calabresi," note 202 supra, at 395. See also Nathan v. Farinelli, No. 74-87 Eq. Mass. Sup. Jud. Ct., July 3, 1974, at 12; Note, "Medical Experiment Insurance," *Columbia Law Review* 70:965, 1970.

#### APPENDIX

In this appendix I set forth commentary about various state statutes governing fetal experimentation.

## 1) California - Health and Safety Code, Sec. 25960

California has two identically numbered sections dealing with fetal experimentation. The wording of the two sections is almost identical. One section prohibits experimentation on any "aborted product of conception" and the other prohibits experimentation on any "aborted product of human conception . . . " Experimentation to "protect or preserve the life and health of the fetus" is not prohibited. Experimentation on "fetal remains" which is defined as "a lifeless product of conception" is also not prohibited. A fetus is lifeless if there is no "discernible heartbeat."

There is no prohibition on experimentation in utero.

## 2) Illinois - Criminal Law and Procedure 38 § 81-18

All tissue removed at the time of abortion must be submitted to a pathologist. The statute goes on to say "There shall be no exploition of or experimentation with the aborted tissue." There is no distinction made between living and dead "tissue." There is no prohibition of experimentation in utero.

Since one can assume that live fetuses are not sent to the pathologist, as a matter of interpretation this section must be concerned with tissue from dead fetuses. Thus, it appears that experimentation on dead fetuses is outlawed but experimentation on live fetuses is not, which makes this a rather unusual provision.

## 3) Kentucky - Crimes and Punishments - 436.026

The sale, transfer, distribution or giving away of any "live or viable aborted child" is prohibited. Whoever "permits" such child to be used for any form of experimentation is also guilty of a crime. Thus, penalties would apply to parents as well as the experimenter if the parent consents to the experimentation. There is no exception for experiments designed to preserve the life or health of the aborted "child." There is no prohibition of in utero experimentation. The minimum sentence under the statute is 10 years.

## 4) Louisiana - Revised Statutes, Title 14 § 87.2

Experimentation on a human embryo or fetus *in utero* is prohibited unless it is to preserve the life or improve the health of the embryo or fetus.

"Human experimentation" on any "live born human being" without the consent of that human being is prohibited if done without the consent of that human being, unless it is done to protect or preserve his life or health. Under the statute, a human being is live born if it is expelled or extracted from its mother, and breathes or shows other evidence of life such as a beating heart, pulsation of the umbilical cord or movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached, and irrespective of the duration of pregnancy.

The breadth of this statute is enormous since it applies to everyone who is alive, regardless of age. We are all "live born human beings." This statute, besides banning fetal experimentation, also bans experimentation on children and mental incompetents who cannot consent for themselves.

Experimentation without consent is made a crime punishable by a minimum sentence of 5 years at hard labor and a maximum or 20 years. An experimenter who fails to obtain adequate informed consent from an adult subject could be subjected to punishment.

## 5) Maine - Maine Revised Statutes, Title 22, Sec. 1574-1576

Any live human fetus, whether intrauterine or extrauterine, or any live born product of conception, may not be used, transferred, distributed or given away for the purpose of scientific experimentation. The definition of live born is essentially the same as that used in Louisiana. Maine's use of the term "any live born product of conception" includes everyone who is now alive. In effect, it prohibits the "use" of any human being for human experimentation, regardless of consent. This ban would seem to include experimentation for the purpose of preserving the life or health of the fetus, or anyone else.

## 6) Massachusetts - Massachusetts General Laws, Ch. 112 § 12J

Live human fetuses, whether before or after expulsion from the womb, may not be used for scientific, laboratory, research, or other kind of experimentation. Procedures "incident to the study" of the fetus in utero are not prohibited if in the physician's judgment the study will not "substantially jeopardize" the life or health of the fetus, and the fetus is not the subject of a planned abortion. The use of the word "study" probably indicates that it is something other than "experimentation" that is permitted. Perhaps the mere observation of the fetus is what the draftsman had in mind.

Diagnostic or remedial procedures to determine or preserve the life or health of the fetus or mother are specifically permitted. It is not clear if this includes experimental diagnostic or remedial procedures.

A fetus is live when, in the medical judgment of the physician, "it shows evidence of life as determined by the same medical standards as are used in evidence of life in a spontaneously aborted fetus at approximately the same stage of gestational development."

A dead fetus can be experimented on with the mother's consent.

The word fetus includes embryos and neonates.

## 7) Minnesota - Public Health Laws § 145.38

"Human conceptus" means a human organism, conceived either inside or outside the human body, from fertilization through 265 days thereafter.

"Living" means "the presence of evidence of life, such as movement, heart or respiratory activity, the presence of electroencephalographic or electrocardiographic activity."

Experimentation on a live conceptus is prohibited, except to protect the life or health of the conceptus. However, research on such a conceptus is permitted if "verifiable scientific evidence" has shown that the research is "harmless."

This statute established what appears to be a definite cutoff point after which experimentation is not regulated, since the exact date of conception is difficult, if not impossible, to ascertain. As a practical matter experimenters will probably use the 265 day figure as a rough guideline.

The legislature also tried to permit harmless experiments. But one doubts if any experiment on such a subject is absolutely harmless, and one also wonders what is "verifiable scientific evidence."

## 8) Missouri - H.C.S. Bill No. 1211 (unclassified 1974 laws)

No person shall use any fetus or premature infant aborted live for experimentation. This applies to fetuses in utero and after abortion.

Experiments on a "premature infant" born alive to preserve its "life and health" (emphasis added) are permitted. Apparently, experimental procedures to protect the life or health of the fetus in utero are prohibited.

## 9) Montana - Criminal Code 94-5-617

"Premature infants" born alive may not be used for scientific research or experimentation unless it is for the purpose of protecting the life and health of such premature infant. *In utero* experimentation is not regulated.

## 10) Nebraska - Revised Statutes § 28-4,161

The sale, transfer, distribution or giving away of a live or viable "aborted child" for the purpose of experimentation is prohibited. Any person who consents to, aids or abets such sale or transfer is also guilty of a crime.

The experimentation itself does not appear to be prohibited. One who receives such an "aborted child," however, might be guilty of aiding or abetting the transfer. If the mother consents to the transfer, she would also be guilty of a crime. No exception is made for experiments that would preserve the life or health of the "aborted child." *In utero* experimentation is not regulated.

## 11) New York - Public Health Law § 4164

New York's statute does not actually deal with experimentation. It states that any viable "child" which results from an abortion is accorded immediate legal protection under the laws of New York. It would thus be treated as any other child for purposes of experimentation.

## 12) Ohio - Am. Sub. House Bill 989 \$2919.14

"No person shall experiment upon or sell the product of human conception which is aborted." No exception is made for experiments to preserve the life or health of the aborted fetus. Both dead and live fetuses are similarly treated. In utero experimentation is not regulated.

## 13) Pennsylvania - Session Laws 1974, Act 209, § 5

Same as Montana

## 14) South Dakota - Public Health and Safety 34-23A-1

"Experimentation with fetuses without written consent of the woman shall be prohibited." Apparently both living and dead fetuses, in utero and after abortion, may be used for experimentation as long as the mother consents.

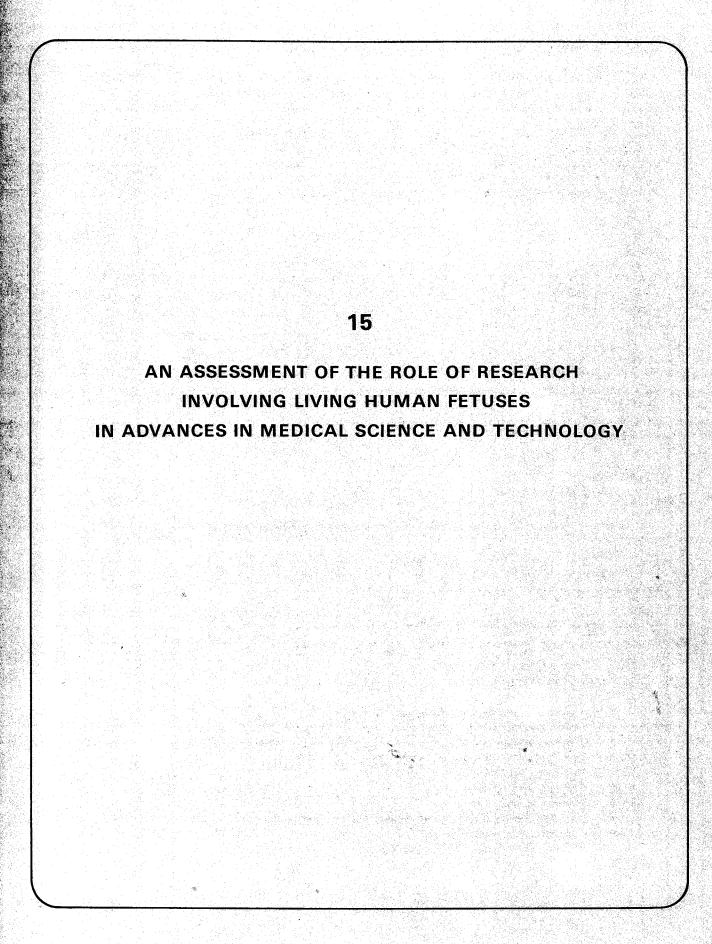
It is interesting to note that if the woman is a minor, her parent, or husband if married, must consent to the abortion. It appears, however, that a minor woman can consent to fetal experimentation on her own.

## 15) Utah - Criminal Code 76-7-310 to 311

Live "unborn children" may not be used for experimentation. They may be tested for genetic defects. No exception is made for experiments to preserve the life or health of the "child." There is no prohibition against experimentation on the "child" after an abortion.

## 16) Indiana - Criminal Code vol. 2, Part 2, Secs. 10-112

Indiana's statute on fetal experimentation is not discussed herein, as it was not available for analysis.



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# Contents

SUMMARY	15-1
INTRODUCTION	15-2
OVERALL CONCLUSIONS AS TO THE NEED FOR FETAL RESEARCH	15-3
METHODOLOGY	15-6
CASE STUDIES	
CONGENITAL RUBELLA SYNDROME (RUBELLA VACCINE)	15-9
Medical Significance	15-9
Historical Account	15-10
Contribution of Human Fetal Research to the Development of the Rubella Vaccine	15-13
Effect of a Retrospective Ban on Fetal Research	15-15
Future Outlook	15-15
References	15-17
Principals Interviewed	15-21
AMNIOCENTESIS	15-25
Medical Significance	15-25
Historical Account	15-35
Contribution of Human Fetal Research to Amniocentesis	15-39
Effect of Retrospective Ban on Human Fetal Research on Amniocentesis	15-41
Outlook for Amniocentesis as a Clinical Procedure	15-44
References	15-46
Principals Interviewed	15-54
ISOIMMUNIZATION (Rh VACCINE)	15-57
Medical Significance	15-57
Historical Account	15-59
Contribution of Human Fetal Research to the Control of Rh Hemolytic Isoimmune Disease	15-62
Effect of a Retrospective Ban on Human Fetal Research on the Control of Rh Isoimmune Hemolytic Disease	15-64
Future Outlook	15-67
References	15-68
Principals Interviewed	15-71

# Contents (continued)

RESPIRATORY DISTRESS SYNDROME (RDS)	15-75
Medical Significance	15-75
Historical Account	15-77
Contribution of Fetal Research to RDS	15-84
Effect of a Retrospective Ban on Fetal Research	15-85
Future Outlook	15-86
References	15-87
Principals Interviewed	15-94
ANIMAL MODELS	
ANIMAL MODELS	15-97
Introduction and Summary	15-97
Congenital Rubella Syndrome	15-99
Amniocentesis	15-105
Isoimmunization	15-117
Respiratory Distress Syndrome	15-123
GLOSSARY	15-131
APPENDIX	
DISCUSSION OF THE PROCEDURE AND COMPLICATIONS OF AMNIOCENTES	SIS 15-139
Technique	15-139
Timing of the Procedure	15-141
Complications	15-142
Amniography Illtrasonography Amnioscopy and Fetoscopy	15-145

# An Assessment of the Role of Research Involving Living Human Fetuses in Advances in Medical Science and Technology

#### SUMMARY

A study has been made of four important developments in the combined area of fetology-neonatology-pediatrics-obstetrics with emphasis on the assessment of the role of research involving living human fetuses in the evolution of these developments. The cases chosen for study were: amniocentesis, congenital rubella syndrome (rubella vaccine), Rh isoimmunization (Rh vaccine and therapeutic exchange transfusions), and respiratory distress syndrome.

As in other scientific or technical developments, progress occurred through essentially discrete paths of research which, however, were mutually reinforcing and which led to a significant advance in medical science. Detailed accounts and historiographs of each case were developed and these are presented in later sections.

Research in each of these cases involved both animal models and living human fetuses to varying degrees and in varying ratios. Later sections discuss in some detail the estimated effects that a ban on research on living human fetuses would have had on each development. Briefly stated here, adequate animal models were not available at the times needed and only in isoimmunization has appreciable progress since been made towards an adequate model. Thus, the developments would have been halted indefinitely, except perhaps for the Rh vaccine which would have been delayed for at least five, and more probably ten years. Also very recently progress has been made towards a model useful for respiratory lung distress.

With the benefit of retrospection, it is concluded that investigators proceeded to clinical trials with very high ratios of benefit to risk in each case. The benefits have indeed been high-rubella and Rh vaccines can eliminate fetal, neonatal and later mortality and morbidity caused by rubella, and Rh incompatibility in the expectant mother. Prior to the development of the Rh vaccine, multiple exchange transfusions were developed for effective therapy of both the fetus and the neonate. Consequent social and economic gains are obvious. In the case of rubella, the National Foundation-March of Dimes estimated that the number of cases of rubella and congenital rubella syndrome in the United States dropped 57 percent to 11,836 cases in 1974, compared to 1973. In the prevaccine years 1966-68, the number of cases was 47,500 per year. The gains resulting from the treatment or prevention of Rh isoimmune hemolytic disease are also great. It is estimated that the annual number of stillbirths resulting from the disease was 10,000 before the development of the therapeutic and prophylactic methods. The in utero exchange transfusions alone can rescue 50 percent of

these fetuses. It is estimated that pre- and postnatal exchange transfusions have saved 200,000 lives in the period between 1940 and 1960. The development of the Rh vaccine can prevent the disease in an estimated 25,000 infants at risk each year in the United States. In the case of respiratory distress syndrome, the gains are not yet so dramatic, but advances in the understanding of the disease and its detection have led to both prophylactic and therapeutic approaches of great promise. Amniocentesis has made major contributions to the other cases and, moreover, has led to a wide range of diagnostic procedures which for the first time allow the assessment of fetal health and development in utero.

## INTRODUCTION

Advances in embryology and fetology combined with advances in genetics, immunology, virology, cell biology, and other disciplines have resulted in procedures and treatment that enable:

- (1) Diagnosis in utero of numerous genetic, developmental, or teratogenetic defects.
- (2) Reduction or elimination of certain of the risks of such defects to the embryo, fetus, or infant.

The development of such procedures has involved research on living human fetuses and is related to the larger subject of research on living humans. This matter has become of such importance that a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research\* was established in 1974 by the United States Congress. At the time of its establishment, a moratorium was instituted on HEW support of nontherapeutic research on living human fetuses before or after induced abortions.\*\* The National Commission was charged with recommending to the Secretary of Health, Education and Welfare by April 30, 1975 whether this moratorium on research on living human fetuses should be continued, lifted, or modified.

To furnish background information on which to base its recommendations, the National Commission contracted with the Columbus Laboratories of Battelle Memorial Institute to make an assessment of the role of research involving living human fetuses in certain advances in medical science and technology. The advances to be considered were:

- (1) Congenital Rubella Syndrome (Rubella Vaccine)
- (2) Amniocentesis

<sup>\*</sup>Hereinafter referred to as the "National Commission."

<sup>\*\*</sup>Public Law 93-348, Section 213.

- (3) Isoimmunization (Rh Vaccine)
- (4) Respiratory Distress Syndrome.

Of these cases, amniocentesis is a general technique that makes possible a wide range of diagnostic procedures; congenital rubella syndrome and isoimmunization are concerned primarily with the prevention of defects; and respiratory distress syndrome is concerned with the prior warning and treatment or prevention of a very serious neonatal problem.

Each case was to be studied retrospectively and the significant steps leading to the final procedure were to be identified. The use of living human fetuses in the course of the research was to be studied intensively and, most importantly, the impact of the substitution of other procedures for living human fetuses was to be projected as far as possible. That is, an attempt would be made to answer the question, What would be the estimated effects of such substitution on (a) the time to develop the procedures; (b) changes in morbidity and mortality; (c) economic costs; and (d) related scientific advances?

While these were the objectives of the program, both the National Commission and Battelle-Columbus recognized that the time available (from February 4, 1975, to the March 7, 1975, submission of the draft report) would impose limitations.

The following sections describe the methodology used, the four individual cases, and the overall conclusions drawn from the four cases. Although the report is intended for the informed layman, the use of medical and scientific terms was unavoidable. Therefore, a glossary of technical terms has been provided.

In this report the term "research on living fetuses"\* embraces any experimentation on either the pregnant woman or the fetus in which either drugs or surgical procedures are involved. The "fetal period"\* is to be understood as the time from implantation to delivery, including the first seven to eight weeks, which are usually referred to as embryonic.

## OVERALL CONCLUSIONS AS TO THE NEED FOR FETAL RESEARCH

It is apparent from a study of the development of the four selected cases, amniocentesis, isoimmunization, respiratory distress syndrome, and congenital rubella syndrome, that research on living human fetuses played a significant role in each. The concern here is the estimation of the probable effect that a ban on research involving the use of living human fetuses would have had on the course of these developments. The phrase "research on living human fetuses" has been defined\* as any research done on either the pregnant woman or the living fetus, or in short, any experimentation that could perturb the living fetus or its environment. To carry such a restriction to the ultimate would, of course,

<sup>\*</sup>These definitions supplied by the staff of the National Commission.

prevent new therapeutic, prophylactic, or diagnostic procedures for fetuses or pregnant women from reaching clinical usage. First clinical trials would constitute such research and thus be automatically proscribed. In light of this, we have considered fetal research as somewhat analogous to the accepted method of drug development. New drugs are evaluated in animal models as to toxicity and efficacy to the point where it is felt by competent judges that clinical trials are warranted. The risk involved in this final step is dependent upon the adequacy of the subjective judgment and of the animal model used. No amount of animal use will insure complete safety in first clinical trials if the animal models do not very closely mimic the human subjects. Thus the four developments studied here must be considered with regard to the availability of adequate animal models for the several lines of research and the multiple steps in each for the different cases. In effect, this study has focused on the possibility of greater use of animal models and the consequences of this change in each of the developments.

Although "cases" are being studied here, it must be noted that each was composed of several parallel efforts that were mutually reinforcing and which together led to an advance in a diagnostic method or treatment or prevention of a disease state. Thus a procedural change or delay in one contributing research approach could have a profound effect on the total development. This is true even in what appears to be an independent development. For example, amniocentesis had its origin in 1882 as a palliative procedure for the treatment of polyhydramnios. Over the years it was found that the amniotic fluid withdrawn in the procedure could furnish much information as to the health of the fetus and allow the identification and measurement of the progression of many fetal disorders. This later use of the procedure contributed significantly to the understanding and eventual prophylaxis or treatment of two of the cases studied here, Rh isoimmunization and respiratory distress syndrome. This procedure, obtaining amniotic fluid, is unique among the developments studied in that no record was found of preceding animal studies. Since its first use, there have been many animal studies--primarily to determine suitability of the animals as fetal models--but no animals have been found to be adequate as models for the technique itself. A detailed exposition of the model shortcomings may be found in the section on amniocentesis.

With the other cases, which are concerned with therapeutic and prophylactic procedures, adequate animal models were also unavailable. In congenital rubella syndrome, once the association between rubella in the gravid human and the congenital defects was established, preparation of the vaccine could be thought to be straightforward. However, no animal is known which could have shown that the attenuated live virus vaccine given to a pregnant woman would traverse the placenta to infect the fetus, and that it is therefore necessary that the vaccine be administered well before pregnancy.

In respiratory distress syndrome, amniocentesis was essential in obtaining human amniotic fluid which would allow the determination of the vital lecithin/sphingomyelin ratio that measures the fetal lung maturation. The effect of corticosteroids was widely studied in various animals, but the animal models were deficient because of a placental barrier to the drug that is absent in the human, and because the lung-surfactant system is different. It should be noted

that this steriodal hormone treatment is still experimental. Considerable further research is necessary and a valid mother-placenta-fetus model is not yet known. A more recent treatment for respiratory distress syndrome is the administration of plasminogen to the neonate. Promising results have been obtained but its ultimate effectiveness cannot yet be assessed. Rationale for the treatment was based on a knowledge of the etiology of the disease but, given the etiology, development of the treatment did not involve research on living human fetuses. Prior determination of the probable occurrence of the disease by determination of the L/S ratio through amniocentesis would give warning that treatment would be needed.

In Rh isoimmunization, again use of both animals and living human fetuses is found. As in the respiratory distress syndrome, amniocentesis is found to be central to research leading to an understanding, characterization, and detection of the disease. Both animal and living human fetal research were involved in the steps leading to therapy (transfusions) and prophylaxis (Rh vaccine). These animal models also were deficient, as is described later, and research involving living human fetuses was necessary to reach definitive conclusions. Today the course of research could be different -- in the mid-1960s, intensive research began on the isoantigens of lower primates and the mechanism of isoimmune disease in these animals. It is conceivable that the use of these animals could have eliminated some of the use of living human fetuses, but the Rh vaccine was developed before the animal models became available. Interruption of the Rh isoimmunization study in order to wait for the primate research would have delayed the development of Rh vaccine accordingly. It is doubtful and even improbable that the risks to the eventual clinical subjects would have been appreciably decreased by the added primate work.

Special attention should be paid to the place of amniocentesis. As noted, this procedure went into clinical use without prior animal studies, and even after more than 90 years, no adequate animal model has been found. Had the ban on fetal research been in effect, amniocentesis would not be used today. The importance of amniocentesis in the research leading to prevention or treatment of respiratory distress syndrome and Rh isoimmune hemolytic disease cannot be overstated. Not only does amniocentesis enable detection and monitoring of the progression of the diseases in utero, but its use was vital in characterizing the diseases and the etiologies. Without this basic knowledge, there would have been no basis for the successful research directed towards prevention or cure. Postnatal transfusions for Rh hemolytic disease were begun before the basic knowledge was gained, but they, of course, do not apply to stillborns, nor do they prevent prenatal damage.

Thus the conclusion is reached that in the four cases studied, adequate animal models were not available and—with the exception of Rh isoimmunization—the prospect of adequate models becoming available is small. As in the case of therapeutic drugs, dependence must be placed on the judgment of qualified persons that proceeding to research involving living human fetuses is justified on the basis of risk/benefit considerations.

Because of the current interest, instances of fetal research can also be classified as to "therapeutic" or "nontherapeutic" application. That is, the

procedure was defined according to the objective either of aiding the individual fetus involved or of gaining knowledge that would contribute to the well-being of fetuses in the future. The findings follow:

# Congenital Rubella Syndrome (Rubella Vaccine)

The fetal research here involved fetuses whose abortions were planned. The objective was to determine if the vaccine given to the pregnant mother would infect the fetus. Thus it was for the benefit of future fetuses and is classified as nontherapeutic.

## Amniocentesis

In respiratory distress syndrome, amniocentesis contributed to both therapeutic and nontherapeutic fetal research, as will be seen in those sections. Fetal research involving amniocentesis has led to methods that can diagnose fetal abnormalities. Because at this time remedies for a large majority of these abnormalities are not known, most of this research must be classified as nontherapeutic to the subject fetus. It should be noted, however, that the procedures can be of immediate therapeutic benefit to the pregnant mother.

## Isoimmunization (Rh Vaccine)

Early fetal research here had the dual objectives of detecting and characterizing the disease in the fetus. Detection would give prior warning that an exchange transfusion would be necessary. Research directed towards characterization, while of benefit to future fetuses, would also identify those at risk and thus be of immediate therapeutic value. Intrauterine exchange transfusions were initiated as a direct therapeutic measure.

## Respiratory Distress Syndrome

Fetal research directed toward detection of the impending disease is classified as therapeutic because it showed the need for delay of the delivery or the need for postnatal treatment. In fetal research involving steroids, the first (1961) was to determine if cortisol administered to pregnant women would cross the placenta. This is classified as nontherapeutic. In the other steroid fetal research, the objective was the development of therapy that would benefit the fetus involved and so is therapeutic.

#### METHODOLOGY

The methodology was in general derived from that used in the Battelle study for the National Science Foundation on the interactions of science and technology in the innovative process.\* In that study the objectives included the identification

<sup>\*&</sup>quot;Interactions of Science and Technology in the Innovative Process: Some Case Studies," Final Report by Battelle, Columbus Laboratories to National Science Foundation, Contract NSF-C667, March 19, 1973.

and characterization of significant and decisive events, and assessment of their importance to the innovative process. Any general or qualitative characteristics that were common to the eight cases of innovation were also identified.

In the present program primary concern was the significant steps in each of the four cases that were found to include, as an essential element, research on living fetuses. These steps were then studied in detail to estimate the effects of substitution of animal models (or perhaps in vitro methods) for living human fetuses.

Thus the project proceeded chronologically as follows:

- 1. Construction of an historical outline of the development of each case, showing the chronology of the steps contributing to the development of the clinical procedure or treatment. These are described in the narratives and in diagrammatic form in the sections on the individual cases.
- 2. Identification of the significant steps and determination of those in which living human fetuses were used in the research.
- 3. Estimation of the effects of a delay in research on living human fetuses, and evaluation of the possibility of alternate pathways. The latter could include the use of animal models or in vitro methods.
- 4. Comparison of the probable progress and final results from the use of alternate routes as compared with the actual path involving the use of living human fetuses.
- 5. Assessment of the significance of the development.
- Determination of any general conclusions or principles that are suggested by the foregoing assessments.

To carry out this study, an interdisciplinary team was assembled which included case leaders from disciplines appropriate to each case, supported by other life scientists, information scientists, librarians, and various consultants and advisers. Management of the program, because of its interdisciplinary nature, was provided by members of the Research Council of Battelle-Columbus.

After definition of the program and organization, the initial step was the literature searches in each of the four cases. Initially, machine searches were performed at the National Library of Medicine, as arranged by Dr. Duane Alexander of the National Commission and Miss Charlotte Kenter of the National Library of Medicine. These searches included MEDLARS II from January 1972 to the present, CATLINE from 1964 to the present, and BACKFILE from January 1969 to September 1971. Many of the articles, books, and reports listed in the search results

were obtained through local libraries. A review of these publications identified many references to earlier work. Concurrently, searches were made of local sources at Battelle, The Ohio State University School of Medicine, and hospital libraries by the project staff, including an information scientist.

Because of the pressure of time, the National Commission recommended the use of a number of consultants who were active participants or knowledgeable in the various fields. These consultants were expected to supply not only information from personal experience, but also references to other work. Scheduling difficulties resulting from the short time available prevented optimum utilization of this group. In addition, other experts both in Columbus and elsewhere were consulted.

Further aid in gathering information to be analyzed was given by an obstetrician-gynecologist of the Human Affairs Research Center of Battelle Memorial Institute in Seattle, and by a Columbus geneticist, serving as a research associate to the project.

Concurrently with the literature search, analysis proceeded to identify and describe the significant steps in each case. The analyses, literature search, and inputs from the consultants were mutually reinforcing throughout the project.

Throughout the project, meetings were held among the groups to insure commonality of methods and objectives, and to identify features and conclusions common to the subgroups. Overall conclusions drawn from this study therefore represent a consensus of the project team.

Each of the cases is reported separately in the following sections. For each case, the significance of the development to the mother and fetus (or neonate) is described. Important steps in each development are described narratively and shown in an historiograph. These latter show the steps in the characterization, etiology, and detection of the disease states and the development of therapeutic or prophylactic procedures. In the case of amniocentesis, the history and applications of the procedure are shown. In each historiograph, the steps are coded to show the experimental animal involved.

Although the events are shown chronologically, it is not implied that each event was a direct consequence of the preceding. Arrows were used to show dependence on a previous finding. Also, the listing of an event and the senior author is not to be taken as showing absolute priority for a given development. Time did not allow rigorous establishment of priority. The historiographs do show the paths of the developments and the place of research involving living human fetuses in the overall history.

Because of the importance of animal models to this study, further and more detailed information was obtained and combined with the information found in each case study to form an additional section of the report. This furnishes additional bases for the conclusions reached in this study.

CASE STUDIES

#### CONGENITAL RUBELLA SYNDROME (RUBELLA VACCINE)

#### Medical Significance

In discussing the medical significance of congenital rubella, several points need to be made.

- (1) Congenital rubella is a disease that involves many body organs and results in a wide range of defects. The physical findings are often accompanied by a variety of behavioral manifestations.
  - For proper management of the multihandicapped rubella child, facilities are required that go beyond just the deaf or deaf-blind child for which they are currently designed. Facilities are needed to deal with the multiple problems that may arise with certain children.
- (2) Congenital rubella is not only a multisystem disease, but a continuing disease. Therefore, long-term evaluations are necessary so that defects not evident at birth are not overlooked and so that the etiology of later problems can be identified.
- (3) Mental retardation is a major consequence of congenital rubella. In one study, 9 37 percent of infected children had varying degrees of retardation. This figure is remarkable when one considers that the expected prevalence in the general population is 2 to 3 percent.
- (4) To the families of rubella children, the disease has a powerful psychological and social impact. The presence of a rubella child has an effect on the entire family and their way of life.

It is clear that congenital rubella has a profound effect both on the affected child and the family. The need, therefore, to protect the pregnant female from infection by the use of appropriate vaccines is pressing. To this end, rubella vaccines have been available since 1969, and what follows is an indication of their effectiveness. Questions remaining to be answered regarding vaccine effectiveness are described in the section entitled "Outlook."

Rubella first became a nationally notifiable disease in 1966, when all states agreed to submit a weekly report to the Center for Disease Control (CDC) of the number of reported cases of rubella.

Congenital rubella syndrome (CRS) also became a notifiable disease in 1966. The National Registry for Congenital Rubella Syndrome was established in 1969 for the collection and analysis of detailed reports on all reported cases.

With the licensing of live, attenuated rubella virus vaccine in 1969, large-scale immunization campaigns were carried out in the United States to control rubella and, therefore, prevent the occurrence of congenital rubella syndrome. Prior to 1969, epidemiologic studies showed that rubella occurred primarily in young children who, in turn, were the primary source of infection for pregnant women.<sup>62</sup> The Public Health Service Advisory Committee on Immunization Practices<sup>44</sup> and the Committee on Infectious Diseases of the American Academy of Pediatrics<sup>2</sup> recommended vaccination of prepubertal children on a large-scale basis, reducing virus transmission and preventing congenital rubella, in short not subjecting adult women to the risks of intensive vaccination.

Since the introduction of the rubella vaccine into widespread use, the number of reported cases of rubella decreased steadily from 1969 (57,686 cases) to 1972 (25,501 cases), the lowest yearly figure since the beginning of nation-wide reporting. In 1973, 27,901 cases were reported to the CDC (9.5 percent over 1972). Most of the 1973 increase occurred in the first 28 weeks of the year with reports for the remainder of 1973 falling to 50 percent below those of the previous year. This downward trend has continued through the first 10 months of 1974 with a decrease of 60 percent below the corresponding period in 1973.

Since the introduction of the rubella vaccine, the number of reported CRS cases has declined since 1969. For the first 12 months following vaccine administrations, approximately 91 cases of CRS were reported. Over the next three 12-month periods, there were 54, 40, and 25 cases of CRS reported to the National Registry for Congenital Rubella Syndrome.

The steady decline over the past four years of reported rubella and congenital rubella syndrome cases is testimony and justification for the research on rubella virus disease that culminated in the development of several live attenuated vaccines. Although the results of the last four years are encouraging, only careful surveillance for rubella and CRS will reveal whether childhood vaccination programs continue to be effective in interrupting transmission of disease to pregnant women and in reducing fetal wastage and congenital malformations.

#### Historical Account

## Clinical Studies of Rubella and the Congenital Rubella Syndrome

Rubella was first described as a disease entity by de Bergen in 1752. The disease was reported to be distinct from measles by Veale in 1866. Rubella in children and adults is generally characterized as a mild exanthem which rarely

produces complications. However, as the result of an epidemic of rubella in Australia in 1939-1940, an unusual number of cases of congenital cataract were observed from areas throughout Australia. These findings prompted Norman Gregg in 1941<sup>19</sup> to conduct retrospective studies which associated for the first time maternal rubella with congenital malformations.

Shortly after Gregg's report two large-scale investigations were conducted in Australia. Swan et al.,49 studied congenital defects in neonates in southern Australia; in New South Wales a committee was appointed by the Director General of Health to investigate Gregg's observations. These investigations confirmed and expanded the original findings. The major congenital defects found were deaf-mutism, eye and heart disease, and possible mental defectiveness. In addition, there was evidence that the type of defect was related to the time when maternal rubella occurred; the highest risk was in the first trimester of pregnancy.

Following the original reports by the Australians, observers in other countries reported similar findings. Investigators approached the subject from different viewpoints according to their own specialities. Carruthers (1945) reported on severe deafness in the neonate. Dogramaci and Green (1947) described congenital heart disease. In 1949, Kamerbee reported on progressive deafness in the neonate, and Mutrux observed retarded myelinization as an effect of congenital rubella. Other investigators have studied the short-term and prolonged effects of congenital rubella in regard to temporal bone involvement and cataracts and neurological damage.

The United States epidemic of rubella in 1963-1965 confirmed and expanded on the defects observed previously. Rudolph et al., described heart and eye defects. Severe neurological disturbance was identified by Desmond et al., and in 1973, Rorke 47 described ischemic brain damage resulting from congenital rubella.

# Isolation, Identification, and Association of Rubella with Congenital Rubella Syndrome

The focus on rubella began with Gregg's observations in 1941 associating maternal rubella with congenital abnormalities. The development of laboratory techniques permitting specific diagnosis of rubella, however, did not occur until some 20 years later. The rubella virus was isolated in 1962, independently, by Weller and Neva<sup>61</sup> using human amnion cell culture and Parkman and associates <sup>38</sup> using African green monkey kidney cells. Subsequently *in vitro* studies by Plotkin <sup>48</sup> and Rawles <sup>45</sup> have shown that rubella-virus-infected cells undergo mitotic inhibition and chromosome breakage.

Selzer,<sup>50</sup> and Alford et al.,<sup>1</sup> were successful in isolating rubella virus from human fetal tissue, demonstrating for the first time a definitive etiologic agent of the congenital rubella syndrome. Monif and Sever<sup>35</sup> reported that rubella virus could be isolated from a variety of clinical specimens, including throat swabs, rectal swabs, cerebrospinal fluid, liver biopsy, and urine. In addition, several investigators<sup>20,36,46,48</sup> have isolated rubella virus from the lens of the

eye of congenitally infected fetuses. Hambridge et al.,20 reported that infants with congenital rubella syndrome excrete rubella virus in the urine for many months after birth, creating a potential source of contact infection.

Following the isolation of rubella virus in cell cultures, serological techniques to detect immunity to rubella were rapidly developed. Parkman et al.,40 described a virus neutralization test for detection of serum antibody. It was shown that following infection with rubella virus, neutralizing antibodies developed which persisted indefinitely conveying a high order of protection against reinfection. Other diagnostic serological techniques have also been described. Brown et al.,5 demonstrated that antibodies to rubella virus could be detected by the immunofluorescence test. Sever et al., 52 described a complementfixation test for detection of immunity to rubella. A most significant finding was reported by Stewart et al.,54 that rubella virus would agglutinate erythrocytes (hemagglutination) and that antibody to the virus would inhibit hemagglutination. As with neutralizing antibodies, hemagglutination-inhibition (HAI) antibodies appear at the end of the first week after symptoms of rubella, reaching peak levels 10-21 days after onset and persist indefinitely. Consequently, for diagnostic purposes, an acute serum sample is obtained at onset of symptoms, and after two weeks a convalescent serum sample is obtained. A fourfold rise in antibody titer is diagnostic. During the years 1967-1969, several independent investigators 13,18,22,29,51 conducted comparative studies of diagnostic techniques for detection of rubella. As a result, the HAI test has largely replaced the neutralization, complement fixation, and immunofluorescence tests for determining immunity status to rubella.

Tondury 58 reported that the placenta plays a role in maternal-fetal transmission of rubella. These observations were confirmed by Singer 55 and extended by Hancock, 21 who described the development of antibodies of the IgM type in the newborn resulting from in utero infection. In considering the diagnostic implication of this finding, it is significant to note that antibodies of maternal origin which cross the placenta are of the IgG type and the IgM antibody is of fetal origin. Both IgG and IgM antibodies can be measured by the HAI test. During the early postnatal months, the transplacentally acquired IgG is lost; however, IgM production is continued. Therefore, the persistence of HAI antibodies (IgM) through the first year of life supports the diagnosis of congenital rubella.

A significant refinement of the HAI test was described by Cooper et al. 10 They found that heparin-manganese chloride treatment of sera would remove non-specific inhibitors of rubella hemagglutination allowing a reliable detection of HAI antibodies.

In 1970, the Center for Disease Control (CDC) recognized the need for standardizing the rubella HAI test, and consequently formulated a standard protocol for the performance of the test based upon comparative studies among several laboratories.

## Development of Vaccines

Following the isolation of rubella virus, impetus was provided to develop a vaccine. Since rubella is generally a mild illness, the principal objective of the vaccine is to prevent infection of the fetus and the resulting congenital rubella syndrome.

In 1966, Parkman, Meyer, and associates  $^{39}$  attenuated rubella virus by 77 serial passages in primary African green monkey kidney (GMK) cell culture (HPV-77). The first clinical vaccine trials were by Meyer et al.,  $^{34}$  using HPV-77 rubella strain as a vaccine. Subsequently, other attenuated rubella strains have been derived from HPV-77, among which are HPV-77 passaged five times in duck embryo fibroblast cell culture (HPV-77DE5) and HPV-77 passaged 12 times in dog kidney cell culture (HPV-77DK12). In addition, an attenuated rubella virus strain (Cendehill) passaged 51 times in primary rabbit kidney cell culture has been developed.

Experimental animal models for studies of rubella have not been particularly rewarding, although congenital infection can be induced in the rhesus monkey. Prior to licensing of live attenuated rubella vaccine in 1969, studies were conducted in the rhesus monkey. The findings were that the vaccine virus did not cross the placenta.

Subsequent vaccine trials using HPV-77 rubella strain derivatives and Cendehill strain have demonstrated that attenuated rubella vaccines do confer seroconversion in approximately 95 percent of vaccinees. However, it is now apparent that, contrary to the findings in rhesus monkeys, attenuated rubella vaccine virus can cross the placenta and infect the human fetus. Vaccine virus has been recovered from fetal tissue after accidental vaccination of pregnant women <sup>17, 28, 42</sup> and purposeful inoculation of vaccine virus in women about to undergo planned abortions.<sup>4, 5, 9</sup>

In 1971, the United States Public Health Service initiated a "Herd Immunity" program. Because, in an epidemiological sense, children represent the major "herd" of susceptibles that the virus requires to maintain itself, a general inoculation of children ranging in age from one year to puberty was initiated. However, outbreaks continued with cases in other unvaccinated age groups. An epidemic occurred in 1971 in Casper, Wyoming, involving 1,039 persons primarily in two high schools and three junior high schools. These findings have prompted several authors to propose that the concept of herd immunity is invalid, and that outbreaks among adolescents and adults demonstrate the inadequacy of childhood vaccination. 3, 25, 26

## Contribution of Human Fetal Research to the Development of the Rubella Vaccine

Antecedent to the development of the rubella vaccine was the isolation of rubella virus in African green monkey cells in culture. With the inherent risk

to the fetus if infected with the wild-type virus, it was necessary to attenuate the virus so that the immunizing properties of the virus would be retained while at the same time eliminating the potential biohazardous nature of the rubella virus.

The initial association between rubella virus infection in utero and the development of congenital defects was derived from retrospective studies. The first definitive relationship between in utero rubella infection and what is termed the congenital rubella syndrome (CRS), occurred in 1963 when Selzer was able to isolate virus from fetal tissue. The involvement of the virus during gestation was expanded with the description of both the role of the placenta in maternal-fetal transmission by Tondury in 1966 and the isolation of IgM antibodies in the newborn by Hancock in 1968. It became clear, therefore, that infection by rubella virus during early pregnancy could result in transplacental passage of the virus with subsequent infection of the fetus. In utero infection could then result in one or a number of congenital defects observable at or several years after birth. This information could have been obtained only from studies of the gravid female and fetal tissue.

As mentioned in the first paragraph, although the vaccine for rubella is attenuated, it is still live. It, therefore, may still be hazardous to a susceptible fetus. To examine this possibility, the use of an experimental animal model system would be ideal, so that the experimental work and associated risk to humans would be unnecessary. To this end, the rhesus monkey was used. As with the human, infection with wild-type virus of the pregnant rhesus monkey results in transplacental passage of the virus with subsequent infection of the fetus. However, infection of the pregnant rhesus monkey with attenuated vaccine virus did not cross the placenta and, consequently, did not infect the fetus. If there is to be any value derived from an animal model system, the information should be able to be extrapolated to the human situation. However, a case has been reported by Phillips et al., in  $1970,^{42}$  of a young woman who discovered she was pregnant following voluntary entrance into a vaccination program. The vaccine was given at approximately three weeks gestation and the pregnancy terminated at eight weeks. Rubella was successfully isolated from the decidua. Subsequently, purposeful inoculation of pregnant women about to undergo planned abortions 4,59 and accidental vaccination of pregnant women 17,28 have resulted in recovery of vaccine virus from fetal tissue.

It appears, therefore, that reliance solely on information from animal model systems could lull one into a false feeling of security. One is forced to realize that the only way to either understand the biological behavior of a virus in humans or assess the risk to humans associated with vaccination, is to perform the studies in humans.

Had the fortuitous, accidental inoculation of pregnant women not been done and had the results from the rhesus monkey studies been used to conclude the safety of the vaccine in the pregnant female, exposure of pregnant women might have had tragic consequences for fetuses otherwise destined for normal, uncomplicated development.

### Effect of a Retrospective Ban on Fetal Research

From what has been discussed previously, human fetal research has been central to an understanding of the biological behavior of rubella virus and in the definitive association between in utero rubella infection and congenital abnormalities. Beyond this, it would have been impossible to define the relationship between gestational age and the consequences of rubella infection without human studies. There is no animal model system in which the development of the fetus in terms of size and function relationships is comparable to the human model.

By the use of the rhesus monkey, the potential teratogenic activity of the rubella virus vaccine was masked. This potential was realized only when the virus vaccine was administered accidentally to pregnant women or intentionally to pregnant women about to undergo planned abortion.

Also, because IgM antibody does not cross the placenta, the demonstration of IgM specific for rubella virus in cord serum indicated an immune response by the fetus following direct exposure to the rubella virus. This finding and its correlation with potential congenital rubella syndrome could have been made only by an analysis of the human model.

Although vaccine development could have been accomplished without the use of human subjects, the need for its development would have never been recognized without the human studies that definitively linked in utero rubella infection with congenital abnormalities.

It would be unfair if one did not concede that there are animal model systems for a variety of general viral infections, and that they themselves teach some remarkable biology. However, it would be equally unfair and perhaps tragic to conclude that the response of animals to a particular virus infection is the same as the response of the human to the same virus.

The original association between *in utero* rubella infection and congenital abnormalities was made either retrospectively or by examining fetal tissue from spontaneous abortions. Only the accidental vaccination of pregnant women or intentional vaccination of pregnant women about to undergo planned abortions fall into the area that is considered "research on living human fetuses." However, without these latter studies, the risk to the fetus attendant to vaccination of the pregnant woman would not have been recognized.

### Future Outlook

With regard to the future of rubella vaccination as an effort to prevent the congenital rubella syndrome, there are several areas of concern which need to be addressed. These areas of concern clearly dictate what needs to be done if further research is permitted.

- (1) Because pharyngeal shedding of the vaccine virus occurs, is there a risk to the fetus if unvaccinated pregnant women become infected from a vaccinated child?
- (2) Although spread of virus by this route may be uncommon, the relationship between a mother and her young vaccinated child may present a unique epidemiological setting.
- (3) Although vaccinated children with high levels of antibody are resistant to clinical evidence of rubella infection when challenged with wild-type virus, virologic evidence of reinfection is clear from isolation of challenge virus in pharyngeal secretions.

The question, therefore, is what is the threat to pregnant women upon contact with an asymptomatically reinfected child? In addition, are there other criteria of immunity that would be more useful in predicting susceptibility to reinfection following immunization?

It was thought from epidemiologic studies that the risk of rubella embryopathy is essentially confined to infants whose mothers have suffered clinically
manifest rubella during pregnancy. 31, 32, 49,53 It is reasoned, therefore, that
because vaccine-induced antibodies have reliably prevented clinical rubella after
natural or artificial challenge, the fetus of a mother, whose rubella immunity is
vaccine induced, would be protected, even if the mother were infected during pregnancy. However, recent evidence suggests that subclinical infection of the pregnant female with rubella virus can also result in congenital abnormalities.

The uniqueness of the rubella vaccine lies in its purpose; not to protect the recipient from disease, but rather to protect a hypothetical fetus, which may not be conceived for many years after vaccination, from infection and deformity. To this end, there has been no test of its effectiveness in accomplishing its purpose—the prevention of embryopathy. This question could be addressed by studies on women who, for a variety of reasons, would have their pregnancies voluntarily terminated. If further research were permitted, effects of virus challenge could then be evaluated on the aborted fetus.

Therefore, the use of rubella vaccine could be very effective, and its future bright, in preventing the congenital rubella syndrome. However, before its usefulness can be assessed with any degree of reliability, the above mentioned points need to be clarified. The only way to clarify these points is to study the human fetus. If further human fetal research is permitted, progress can then be made to determine if the rubella vaccine can accomplish its stated purpose—to prevent virus—induced embryopathies.

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### Principals Interviewed

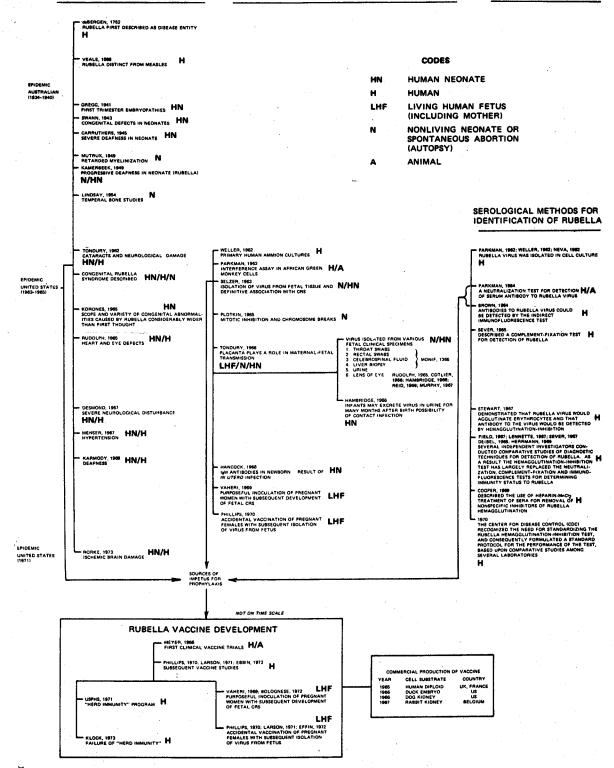
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#### CHARACTERIZATION OF RUBELLA AND CONGENITAL RUBELLA SYNDROME

## ISOLATION, IDENTIFICATION, AND ASSOCIATION OF RUBELLA WITH CONGENITAL RUBELLA SYNDROME (CRS)

DETECTION



#### AMNIOCENTESIS

## Medical Significance

Amniocentesis may be defined as a technique for obtaining amniotic fluid by inserting a needle into the amniotic cavity. This technique may be performed in the early second trimester for purposes of detecting genetic defects; for purposes of removing amniotic fluid, subsequently followed by the injection of an abortifacient for midtrimester abortion; or in the third trimester for the detection of hemolytic disease, fetal distress, or fetal maturity.

The intrauterine diagnosis of amniotic fluid and cells is assuming increasing importance in the management of developmental, metabolic, and cytogenetic defects in the fetus because fetal abnormality represents an important cause of perinatal mortality and morbidity. The primary indications for using amniocentesis can be categorized into fetal and maternal as shown by the following outline.

- A. Fetal indications for amniocentesis
  - 1. Sex-linked disease
  - Chromosomal abnormalities
  - 3. Inborn errors of metabolism
  - 4. Rh isoimmunization
  - 5. Fetal maturity determination
  - 6. Fetal distress.
- B. Maternal indications for amniocentesis
  - 1. Polyhydramnios
  - 2. Abortion
    - a. Therapeutic
    - b. Elective.

Each of the above indications will be described below.

Because amniocentesis is a surgical procedure, the procedure itself, its timing and possible complications are of great importance. Accordingly, such information has been included as an appendix to this report. Also included in the appendix is a discussion of amniography, ultrasonography, amnioscopy, and fetoscopy which are adjuncts to or outgrowths of amniocentesis.

#### Fetal Indications for Amniocentesis

1. <u>Sex-Linked Disease</u>. It has been shown that the cells in the amniotic fluid, unless contaminated by maternal blood, are of fetal origin.<sup>47,74</sup> These fetal cells can be examined to determine the sex of the fetus, which is of major importance if the familial history indicates that the pregnancy involves the possibility of a sex-linked genetic disorder through familial history. Sex determination is useful in genetic disorders because the disorder is associated with the recessive gene located on the human X-chromosome. The more common X-linked diseases are shown in Table 1.

Table 1. Common X-Linked Disorders

- 1. Hemophilia
- 2. Duchenne's Muscular Dystrophy
- 3. Nephrogenic Diabetes Insipidus
- 4. Hunter's Syndrome
- 5. Lesch-Nyhan Syndrome
- 6. Fabry'e Disease

Of these X-linked disorders, only the Lesch-Nyhan syndrome, Hunter's syndrome, and Fabry's disease can be diagnosed *in utero* via amniocentesis. Since the mutant gene for the sex-linked disease is carried on one of the X-chromosomes of the female, transmission of the recessive X-linked disease is from a female carrier to an affected male. Thus, a woman carrier transmits the mutant gene to half of their daughters (also carriers) and to half of their sons, who will be affected.<sup>84</sup> As a result of these recessive sex-linked diseases and their manifestations, the diseases are confined almost exclusively to the male population. Amniocentesis serves a very important need in the detection of these male fetuses, who are being carried in suspected women carriers, because they have a 50 percent risk of being affected.<sup>59</sup>

2. Chromosomal Abnormalities. Numerically, the major indication for amniocentesis in the second trimester of pregnancy is to identify chromosomal anomalies. The more common chromosomal anomalies which can be detected by amniotic fluid cell cultures and karyotyping are identified in Table 2.

Chromosomal anomalies can reflect either an absence of chromosomal material (Turner's syndrome) or an excess as shown by the other abnormalities. In trisomies, one of the explanations for a chromosomal gain is nondisjunction, or

a failure of the gamete to split equally during the meiotic division. However, if nondisjunction occurs during mitosis and after fertilization, the result is an individual with cells of two or more different chromosomal constituents, i.e., a chromosomal mosaic.<sup>56</sup>

Table 2. Chromosomal Aberrations Detectable by Amniotic Fluid Cell Culture and Karyotyping 54

1. Down's Syndrome

Trisomy 21
Translocation D/G

- Turner's Syndrome (XO)
- Klinefelter's Syndrome (XXY)
- 4. Trisomy 18 (E group) or Edward's Syndrome
- 5. Trisomy 13-15 (D group) or Pataus' Syndrome
- 6. Cri du chat Syndrome 46 (Bp)
- 7. XXX females
- 8. XYY males

Significant chromosomal abnormalities have been estimated to occur about once in every 200 live births. Over 700,000 infants with such abnormalities are being born each year worldwide. Of this number, 20,000 such infants are born in the United States alone. The most frequently encountered chromosomal aberration is mongolism (Down's syndrome), with the incidence of this abnormality dependent upon the age of the mother. With such a large number of infants being born each year with a chromosomal abnormality, the use of amniocentesis to diagnose these abnormalities in utero, especially in high risk patients, is becoming an accepted clinical practice.

3. <u>Inborn Errors of Metabolism</u>. The metabolic diseases (inborn errors of metabolism) may be diagnosed from amniotic fluid, cultured amniotic fluid cells, or uncultured amniotic fluid cells. As Milunsky points out, <sup>84</sup> "Progress has basically occurred in a stepwise fashion from the study of disorders in vivo to the delineation of specific abnormalities in tissues, to the recognition of these abnormalities in cultured skin fibroblasts, leukocytes, and finally cultured amniotic fluid cells."

Critical to the prenatal diagnosis of these metabolic diseases is the assumption that cultured skin fibroblasts or amniotic fluid cells will continue to demonstrate the specific characteristics of that disease throughout successive cultures. This is critical because the metabolic diseases are usually identified by a particular deficient or reduced enzyme activity or by a specific accumulating storage substance. The assumption that cultured amniotic fluid cells do retain their enzymatic activity through successive cultures appears to be valid. Thus, the metabolic disorders identified to date, involving either amniotic fluid, cultured amniotic fluid cells or noncultured amniotic fluid cells, number 16 with the possibility of identifying 15 more. These are given in Tables 3 and 4. A more recent estimate suggests more than 40 biochemical disorders can now be diagnosed in utero.

Table 3. Metabolic Disorders Diagnosed Prenatally To Date<sup>54</sup>

		Disorder	Diagnosis Made From
1.	Diso	rders of Lipid Metabolism	
	(a)	Gm, gangliosidosis (Tay-Sachs)	Noncultured amniotic fluid cells Cultured amniotic fluid cells Amniotic fluid
	(b)		Cultured amniotic fluid cells
1	(c)	Krabb's disease	Cultured amniotic fluid cells
	(d)	Niemann-Pick disease, Type A	Cultured amniotic fluid cells
1	(e)		Cultured amniotic fluid cells
	(f)	Fabry's disease	Cultured amniotic fluid cells
2.	Muco	polysaccharidosis	
	(a)	Hurler's syndrome	Cultured amniotic fluid cells Amniotic fluid
3.	Amin	oacid Disorders	
	(a) (b)		Cultured amniotic fluid cells Amniotic fluid
4.	Diso	rders of Carbohydrate Metabolism	
	(a)	Glycogen storage disease Type II (Pompe's disease)	Cultured amniotic fluid cells Amniotic fluid
	(b)	Galactosemia	Cultured amniotic fluid cells
5.	Misc	ellaneous	
]	(a)	Adrenogenital syndrome	Amniotic fluid
	(b)		Cultured amniotic fluid cells
	(c)		
		deficiency	Cultured amniotic fluid cells
	(d)	Cystic fibrosis	Cultured amniotic fluid cells
	(e)	Marfan's syndrome	Cultured amniotic fluid cells

Table 4. Metabolic Disorders in Which Prenatal Diagnosis Should be Possible 54

		Disorder		Enzyme Located In
1.	Disord	ers of Lipid Metabolism		
		m <sub>l</sub> ganliosidosis efsum's disease	Amniotic	amniotic fluid cells fluid amniotic fluid cells
2.	Mucopo	lysaccharidosis		
	(a) H	unter's syndrome	Cultured Amniotic	amniotic fluid cells fluid
3.	Aminoa	cid Disorders		
	(b) C (c) H (d) H	rginosuccinic aciduria ystinosis omocystinuria yperammonemia, Type II rnithine-α-ketoacid trans- aminase deficiency	Cultured Cultured Nonculture	amniotic fluid cells amniotic fluid cells amniotic fluid cells red amniotic fluid cells amniotic fluid cells
4.	Disord	ers of Carbohydrate Metabolism		
	(b) G	ucosidosis lycogen storage disease, Type III lycogen storage disease,	Cultured	amniotic fluid cells
	,	Type IV annosidosis 6PD deficiency	Cultured	amniotic fluid cells amniotic fluid cells red amniotic fluid cells
5.	Miscel	laneous		
		rotic aciduria eroderma pigmentosum	Amniotic Cultured	fluid amniotic fluid cells

Although each one of these metabolic diseases is relatively rare in the general population, some inherited disorders of metabolism may occur with an estimated frequency as high as one in 100 live births. In addition, once there is an affected individual in a particular family, the condition becomes prevalent in that family because most of the inborn errors of metabolism are inherited as autosomal recessives and the risk of an affected offspring is, therefore, one in four in a given sibship. Thus, if both parents were carriers of a specific inborn error of metabolism, the fetus could be monitored via amniocentesis. Eventually, in some of the inborn errors of metabolism, therapy for the fetus might be theoretically possible, either directly or via the mother.

4. Rh Isoimmunization. Ever since the demonstration of the relationship between pigment content of the amniotic fluid and the severity of hemolytic disease of the newborn, amniotic fluid analysis has become a standard procedure in the management of the rhesus sensitized pregnant woman. There is little argument that this observation popularized amniocentesis in the United States. However, with the development of Rh vaccine, hemolytic disease in the newborn is now almost totally limited to Rh-negative women who were sensitized prior to the availability of Rh vaccine and to the small percentage (2 or 3 percent) of Rh-negative women who become sensitized without apparent cause.

Maternal isoimmunization presents a varied pathologic and clinical manifestation of the hemolytic disease syndrome in either the fetus or newborn. When maternal antibodies (Rh-positive) gain access to the fetal circulation, they are adsorbed upon the Rh-negative erythrocyte. These adsorbed antibodies act as hemolysins which cause the breakdown of the fetal red blood cells with the resultant erythroblastotic fetus.

With the discovery that the height of the spectrophotometric peak at  $450~\text{m}\mu$  (corresponding to unconjugated bilirubin) correlated well with the severity of the fetal hemolytic condition, it became possible to treat the erythroblastotic fetus via intrauterine blood transfusions. Because the intrauterine determination of the fetal blood groups is possible, it is now possible to match the fetus's blood group with the planned intrauterine blood transfusion.

A recent advance in regard to intrauterine transfusions has been the association of the estriol concentration in amniotic fluid with fetal well-being. It has been demonstrated that an increase in amniotic fluid estriol levels correlates well with increased fetal survival. In conclusion, the role of amniocentesis in the past treatment of erythroblastosis fetalis is apparent, but the value of the technique in this instance should be decreasing with the advent of the vaccine.

5. <u>Fetal Maturity Determination</u>. Another indication for amniocentesis is to determine the gestational age, since there are conditions where it is desirable to terminate the pregnancy prematurely to assure the viability of that fetus. The determination of gestational age would be warranted in a diabetic pregnancy, in erythroblastosis fetalis, in severe preeclampsia, or in a prolonged pregnancy.<sup>46</sup>

Other methods such as examining the external uterus, ultrasonography, fetal electrocardiograms, placental biopsies, measurements of the urinary estriol excretion, amniography, fetal encephalography, and auscultation of the fetal heart have not always provided the desired information about the fetus. As a result, recent attention has been directed toward the amniotic fluid for providing an indication of fetal maturity. The four principal methods which have been used to date include:

- (1) The spectrophotometric analysis of amniotic fluid for bilirubin
- (2) The measurement of amniotic fluid creatinine

- (3) The detection and staining of exfoliated fetal cells from amniotic fluid
- (4) The lecithin/sphingomyelin ratio in amniotic fluid.

The association of fetal maturity and the disappearance of bilirubin in unsensitized pregnancies was noted by Mandelbaum et al. 76,77 They observed a precipitous decline and disappearance of the absorbance bulge at 450 mµ at 36 to 38 weeks' gestation. The second method, involving creatinine determination in the amniotic fluid, has shown that with increasing fetal age, there is also an increase in the amniotic fluid creatinine. The concentration of creatinine remains almost constant or gradually increases from 32 to 36 weeks, after which there is a more marked increase. Thus, in contrast to creatinine, the bilirubin concentration is highest in midtrimester and thereafter decreases in a linear manner until it virtually disappears at 36 or 37 weeks. Feecently, Foulds and Pennock have shown that the creatinine method is probably unreliable for estimating fetal maturity in clinical practice.

A third method for determining fetal maturity is to stain the exfoliated cells obtained in amniotic fluid. The lipid-containing cells of the amniotic fluid, upon staining with Nile blue sulfate, are seen as orange-colored cells. The concentration of these cells usually increases markedly after 36 weeks gestation, and the presence of greater than 50 percent of the cells stained orange usually indicates the gestation is at term.<sup>94</sup>

A fourth method for determining fetal maturity involves determining the lecithin/sphingomyelin ratio in amniotic fluid. This ratio is of importance in defining the fetus's pulmonary maturity since a frequent consequence of premature birth is the respiratory distress syndrome. In 1971, Gluck et al., suggested that surface-active phospholipids may come from the fetal lung. In addition, he suggested that there are two metabolic pathways for lecithin production and that the more mature and stable pathway becomes dominant about the thirty-fourth to thirty-fifth week. This pathway is associated with an increase in the amount of lecithin in relation to sphingomyelin found in the amniotic fluid. Thus, if the lecithin/sphingomyelin ratio is 2.0 or greater prior to delivery, it is rare to have a neonate die from hyaline membrane disease. On the other hand, if the level is below 1.5, there is a 50 percent chance (without special neonatal care) that the neonate will die from hyaline membrane disease, since the incidence of hyaline membrane disease decreases markedly after 34 to 35 weeks' gestation.

6. Fetal Distress. For many years, the presence of meconium in the amniotic fluid was associated with fetal distress. However, transabdominal amniocentesis for the detection of meconium staining of the amniotic fluid did not become popular until 1962.65 Even then there was limited use of meconium staining as an indicator of fetal distress because the mechanism provoking the release of meconium by the fetus was not fully understood. Thus, a meconium-stained amniotic fluid is not a very accurate diagnostic procedure prior to labor but can be a reliable screening method for higher risk cases.65

In 1962, Saling $^{103}$  introduced the technique of amnioscopy. Its value was in observing the amniotic fluid directly for meconium staining in certain

high-risk pregnancies. Thus, compared to amniocentesis, it was more convenient to use but it suffered from the disadvantage of inability to assess the color as accurately as via amniocentesis. The yellow color of bilirubin is very obvious, but the color may be confused with hemoglobin so that spectrophotometric analysis must be the basis of clinical judgment.<sup>38</sup>

## Maternal Indications for Amniocentesis

The maternal indications for amniocentesis are polyhydramnios 18 and either a therapeutic or elective abortion. Polyhydramnios refers to the excessive accumulation of fluid in the amniotic cavity. At term, the normal volume of amniotic fluid is 1.0 to 2.0 liters. However, in polyhydramnios, the volume of fluid is greater than 2.0 liters and is often excessive. More importantly, the incidence of fetal malformations, especially those of the central nervous system and gastrointestinal tract, are extremely high when polyhydramnios is present. There is no satisfactory treatment for polyhydramnios other than removal of the excess fluid. This can be accomplished via abdominal amniocentesis and the main objective is to relieve the patient's distress or to avoid the uterine dysfunction which usually accompanies labor in the presence of hydramnios.56 However, withdrawal of fluid via amniocentesis may lead to premature labor.

Although amniocentesis as a procedure is usually thought of in terms of removing amniotic fluid, there are situations in which fluid is instilled directly into the amniotic cavity, either for diagnostic (amniography) or therapeutic purposes. This might be the case when an abortion is considered. In the former case, amniocentesis might be performed twice, once to diagnose a suspect genetic disease and again to withdraw large amounts of amniotic fluid that is subsequently replaced by an abortifacient to induce an abortion. In the latter case, no prior amniocentesis need be performed, but the procedure itself is identical to that described for a therapeutic abortion.

As can be seen from the above, there are many indications for using amnio-centesis in prenatal care, either as a diagnostic aid or for carrying out a therapeutic procedure. The risks and complications associated with amniocentesis are relatively rare (the current work estimate is 1 to 2 percent), but these risks and complications must be weighed against the indications for using the procedure.

An indirectly associated parameter which also must be evaluated in employing amniocentesis is the accuracy of the diagnostic technique being performed. The diagnostic accuracy of a test can be affected by the cell origin, cell growth in culture, or the culture medium.84,102,106

Difficulties can be encountered in the utilization of amniotic fluid per se. These difficulties include (1) the possibility of maternal blood admixture which could lead to errors in the interpretation of many different enzyme analyses, (2) the amniotic fluid may become contaminated with bacteria, (3) variations in amniotic fluid cell number and viability, especially the uncultured cells, may lead to an unreliable diagnostic test, (4) changing protein content in the amniotic fluid with gestational age makes a biochemical analysis difficult if it requires expression per milligram of protein, and (5) the unknown

quantity and quality of fetal urine in early gestation further complicates the use of amniotic fluid alone in making a prenatal diagnosis.84

Some of the more common difficulties encountered in working with cells from amniotic fluid are as follows: (1) at different stages of gestation, the cells may show enzyme activity changes; (2) cultured cells divide every 16 to 30 hours, in contrast to the generation time of 30 to 90 days in the living organism; (3) cyclical changes in enzyme activity have been observed; (4) metabolic activity of the cells may be profoundly affected during the initial establishment of a culture, since there is a lag phase in establishing a culture; (5) long periods of time may be required to grow sufficient amniotic fluid cells; (6) the culture medium and serum used to grow the cells may effect the cellular enzyme activity; and (7) since trypsin remains the most effective agent for cell dissociation aimed at primary isolation or passage of cells in vitro, the toxic effects of trypsin must be taken into account.84

It would appear that even with all these factors which might affect the accuracy of the prenatal diagnosis, the accuracy of diagnosing a particular genetic defect has been relatively high, i.e., greater than 90 percent.89 another study, only ten errors were made in a total of 1,633 cases studied.84 Of these ten errors, the fetal sex was inaccurately diagnosed in seven cases, but none of these cases involved X-linked diseases. However, fetal sex determination is now almost 100 percent diagnosable with the advent of the fluorescent acridine derivative for staining chromosomes which now complements the Barr-body technique.

## An Example of the Impact of Amniocentesis In Diagnosing a Significant Congenital Disorder

Although there are minimal risks and complications associated with amniocentesis, as pointed out in an earlier section, the impact of amniocentesis as a diagnostic aid in the management of congenital disorders is significant.

Of the known chromosomal aberrations, the most frequently encountered is Down's syndrome or mongolism. This abnormality has an especially high risk with advancing maternal age. Bodensteiner and Zellweger14 performed a study on mongolism in 1971 in which they calculated the incidence of mongolism for the state of Iowa (approximately 3 million population with 50,000 live births/year). In their study, five groups of women were identified with a high risk for mongolism (Table 6).

Groups of Women Identified as Possessing Table 6. A High Risk for Down's Syndrome 14

- Women 40 years of age and over 1.
- Women 35-40 years of age with a previous mongoloid child 2.
- 3. Mongoloid women
- 4. Parental mosaicism with a 21 trisomic cell population
- Familial translocation (G/G and D/G)

Of the above five groups, only the first two contribute significantly to the incidence of mongolism. In the first group (women 40 years of age and over), they found that about 2 percent of the children born would be mongoloid. In this group there was an average of 1000 births per year (with a defect incidence rate of 1 per 50 live births), which meant 20 cases of mongolism could be detected in this group per year.

In the second group, the mongolism incidence of all mothers in the age group (35-39 years) is approximately 1 per 250 live births. However, if the mother has given birth previously to a mongoloid child, the incidence increases to 1 per 80 live births. In the Iowa study, there were approximately 6,000 births out of the total 50,000 live births per year which were born to mothers in the age group (35-39 years). Of this total only 40 mothers had previously given birth to a mongoloid child so that every two years one case of mongolism could be detected in this group.

There are, however, many practitioners who feel that even mothers 35-39 years old should be considered in the "high risk" group and should not simply be confined to a mother in this age group who has previously given birth to a mongoloid child. If one accepts this statement, then in the Iowa study, there would have been 20 more cases of mongolism detected since the incidence for all mothers in this age group is 1 per 250 live births.

In summary, Bodensteiner and Zellweger<sup>14</sup> have shown that according to their classification, the advance detection of 20 cases of mongolism per year would be possible via amniocentesis. If group two were expanded to include all mothers 35-39 years of age, a total of about 45 cases of mongolism could be detected. Extrapolation of the Iowa statistics, which are probably consistent with the national average, would suggest that approximately 2,880 children with Down's syndrome could be detected each year (assuming 3.2 million births/year).

It has been estimated that if these defective children were institution-alized, the cost to society each year would be \$17,500,000 (\$6100/year/case)<sup>84</sup> while the cost of routinely providing amniocentesis and prenatal genetic studies to the 448,000 patients which would produce the 2,880 children with Down's syndrome would be approximately \$67 million. If all positively diagnosed cases were aborted at a cost of \$400 per procedure, the additional cost would be about \$1.2 million. However, if one assumes an average life expectancy for the defective child of 50 years, the cost of caring for 2,880 individuals over that time span would be almost \$875 million dollars. Thus, each year with the birth of a similar number of mongoloid children, a future commitment of \$875 million per year is created, versus \$68.2 million per year to diagnose all high risk pregnancies and abort those positively diagnosed. It should be kept in mind that these figures are for Down's syndrome only and that there are about 6,100 seriously defective offspring per year based on 3.2 million live births per year.<sup>84</sup>

#### Historical Account

Amniocentesis as a case differs from the others studied here in that it is a procedure used primarily as a prelude to a diagnostic procedure, whereas the other cases involved the development of a therapeutic or prophylactic treatment. Comparatively little research in the strictest sense has been done on amniocentesis as a procedure. In view of this, we have chosen to emphasize the key ancillary procedures which have been developed and used in conjunction with amniocentesis and the use and application of the procedure as it relates to fetal diagnostic tests and therapeutic methods.

## Key Ancillary Procedures

In 1882, Schatz<sup>104</sup> introduced the concept of puncturing the amniotic cavity by the transabdominal route for therapeutic purposes, i.e., the removal of fluid in polyhydramnios. Thus was born the idea of amniocentesis. The first ancillary procedure to be used in conjunction with amniocentesis occurred in 1930 when Menees et al.,<sup>80</sup> injected strontium iodide into the amniotic cavity. By employing amniocentesis, they developed amniography which permitted the visualization of fetal soft parts and localization of the placenta. They also noted that amniography could be of value in diagnosing placenta praevia and determining the exact relation of the placenta to the cervical canal.

Although meconium staining of the amniotic fluid had been known to be a sign of fetal distress, the use of amniocentesis for the detection of meconium staining did not become popular until Kubli's work in 1962. In addition to using amniocentesis for identifying meconium stained amniotic fluid, Saling, 103 in 1962, introduced amnioscopy. This technique employed an endoscope that could be introduced through the dilating cervical canal at term. After passage through the cervical canal, the amniotic fluid could be examined directly through the intact membranes to demonstrate the presence of meconium and monitor fetal distress. However, it suffered from the major disadvantage that fluid was not collected via this procedure. Thus, one could not perform biochemical or photometric evaluations on the amniotic fluid.

A recent outgrowth of amnioscopy, fetoscopy—the transabdominal insertion of an endoscope into the gravid uterus—has been developed. This useful diagnostic tool allows the clinician to visualize the intrauterine contents and make clinical diagnoses based on the information obtained.

Intrauterine blood transfusions for treatment of fetal hemolytic disease is an ancillary procedure developed as a consequence of amniocentesis. However, this topic is discussed under a subsequent section on Rh isoimmunization.

The demonstration by Gottesfeld in 1966<sup>55</sup> that ultrasound could be used to localize the placenta prior to amniocentesis will probably be one of the key developments in reducing the risks and complications associated with amniocentesis. In their study, the use of ultrasound correctly predicted the position of the placenta in 97 percent of the cases.

## Significant Events as Regards Diagnostic Tests and Therapeutic Methods

Rh Isoimmunization. The chronological events which would relate directly to amniocentesis in diagnosing and treating fetal hemolytic disease was initiated by the discovery of the Rh antigen, so called because it was found originally on the red cell of the rhesus monkey, by Landsteiner and Weiner. In 1940, they reported that the erythrocytes of 85 percent of a group of Caucasians reacted positively with the antirhesus serum, whereas 15 percent did not. Thus, the former group contained the antigen and were termed Rh positive while those that did not, were referred to as Rh negative.

In 1956, Bevis<sup>11</sup> postulated that the severity of hemolytic disease could be determined by measuring the "blood pigments" present in amniotic fluid. The specific blood pigments measured were bilirubin and oxyhemoglobin and their concentration in the amniotic fluid indicated the degree of hemolysis which was occurring in the fetus.

When Coombs et al.,<sup>21</sup> in 1956 introduced a technique for detecting blood group antigens on epidermal cells, by specific mixed agglutination, they opened a pathway for the detection of fetal antigens via amniotic fluid cells. That same year, Fuchs et al.,<sup>48,44</sup> developed a method for the determination of the fetal ABO blood groups in amniotic fluid. They found that it was possible to detect A and B antigens in the amniotic fluid cells which were of fetal origin.

In 1957, Walker 123 expanded on the clinical application of Bevis' technique by examining the spectral absorption curves of amniotic fluid in rhesus sensitized patients. He claimed that it was possible to predict which babies were affected by hemolytic disease provided the amniotic fluid was obtained prior to the thirty-fifth week. This development led to Liley's findings 69 in 1961, where he confirmed Bevis' and Walker's techniques, that the spectral absorption curve of liquor amnii presents diagnostic features in hemolytic disease and shows that the size and progress of the characteristic peak at 450 m $\mu$  reflects the severity of anemia. In addition, Liley was able to show that the size and trend with maturity of the 450 m $\mu$  peak provided an indication of the severity of anemia and prognosis for the fetus.

The refinement in prognostic precision of pregnancies complicated by rhesus sensitization led Liley in  $1963^{70}$  to try the first intrauterine transfusion of blood into the fetal abdomen.

As a result of the successful intrauterine transfusions, Liley in 1965<sup>71</sup> suggested that Rh isoimmunization could be readily managed via amniocentesis and intrauterine fetal blood transfusions. His experience suggested "that fetal transfusion could ensure survival of some 70 percent of otherwise fatally affected erythroblastotic babies, but that survival falls to zero if treatment is delayed until the development of gross hydrops and ascites." This became a landmark development in the history of amniocentesis.

Genetic Defects. In 1949, Barr and Bertram<sup>8</sup> demonstrated that neurons obtained from the brain, spinal cord or sympathetic ganglia of mature cats of

both sexes could be readily sorted into two groups even without prior knowledge of the sex. This observation set the stage for human sex determination in fetal cells.

In 1955, Marberger et al., 78 and Moore and Barr 87 demonstrated that sex chromatin could also be detected in desquamated cells from mucous membranes. This discovery precipitated the idea that the cells of the amniotic fluid might indicate the sex of the fetus. Toward the end of 1955, within a period of five weeks, four groups of investigators independently developed the antenatal determination of fetal sex in amniotic fluid. 111,110,47,74 This development was to be very significant as regards the use of amniocentesis for the prenatal diagnosis of sex-linked diseases. Finally, in 1960, Riis and Fuchs 99 obtained amniotic fluid for the antenatal sex determination from two mothers who were carriers of an X-linked disease (hemophilia). Although, in both cases, the fetal sex determination on the amniotic fluid indicated a girl fetus, this was the prelude to using amniocentesis to diagnose a prenatally heritable disease.

The first inborn error of metabolism was diagnosed via amniocentesis in Jeffcoate et al., 63 showed that the adrenogenital syndrome could be ana-1965. lyzed in the amniotic fluid via the concentration of pregnanetriol at term from affected pregnancies. However, a more recent study 82 has shown that the disease cannot be predicted during early or midpregnancy. Then, in 1966, another major landmark occurred in the history of amniocentesis. This was the successful culturing of fetal amniotic fluid cells by Steele and Breg<sup>112</sup> and Thiede et al., 117 in sufficient quantity to permit karotyping of the cells. In addition, this would pave the way for studying other inborn errors of metabolism since many of these diseases would be identified by measuring the absence of enzyme activity in cultured cells. In addition, during that same year Danes and Bearn<sup>25</sup> demonstrated that mucopolysaccharide storage disorders could be identified by measuring the intracellular metachromasia in tissue cultures from patients suffering from this disease. This would open the way for the intrauterine diagnosis of these and related disorders.

In 1967, Jacobson and Barter<sup>62</sup> published an article which postulated the management of genetic defects via amniocentesis. They made the intrauterine diagnosis of a D/D translocation carrier at 17 weeks gestation after they had shown the mother to be a D/D translocation carrier. In their study, although the D/D translocation had been identified and the fetal cells karotyped, the mother elected to carry the pregnancy to term. Postnatal studies confirmed the correct diagnosis of the fetus, i.e., a D/D translocation carrier. Earlier, two simultaneous abstracts by Jacobson<sup>61</sup> and Turner<sup>120</sup> had shown that the prenatal diagnosis of chromosomal translocations could be of definite assistance in the management of genetic defects.

These studies were followed by the first therapeutic abortion of a Down's syndrome fetus by Valenti et al., in 1968. The fetal cells, obtained from a balanced carrier of a D/G chromosome translocation during the eighteenth week of pregnancy, were analyzed after 22 days of *in vitro* cultivation. The karotypes indicated a D/G fusion chromosome characteristic of Down's syndrome. The pregnancy was interrupted on this basis and a male fetus was delivered which showed the dermatoglyphic and anatomic changes compatible with the prenatal diagnosis.

That same year Nadler 88 successfully diagnosed Down's syndrome at 10 weeks' gestation by chromosome analysis of cultivated amniotic fluid cells obtained just prior to the therapeutic abortion.

As can be seen from the foregoing paragraphs, the use of amniocentesis in the prenatal diagnosis of genetic defects was expanding rapidly. Additional significant events in 1968 and 1969 included the following: (1) the in utero identification by Fujimoto et al., 49 of a fetus heterozygous for the Lesch-Nyhan syndrome, an X-linked metabolic disease. This was identified via cultured amniotic fluid cells; (2) the first diagnosis of an inborn error of metabolism (galactosemia) in cultured amniotic fluid cells by Nadler.88 The significance of this development was that the inborn error was identified by showing the absence of normal enzyme activity in the cultured cells; 43 (3) the first intrauterine diagnosis of Hurler's and Hunter's syndrome in cultured amniotic fluid cells by Fratantoni et al.40 Both of these syndromes involve genetic disorders of mucopolysaccharide metabolism with Hurler's syndrome being an autosomal recessive disease and Hunter's syndrome, an X-linked recessive disease; and (4) the in utero detection of Type II glycogenosis (Pompe's disease) by Nadler and Messina 91 on uncultured amniotic fluid cells. They point out that the ability to use uncultured cells for the detection of enzyme activity (i.e., the absence of  $\alpha$ -1,4-glucosidase activity in fetal cells) permits rapid identification of the affected fetus, drastically reduces the time interval between amniocentesis and diagnosis, and obviates the need for specialized tissue culture technique.

The use of amniocentesis in prenatal genetic diagnosis expanded rapidly during the sixties. The significant events since 1969 include the following:

- (1) The prenatal diagnosis of Tay-Sachs disease (a Gm<sub>2</sub> gangliosidosis disease) by Schneck et al., in 1970.<sup>104</sup>
- (2) The demonstration by Holenberg et al.,58 in 1971 that human fetuses could synthesize hemoglobin A suggested that genetic counseling for disorders of hemoglobin (i.e., sickle cell anemia and homozygous beta thalassemia) might be possible. Kan et al.,64 in 1972 extended this observation by detecting the sickle cell trait in a 15-week-old fetus of a mother who also had the sickle cell trait. In their studies, blood was either obtained from the umbilical cord of the fetus at the time of therapeutic abortion or from the placenta, obtained accidentally during amniocentesis for Rh incompatibility at the end of the eighth month of pregnancy.
- (3) The discovery by Brock and Sutcliffe  $^{15}$  in 1972, that a correlation exists between a raised  $\alpha$ -fetoprotein level in the amniotic fluid and severe neurological defects in the fetus.

Fetal Maturity. Amniocentesis has been used for determining fetal maturity and the significant chronological events include the following:

(1) The method of Brosens and Gordon in 1966<sup>16</sup> for estimating fetal maturity via the cytologic examination of the amniotic

fluid. They were able to determine the percentage of amniotic fluid cells, i.e., cells containing lipid substances stained orange when exposed to Nile blue sulfate. An increase in the percentage of cells taking this stain was observed after 38 weeks' gestation.

- (2) The association of fetal maturity and the disappearance of bilirubin in unsensitized pregnancies by Mandelbaum et al., in 1967. They observed a precipitous decline and disappearance of the absorbance bulge at 450 mµ at 36 to 38 weeks' gestation.
- (3) Another development in 1967 was the relationship demonstrated by Pitkin and Zwrick 96 between the amniotic fluid creatinine concentration and gestational age. With increasing fetal age there was also an increase in the amniotic fluid creatinine.
- (4) An association between gestational age and osmolality was made by Miles and Pearson in 1969.83 They reported a downward trend in osmolality with gestational age and stated that an osmolality less than 250 milliosmoles/L was suggestive of fetal maturity.
- (5) The discovery by Gluck et al.,<sup>51</sup> in 1971 that the respiratory distress syndrome could be detected via amniocentesis. Their studies showed that changes in phospholipids in amniotic fluid reflect those changes occurring in the developing fetal lung. A sudden increase in the lecithin concentration after 35 weeks indicates maturity of the pulmonary alveolar lining, and the respiratory distress syndrome should not occur if the fetus is born at this time.

## Contribution of Human Fetal Research to Amniocentesis

#### Technique

In the early usage of amniocentesis on humans, it soon became apparent that the transcervical and transvaginal (both fornix anterior and fornix posterior) approaches to the amniotic sac were unduly traumatic, unless performed at term.<sup>29</sup> The most significant complications were induced premature labor and/or hemorrhage. More recent investigation has confirmed these observations.<sup>34,45,50,86,108</sup> Consequently, transabdominal invasion of the amniotic sac became the method of choice to withdraw amniotic fluid. As a direct result of human investigations, this method has been refined in several areas as described below. These refinements have resulted in what is now an accepted medical procedure when indicated, with minimal risk to both the mother and the fetus.<sup>19</sup>

Before the introduction of ultrasound, palpation<sup>5</sup> was the generally accepted method of determining fetal and placental position, although amniography was and still is used in some cases, usually during the third trimester. It soon became evident that a fairly high degree of technical competence was required to avoid complications such as placental or fetal puncture. The operation should be performed by an experienced obstetrician. The need for strict aseptic procedures to avoid various types of sepsis became apparent. Some advocate virtual surgical type conditions even though the operation is routinely performed as an outpatient or office procedure. The optimum site for puncture is still not agreed upon but as pointed out before, the prime criterion is avoidance of the placenta and fetus.

The type and degree of sharpness of the needle has resulted from human evaluation. It is generally agreed that a needle with a relatively obtuse angled tip and low degree of hone is useful in ascertaining the layers of tissue being traversed and determining when the amniotic cavity is entered. Many recommend the use of a 22-gauge or smaller needle to minimize abdominal trauma while others advocate an 18-gauge needle to traverse the maternal skin and subcutaneous tissue. A 20-gauge needle is then inserted through the larger needle into the amniotic cavity. The latter procedure supposedly further reduces the possibility of sepsis.

The introduction of ultrasonography in obstetrics, 30 almost simultaneously with midtrimester amniocentesis, inevitably resulted in the use of this method to localize the placenta and fetus. Palpation for this purpose is often difficult at 14 to 18 weeks when amniotic taps are made for diagnosing congenital disorders. Many now use ultrasound routinely prior to amniocentesis in order to minimize procedural risks.

Amnioscopy and fetoscopy, although not directly related to amniocentesis, have been developed as a result of a desire to increase the knowledge of the intrauterine environment, heretofore only available by amniocentesis. These potentially useful diagnostic tools would, therefore, not have been developed without the interest in amniotic fluid generated by utilizing amniocentesis.

#### Diagnostic and Therapeutic Procedures

Amniocentesis as a procedure was developed through research involving living human fetuses over a period extending back to at least 1882. As previously noted, the major impact of the procedure has been to provide a means of obtaining amniotic fluid so that diagnostic tests and therapeutic methods could be performed during either the second or third trimester of pregnancy.

A total of thirty congenital anomalies can presently be detected in utero during the second trimester of pregnancy, i.e., three X-linked disorders (see Table 1), eight chromosomal aberrations (see Table 2), and sixteen inborn errors of metabolism (see Table 3). The detection of anomalies is dependent upon determining the sex chromatin of the fetal cells, being able to karotype the cells, or being able to culture the cells obtained in amniotic fluid. In the case of the inborn errors of metabolism, many different enzyme assays are critical for determining the metabolic defect in the cultured cells.

The estimation of fetal maturity is made by the quantification of certain compounds in the fluid such as bilirubin, creatinine, lecithin, and sphingomyelin and by staining exfoliated fetal cells with Nile blue sulfate. These substances are a direct result of the fetus' metabolism. The hemolytic problems are associated with the degree of anemia in the fetus resulting from transfer of Rh antibodies from the mother to the fetal circulation. In this situation, the contribution of living human fetuses has been in the area of intrauterine transfusions which serve the purpose of correcting the anemia present in the fetus.

Additional contributions of human fetal research in the development of amniocentesis for therapeutic purposes occurred in the correction of polyhydramnios and the induction of abortion.

## Effect of Retrospective Ban on Human Fetal Research on Amniocentesis

#### Technique

The only animal models which might be suitable for developing the technique of transabdominal amniocentesis would have to be monovular and possess a unicornuate uterus.<sup>32</sup> This statement is based upon the fact that the technique could not be satisfactorily evaluated either *in uteri* containing multiple fetuses or in a bicornuate uterus because of the obvious structural differences relative to humans. These restrictions reduce the potential animal models to higher primates, e.g., monkeys, chimpanzees or baboons.

However, some suggest that even these higher primates do not serve as satisfactory models for the following reasons:

- (1) Significant difference in the amniotic fluid: fetal size ratio relative to humans leading to invalid extrapolation of a technique developed in these animals to humans
- (2) Difference in skin and subcutaneous tissue composition such that development of skill by the operator would not be applicable to humans
- (3) Difference in boney pelvis structure to the extent that this hard tissue, in many cases, would not allow invasion of the uterus at the desired human site<sup>32</sup>
- (4) Placental position in some of these species is characteristically anterior so that transabdominal entry into the uterus would always be through the placenta 32
- (5) Size of the uterus is always smaller at equivalent stages of pregnancy

(6) Size differences also introduce the problem of needle diameter and length. Properly sized needles for humans could not be determined without direct evaluation on humans.

As a result of human amniocentesis, many investigators are now routinely performing amniocentesis in monkeys and other subhuman primates (e.g., Ref. 97). This would lead one to believe that indeed the higher primates could have been used as models to perfect the technique. However, the reasons cited above are considered valid by some investigators and the technique for later second and third trimester amniocenteses could never be perfected in these primates because their offsprings never obtain an equivalent size.

It is true that the technique of withdrawing amniotic fluid insofar as identification of the tissue layers and avoidance of the placenta and fetus could have been developed using gravid human cadavers. The obvious problems of the supply of fresh cadavers whose death did not involve or disturb the fetal surroundings makes this an impractical solution. Even if a reasonable supply were available, situations of bleeding and fetal motion could not be analyzed in a cadaver. In any event, nothing would be learned as to possible effects on the outcome of the fetus.

In conclusion, a ban on human fetal research with regard to developing improved techniques of amniocentesis would have resulted in its nonutilization due to inadequate or inappropriate alternate models with which to develop and perfect the method. The ramifications of the unavailability of this technique are overwhelming considering the multitude of highly useful and desirable diagnostic and therapeutic procedures which rely on amniocentesis. These procedures are discussed below.

#### Diagnostic and Therapeutic Procedures

If it is accepted, as in the preceeding section, that the development of amniocentesis was dependent upon research involving living human fetuses, the effects of a ban on human fetal research in the antenatal diagnosis and therapy via amniocentesis would have been far reaching indeed.

The contributions of human fetal research to the development of amniocentesis as an accepted clinical procedure have included the following:

- (1) Detection of genetic defects
- (2) Detection of Rh isoimmunization
- (3) Detection of fetal maturity
- (4) Relief of polyhydramnios
- (5) Induction of a therapeutic or elective abortion.

The effect of a ban on human fetal research involving the respiratory distress syndrome and Rh isoimmunization will be covered in other sections of this report. The development of these antenatal diagnostic tests and therapeutic procedures would have been affected to the extent of the contribution of amniocentesis in humans to each.

An important question in determining the effect a ban on human fetal research would have on the prenatal diagnosis and therapeutic procedures developed as a result of amniocentesis, is whether or not an animal model could have been substituted for the advances made to date. Each of the above indications for performing amniocentesis will be considered.

Detection of Genetic Defects. There are no known animal models for identifying the X-linked diseases presently detectable by amniocentesis in the human. The diseases detectable in utero include the Lesch-Nyhan and Hunter's syndromes, and Fabry's disease. Other animal models may possess X-linked diseases but the gene makeup is completely different from the human. Since X-linked diseases are detected by biochemical means, if the gene makeup is different, there would be no association between other species and their X-linked diseases and those X-linked diseases detectable in humans. The same situation would prevail for the cytogenetic studies used to detect chromosomal aberrations since the chromosomal number and gene content is different. Thus, a suitable animal model does not exist for detecting chromosomal aberrations. In addition, there is no animal model for the various inborn errors of metabolism which have been identified by antenatal diagnosis.

A recent study<sup>73</sup> has identified a model for the antenatal diagnosis of spina bifida in the Lewis rat. This is of importance since a number of investigators<sup>109,115,126,92</sup> have recently stressed the importance of the assay of alphafetoprotein in the amniotic fluid in pregnancies in which the fetus had anencephaly, myelomeningocele, or spina bifida. Thus, there may be an animal model available for the detection and study of neural tube defects.

Fetal Maturity. The use of primates as a model for determining fetal maturity has been attempted. Although amniotic fluid creatinine levels in the last third of pregnancy in Macaca mulatta are comparable to values in patients, no clear relationship exists between the creatinine concentration and the duration of pregnancy. Similarly, the bilirubin concentration in the amniotic fluid does not show a change with reference to gestational age.

The use of amniocentesis in diagnosing the respiratory distress syndrome is discussed in another section.

Polyhydramnios. The polyhydramnios condition has been observed in diabetic monkeys, 96 and, as a result, amniocentesis could therefore be performed on such a species to demonstrate the effect of fluid removal. However, a primary disadvantage in using monkeys as a polyhydramnios model would be the difficulty in breeding primates which are in captivity and developing a colony of diabetic monkeys.

Induction of Abortion. Any of the higher primates presumably could be used for developing the abortifacients to be used for inducing an abortion in conjunction with amniocentesis. However, regarding the amniocentesis procedure itself, the higher primates are considered an unsatisfactory model for reasons cited earlier.

## Outlook for Amniocentesis as a Clinical Procedure

#### Future of Technique

The technique of amniocentesis has reached a state of refinement such that it is now an accepted medical procedure with several medical indications for its use. The safety of the procedure will increase further with the widespread use of ultrasonography to locate the placenta and position of the fetus. Amniocentesis performed in conjunction with fetoscopy is also a real possible future development. This technique would reduce the incidence of injury to the fetus and, in addition to obtaining amniotic fluid, would allow direct visual examination of the intrauterine cavity.

Some refinements in the technique as it now exists may be possible. For example, the method of using an 18-gauge needle as a speculum through the abdominal tissue and the myometrium followed by insertion of a blunted plastic catheter into the amniotic sac for obtaining the fluid might decrease the incidence of fetal puncture. Indeed, Mann in 1965 and 1966 proposed the use of a plastic catheter to reduce the risk of fetal injury (see Table 5). Special needles designed sepcifically for amniocentesis may also be developed since spinal needles are the most commonly used now. The development of a small ultrasonic transducer in direct conjunction with the puncture procedure is already under way<sup>121</sup> and may prove to be a useful adjunct to complete abdominal ultrasonic screening prior to the operation.

# Possible Effects of Amniocentesis on Future Medical Developments

As Milunsky et al.,84 state, "the advent of prenatal diagnosis through amniocentesis represents the most important advance so far attained in the prevention of the births of infants with irreparable genetic mental defect and fatal genetic disease." The antenatal diagnosis of specific X-linked diseases, chromosomal aberrations, and metabolic disorders via amniocentesis has been used effectively during the last ten years. The treatment of genetic disease via amniocentesis in the future will depend upon many factors. Some of these factors would include: (1) further improvements in the procedure itself; (2) the development of special centers devoted solely to antenatal studies; (3) the development of new diagnostic tests for the specific disease in question; (4) further improvements in the culture medium and tissue culture techniques; and (5) the development of other instrumentation or ancillary procedures which might be used in conjunction with amniocentesis.

At the present time, amniocentesis is concerned largely with detection, but future developments may see more therapeutic uses of amniocentesis, i.e., the injection of materials or deficient substances directly into the fetal circulation, peritoneal cavity, or amniotic fluid. In addition, just as amniocentesis has assisted in the development of other procedures, e.g., ultrasound and amniography, the use of amniocentesis may assist in the development of better procedures for detecting bone development and fetal head size.

In conclusion, genetic counseling is now possible for a number of diseases. More importantly, this counseling can now be based upon actual *in utero* diagnoses via amniocentesis rather than by previous calculated probability risks.

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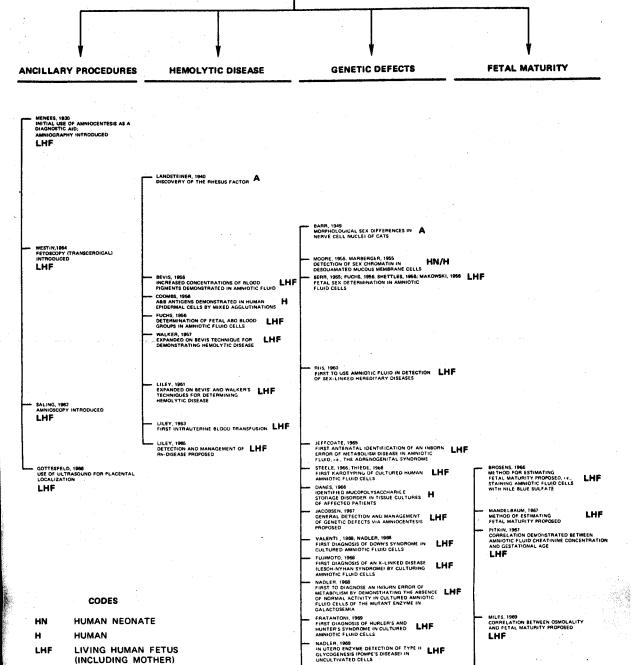
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College of Medicine
Columbus, Ohio



SCHNECK, 1970
FIRST PRENATAL DIAGNOSIS OF TAY-SACHS
DISEASE ISING UNCULTURED AMNIOTIC
FLUID CELLS

HOLLENBERG, 1971
DEMONSTRATED THAT HUMAN FETUSES
COULD SYNTHESIZE HEMOGLOBIN A

KAN, 1972
DEMONSTRATED THE SICKLE-CELL TRAIT IN LHF
UMBILICAL CORD OR PLACENTAL BLOOD BROCK, 1972
CORRELATION DEMONSTRATED BETWEEN A
RAISED & FETOPROTEIN LEVEL IN AMNIOTIC
FLUID AND SEVERE NEURAL TUBE DEFECTS
IN FETUS

SCHATZ, 1862
INTRODUCED AMNIFOCENTERIS FOR
THERAPY OF POLYHYDRAMNIOS

N

(INCLUDING MOTHER)

(AUTOPSY) ANIMAL

NONLIVING NEONATE OR SPONTANEOUS ABORTION

# ISOIMMUNIZATION (Rh VACCINE)

#### Medical Significance

The discovery of the Rh factor and the simultaneous elucidation of erythroblastosis fetalis about 1940 is one of the great milestones of medical science. Techniques have been developed within our lifetime which have effectively controlled the threat of Rh isoimmune disease. These developments over the past three decades have resulted not only in the savings of hundreds of thousands of lives, but also in the successful circumvention of an appreciable number of braindamaged children.

It has been estimated that the total amount of money used to support Rh disease research from 1930 through the successful development of the vaccine in 1966 is about what society pays today for lifetime care for a half-dozen children irreparably brain-damaged by erythroblastosis.<sup>52</sup>

Statistically, the problem of hemolytic disease of the newborn can be enumerated as follows:

- (1) Approximately 12 percent of all marriages in the United States are between Rh-incompatible individuals.
- (2) Of the 3.0 to 3.5 million births which occur yearly in the United States, approximately 25,000 infants could be affected by isoimmune hemolytic disease.
- (3) The number of stillbirths occurring because of isoimmune hemolytic disease prior to the 1940s was in excess of 10,000 per year in the United States. The number decreased to less than 5,000 with the introduction of transfusion techniques. It has been estimated that in the twenty-year period between 1940 and 1960, approximately 200,000 lives were saved by these techniques alone.
- (4) World Health Organization statistics indicate that on a world-wide basis even today 20-25 percent of Rh-positive infants of already Rh-sensitized women are likely to be stillborn in the last trimester. Worldwide statistics are however difficult to determine because of the racial variation of the occurrence of the Rh factor.
- (5) As of 1973, approximately 88 percent of first-pregnancy, Rhnegative women in the United States were receiving the Rh vaccine. Surveys showed 95-100 percent usage in urban areas and as low as 65 percent in rural areas.

The technology developed in the search for an answer to the hemolytic disease of the newborn provided a number of notable approaches and techniques which have been and will continue to be extremely useful in the cure and detection of human diseases which may be unrelated to Rh disease. These include:

- (1) The development of techniques to quantify bilirubin in the serum of newborns so that brain damage due to excessive release of blood pigments can be avoided.
- (2) The initiation of amniocentesis for the detection of bilirubin in amniotic fluid. Amniocentesis is now useful for detection and elucidation of a number of genetic disease of man including  $\alpha$  and  $\beta$  thalassemia and sickle cell disease <sup>10</sup> and may have vast diagnostic potential.
- (3) The initiation and perfection of the intrauterine transfusion technique and the development of fetus visualization techniques (fetology) now used for the detection of other malformations and/or diseases of the fetus, in utero.

One of the more important advancements to stem from the search for a cure for Rh disease is the initiation of the cooperative participation of research scientists and clinicians to obtain a common goal. This philosophical advancement has resulted in the vastly increased efficiency of medical research teams in their goal of the conquest of many of our most dread diseases.

Dr. Louis K. Diamond, one of the pioneering researchers in Rh disease, summarized his feelings in these words at a recent interview: "At present what is happening all over the country and all over the world for that matter, is a close collaboration between the Ph.D. researcher and the clinician. This very marked advance over my early days has proven the fact that many Ph.D. researchers are not only happy to collaborate but are anxious to do so. They wish to prove the usefulness of their bench work in terms of human therapy. This has uplifted the laboratory researcher and made the physicians who limit themselves to clinical work much more anxious to work at the bench to delineate the basic problems of medical science. I believe that this type of cooperative research which combines both clinical facilities and basic laboratory progress is the only rapid way of advancing medical science. In my area it is necessary to combine the talents of basic scientists who know enzymology, immunology, and cell structure with the practical experience of the clinician. I believe that in my lifetime this result has been the greatest advance in research." 10

This approach was used to its fullest extent in the conquest of Rh disease. Due to this dedicated cooperation, researchers and clinicians not only elucidated but also brought under control an extremely serious fetal disease in little more than three decades.

#### Historical Account

# Characterization of Erythroblastosis Fetalis

Although hemolytic disease of the newborn was described prior to the turn of this century, the relationship between jaundice (icterus), hydrops, anemia and eventually brain damage (kernicterus) in newborns was not established until the early 1900s. 15, 21, 24, 51 The early reports were primarily disease descriptions based on fetal autopsies. In 1932, Diamond et al., demonstrated that erythroblastosis was the single disease underlying jaundice, hydrops, and anemia. Following this descriptive phase, a relationship between the level of bilirubin in the infant's serum and kernicterus was established and methods of bilirubin quantification were developed. 2, 26, 44, 46 Subsequent to these developments, the presence of hyperbilirubinemia was shown to be directly related to the delayed brain damage (kernicterus) noted in infants with erythroblastosis fetalis. 26

# Etiology of Erythroblastosis Fetalis

Concurrent with disease interrelationships and their description, the major blood groups (A, B, and O) were recognized. Several additional blood group isoantigens were identified prior to 1939, 1, 2 when Levine and Stetson noted the presence of a non-ABO blood group antibody in the serum of a patient following delivery of a stillborn infant. The following year, it was observed that an antiserum prepared in rabbits against an antigen on the erythrocytes of the rhesus monkey reacted positively with 85 percent of human erythrocytes, which presumably contained the antigen, while 15 percent of those tested were negative. This non-ABO blood group antigen was termed the Rh antigen (subsequently shown to be a system of antigens).

In 1941, Levine et al., demonstrated that Rh sensitization in an Rh-negative mother to an Rh-positive fetus was responsible for the disease pathologies associated with erythroblastosis fetalis. The protection against Rh sensitization afforded by ABO incompatibility between the mother and fetus was postulated in 1943, and subsequently substantiated by statistical analysis reported in 1958.

#### Disease Detection

In the 1950s several procedures for detecting both fetal erythrocytes and/ or antibody to Rh-positive fetal erythrocytes in the maternal circulation proved the relationship between Rh isoimmunization and erythroblastosis fetalis. Fetal hemorrhage into the maternal circulation was documented in 1954 by demonstrating the presence of agglutinins to an Rh-positive fetus in an Rh-negative mother. Placental transfer of fetal erythrocytes was shown the following year, and a test developed to demonstrate the presence of fetal erythrocytes in the maternal circulation. The several procedures for detecting both fetal erythrocytes and

Several approaches to early disease detection were developed following elucidation of the etiology of Rh hemolytic disease. The earliest of these tests involved testing the mother's serum for the presence of incomplete Rh antibodies.9,12 A second approach was based on the detection of bilirubin in the serum of the neonate, 25,43 and somewhat later in the amnionic fluid of the mother. The feasibility of quantifying bilirubin in the newborn with jaundice was demonstrated as early as 1916.43 The establishment of the relationship between bilirubin levels and brain damage in Rh hemolytic disease led to the perfection of a micromethod for determination of bilirubin levels in the serum of diseased infants.<sup>25</sup> This assay provided a basis for the development of exchange transfusion in the affected neonate. 13 The development by Bevis 4 in 1956 of transabdominal aminocentesis for the purpose of determination of bilirubin levels in the amnionic fluid (spectrophotometric analysis) enabled Liley to monitor more precisely the extent of hemolytic disease in the fetus, and led eventually to Liley's highly successful treatment of the diseased fetus in utero by intrauterine transfusion.<sup>38</sup>

Another approach to detection of maternal Rh sensitization against incompatible fetal erythrocytes involved the demonstration of fetal cells in maternal blood.<sup>27</sup> This technique, introduced by Kleihauer in 1957, has been widely applied to monitor the effectiveness of disease prophylaxis. It remains the major method of demonstrating that a transplacental hemorrhage of fetal erythrocytes into the maternal circulation has occurred.

#### Therapy of Erythroblastosis Fetalis

As noted in the previous section, the therapy of Rh hemolytic disease was directly dependent on the perfection of accurate diagnostic procedures and elucidation of the mechanism of the disease process and the resultant pathologic manifestations.

The earliest surgical approach to disease treatment was exchange transfusion of the affected neonate shortly after birth. The first successful exchange transfusion was performed in 1925 for the disease then termed icterus gravis. In the 1940s a great deal of experimentation was performed to perfect this procedure for the early treatment of neonates with previously detected erythroblastosis fetalis. Wiener transfusions via the antecubital vein in infants with erythroblastosis fetalis. Diamond et al., further refined this procedure by using the more accessible umbilical vein and a clot-retarding plastic catheter. The extension of this method to multiple transfusions in the diseased live newborn virtually eliminated the threat of brain damage, and the mortality of neonates with erythroblastosis dropped to about 2.5 percent.

However, the problem of the severely diseased fetus which usually died in utero required a more sophisticated therapeutic approach. This advance became possible following the perfection of amniocentesis to monitor accurately bilirubin levels in the gravid sensitized female. Approximately 25 percent of Rh-positive fetuses in Rh-sensitized females were destined to be stillborn. The intrauterine transfusion introduced by Liley 38 in 1963 was directly responsible for eventually

preventing stillbirth in more than 60 percent of these cases. Adamsons et al., attempted without success to refine this procedure further via hysterotomy. The only additional therapeutic technique which has been applied to erythroblastosis fetalis is phototherapy. This type of therapy is used as an adjunct to exchange transfusion to control rising bilirubin levels in diseased neonates.

#### Prophylaxis of Erythroblastosis Fetalis

Rh sensitization generally occurs following the delivery of the first Rh-positive infant to an Rh-incompatible, Rh-negative, female. Sensitization may also occur due to a slow transfer of fetal erythrocytes across the placenta, following an abortion, or may even be the result of a transfusion reaction. Mechanistically, the sensitization process involves the formation of specific Rh(D) antibody in the female to the Rh antigen on the fetal erythrocyte. In a sensitized female, the 7S immunoglobulin can cross the placenta and lyse fetal red cells. The formation of Rh antibody in the sensitized female is termed an anamnestic response. The current protocol employed to prevent Rh sensitization is based on an observation by Smith in 1909 41 that the presence of excess passive antibody prevented active immunization to the corresponding specific antigen.

The natural protection afforded the fetus in the ABO-incompatible situation led several investigators to speculate on the possibility of simulating this protection by administering serum containing Rh antibodies. Priority for the original proposal that passively administered Rh-antibody at delivery might prevent sensitization apparently belongs to Finn and his associates in Liverpool. Two groups of investigators, Finn et al., 16 and Freda et al., 18 administered Rh antiserum to Rh-negative male volunteers, with the same conclusion, passively administered Rh antibody could prevent sensitization.

The trials of the Rh vaccine in women at risk following delivery of a first Rh-positive neonate began in New York and in Liverpool in 1964. 8, 19 Freda et al., demonstrated in a statistically significant study protection of Rh-negative women following an Rh-positive birth by administration of Rh antibody prepared from concentrated gamma globulin. The positive results of Clarke et al., (Liverpool Group) are perhaps more dramatic due to the almost exclusive use of high-risk individuals in their clinical trials.

During this period the Rh vaccine (RhoGAM), as it would eventually be called, was being developed and was made commercially available in 1968. The vaccine, 7S-anti-Rh antibody, was prepared from the plasma or serum of Rh sensitized, Rh-negative individuals.

The concept of specific Rh antibody mediated suppression of immunization by the Rh antigen was thus demonstrated and the vaccine made available for general use by 1968. This approach to prophylaxis has since been shown to be 100 percent effective by following high-risk Rh-negative women through successful second pregnancies, and minimal prophylactic doses have been established through extensive clinical trials.<sup>50</sup>

# Contribution of Human Fetal Research to the Control of Rh Hemolytic Isoimmune Disease

This section specifically delineates historically the research in which it was necessary to employ either the gravid female or the live fetus as a research subject in order to obtain an understanding of the mechanism of Rh isoimmunization, to diagnose erythroblastosis in utero, or to develop therapeutic procedures. There was very little purposeful research performed upon the gravid woman and/or her fetus until after the underlying hemolytic phenomenon of the disease was correctly described through the use of autopsy of postmortem human fetuses and/or newborns (a period extending from 1913 to 1929). During this time, approximately 20,000 to 25,000 newborns yearly were being affected by the disease. Following this period, there are three major phases of the attack on erythroblastosis which required human fetal research.

### Etiology and Mechanism of Fetal or Neonatal Hemolytic Disease

Due to the unsuitability of available animal models (outlined specifically in the section concerned with the effects of a ban on fetal research) it was necessary to define the mechanism of erythroblastosis in the human situation. This required that:

- (1) It could be demonstrated that immature fetal red blood cells (erythroblasts) could enter the maternal circulation and induce antibody production. Chown characterized erythroblasts in fetal fluids and in maternal blood using gravid females in 1954.7
- (2) The theoretical nature of the immunological etiology of the disease be proven by demonstrating that maternal anti-Rh antibodies did cross the placental barrier to affect the fetus. This was demonstrated by Mengert in 1955 40 using amniotic fluid drawn from the amnionic sac of a viable fetus in utero.
- (3) The role of bilirubin (the blood pigment, released during hemolysis, which causes brain damage) in the fetus be defined because it was known to cause neurological damage in the newborn. Bevis in 1956 through use of the aminocentesis procedure demonstrated that bilirubin levels were not destructive to the fetus in utero but that upon birth the neonate could not control pigment release by its own metabolism.<sup>4</sup>

## Detection of Fetal or Neonatal Hemolytic Disease

Once the disease mechanism had been extensively described it became necessary to detect the extent of disease in susceptible gravid females. This required a definitive series of events.

- (1) Bevis's demonstration in 1956 that bilirubin levels could be detected in fetal fluids drawn from the amnionic sac of a viable fetus *in utero* provided a reliable technique.
- (2) Billing and Lathe's (1958) full elaboration of bilirubin biochemistry.<sup>5</sup>
- (3) The use of bilirubin levels in amniotic fluid drawn from the fetal amnionic sac in utero by Liley to determine the proper timing and type of therapy. 38

# Therapy of Fetal Hemolytic Disease

Prior to the development of the above specific diagnostic techniques, it was found that the technique of multiple exchange transfusions of the newborn was effective in treating hemolytic disease and hyperbilirubinemia after a successful delivery. This technique, however, was useless for the large number of stillborns. Following animal studies and the demonstration that the bilirubin detection technique was of diagnostic value, it was considered feasible to perform an exchange transfusion with the fetus while it still resided *in utero*.

This decision was followed by a number of attempted techniques:

- (1) Transcutaneous approach into the fetal peritoneal cavity (with the fetus lying in utero) to infuse red blood cells was proven successful by Liley in 1964.
- (2) Implantation of catheters under direct vision after partial delivery of the fetus by hysterotomy was proven unsuccessful by Adamsons et al. <sup>1</sup>
- (3) The most successful technique which is now accepted as standard procedure is the intrauterine exchange transfusion. 11

These developments represent only preliminary milestones, most of which were followed by extensive trials and modifications of techniques. In the continuum of research they represent turning points that could not have been optimally achieved in any other fashion. The benefits of these research findings are immeasurable. The perfection of the intrauterine transfusion technique alone resulted in the successful rescue of 50 percent of the fetuses which were previously destined for stillbirth due to hemolytic disease. The development of aminocentesis as a reliable diagnostic tool has resulted in a tremendous broadening of our knowledge of the fetal environment and of fetal maturation. It was through this sequence of critical events in human fetal research that the Rh vaccine was conceived and the threat of Rh disease brought under control.

# Effect of a Retrospective Ban on Human Fetal Research on the Control of Rh Isoimmune Hemolytic Disease

The conquest of Rh disease through the elucidation of the disease, development of effective diagnostic and therapeutic procedures, and eventual prophylaxis of the disease represents one of the major medical achievements of this century. The major portion of this progress occurred over a 30-year period. This is a remarkably short period of time to perform the quantity and quality of research generally required to gain an understanding of any complex disease process and proceed to treat and/or prevent the disease.

The Rh vaccine (RhoGAM) has been clinically so effective in preventing Rh sensitization that Dr. Louis K. Diamond believes that Rh disease will cease to be a problem in this generation. There are of course small numbers of presensitized females, and transfusion accidents due to human error will occur, but generally speaking Rh disease has been effectively controlled.

To assess the effects of a ban on fetal research on the ultimate conquest of Rh hemolytic disease, predating the discovery of the Rh factor, the following questions must be considered:

- (1) Could the mechanism of the disease process have been determined?
- (2) Would effective methods of disease detection have been developed?
- (3) How would affected neonates have been treated?
- (4) Could procedures have been developed to treat the fetus destined to be stillborn, while still *in utero*?
- (5) Would the Rh vaccine, now known to prevent sensitization in cases of Rh incompatibility, have been developed and shown to be effective?

The discovery of the Rh factor, and the ultimate elucidation of the mechanism of isoimmune disease, did not involve human fetal research during the period of disease characterization or the early research which specifically linked Rh(D) incompatibility to erythroblastosis fetalis. This research was performed primarily on affected stillborn infants or neonates. However, to link unequivically Rh incompatibility to erythroblastosis required the demonstration of fetal cells in the maternal circulation and evidence of specific active immunologic reactivity against those cells. This ultimately required that gravid females be tested for the presence of fetal cells prior to the onset of labor and sequentially monitored for antibody levels throughout the gestation period. A ban on fetal research would not have allowed this understanding of the mechanism of isoimmune disease in humans to evolve over the short span of 15 years. Selected animal models could have been used for study, but none closely mimicked human isoimmune disease.

The animal models available for research during the period in which Rh hemolytic disease was conquered will be considered in a later portion of this section.

Soon after Rh incompatibility was postulated to be responsible for the hydrops, anemia, jaundice, and brain damage associated with the disease process designated erythroblastosis, it became apparent that methods of early detection were the only possible means to predict the probability of disease in these fetuses. Tests to assess the presence of Rh antibodies in the circulation of the sensitized gravid female, and the presence and quantity of fetal erythrocytes in the maternal circulation led to the development of prompt exchange transfusions for neonates with erythroblastosis fetalis.

The principal method of early detection of Rh hemolytic disease of the fetus in utero is based on the detection of bilirubin in amniotic fluid. The development of amniocentesis enabled clinical investigators to detect erythroblastosis fetalis much earlier and led to the development of the intrauterine transfusion for the high-risk fetus destined to be stillborn. These procedures required that experimental procedures be performed on both the gravid female and ultimately on the fetus in utero.

Thus, effective procedures for saving these infants both after birth and in utero became available. A ban on fetal research might not have precluded the development of the exchange transfusion or the intrauterine transfusion in animals, and in fact animal models were employed to study these procedures prior to human experimentation. However, in an absence of knowledge of the underlying cause of the disease process, the application of these procedures in the treatment of neonates and fetuses with erythroblastosis fetalis would certainly have been greatly delayed and many fetuses and neonates, especially high-risk fetuses, would certainly have been lost.

Although Rh antibody (IgG) administered to prevent sensitization following the delivery of a first Rh-incompatible infant does not involve the fetus directly, the development of this vaccine is intimately tied to fetal research. All of the research areas in the conquest of erythroblastosis fetalis are interrelated, and the impetus for a prophylactic approach is directly related to an understanding of the disease mechanism and, of course, a desire to eliminate the problem of the high-risk fetus.

In attempting to ascertain the effects of a retroactive ban on fetal research on the control of Rh hemolytic disease, the availability of animal models and their applicability as models in the various phases of this research should be considered. During the course of the research which led to the ultimate prevention of erythroblastosis fetalis, a number of animal models were considered based on several criteria.

- (1) Dog--availability, breeding ease, gestational period and the existence of canine erythroblastosis.
- (2) Rodent species (rat, mouse, rabbit) -- availability, breeding ease, and inducibility of hemolytic disease.

- (3) Donkey or mule--large size of fetus and presence of pathologic erythroblastosis manifestations.
- (4) Primates (chimpanzee and baboon) -- system of comparable blood group isoantigens and isoimmune hemolytic disease.

These models were employed in selected phases of the research but ultimately rejected as models for Rh isoimmune hemolytic disease in humans for the following reasons:  $^{6,\,10}$ 

- Dog--dissimilar placental construction compared with humans; there is no placental transfer of antibodies.
- (2) Rodent species—small fetal size was prohibitive for surgical procedures comparable to human situation and disease manifestations were highly variable even within the same litter.
- (3) Donkey or mule--disease pathology is similar but there is no placental transfer of antibodies; antibodies were passed via colostrum (milk).
- (4) Primates—the advent of intense research on the isoantigens of primates and the mechanism of isoimmune disease in these animals is a recent event. Although these animals may ultimately prove to be adequate models for the study of isoimmune hemolytic diseases similar to erythroblastosis fetalis, the relative unavailability of the primate species, the variability of disease pattern as compared to the human disease, and a lack of knowledge of the blood group isoantigens in these species did not make them ideal models for the type of research required to solve the Rh problem rapidly.

Although there certainly were areas where animal models may have been more extensively employed, if there had been a ban or even a severe curtailment on research involving living human fetuses or pregnant women, the knowledge required for the development of the medical techniques for detection and treatment of Rh hemolytic disease of the newborn would have been immeasurably delayed, and the Rh vaccine as it is used today most probably would not have been possible. This would have resulted in the stillbirth of approximately 450,000 fetuses over the period from 1930 to 1975. Even more devastating would be the medical, social, and economic impact that would have resulted from the birth of tens of thousands of brain-damaged individuals over this same period.

#### Future Outlook

## Future of the Procedures

The outlook for the successful management of Rh hemolytic disease is very bright. With the current use of amniocentesis as a detective and diagnostic tool it is possible to pinpoint with almost total accuracy the endangered fetus. The early diagnosis of erythroblastosis fetalis can now be followed by either early delivery, intrauterine transfusion, or exchange transfusion of the newborn. These techniques are necessary only in those women who have been presensitized or who have not received the Rh vaccine after the first pregnancy. For those women who do receive the Rh vaccine upon the completion of their first pregnancy, the problem of isoimmunization to their fetus and to subsequent fetuses is almost completely eliminated.

# Effects of Future Development on Other Areas of Medical Science

The use of human fetal research in the development of techniques of diagnosis, therapy, and prophylaxis and the generation of theoretical problems in the search for an answer to Rh disease have resulted in the initiation of lines of research which apply to a myriad of scientific and medical disciplines.

The monitoring of antibody levels in the serum of gravid females as well as enzyme, pigment, and antibody levels in amniotic fluid has given researchers powerful tools to describe genetic, maturational, and functional defects of the fetus. The ability to apply Mendelian genetics to parental pairs has further broadened our concept of inborn genetic disorders. With the perfection of fetal and neonatal surgical procedures, it is now possible to attempt to correct certain of these disorders.

Future developments in the area of immunology requiring human fetal research are based on many of the procedures developed during the course of solving the problem of Rh hemolytic disease. Research has begun to attempt to understand and control a variety of immune deficiency diseases. These diseases are generally sex-linked disorders which cannot be reproduced in animal models. Current experiments suggest that it may be feasible to monitor levels of T- and B-lymphocytes and progenitor cells in the fetal circulation. It has been demonstrated that transplantation of lymphoid tissues such as the thymus from aborted fetuses or stillborn neonates may be an effective approach to treating these immunodeficiency diseases. A for addition, fetal research is necessary to a better understanding of the overall ontogeny of the immune response.

This type of research will facilitate the development of fetal surgery, in which transplants may be carried out *in utero*. This could conceivably eliminate the problem of organ transplants between HLA-incompatible individuals. This line of research could of course eventually apply to a variety of congenital defects. These future research developments will not be possible if there is a prospective ban on fetal research.

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CHARACTERIZATION
OF HEMOLYTIC
DISEASE OF THE NEWBORN
(ERYTHROBLASTOSIS FETALIS) ETIOLOGY OF ERYTHROBLASTOSIS FETALIS THERAPY DETECTION LANDSTEINER, 1900 DESCRIPTION OF AB BLOOD GROUP ANTIGENS H/A YLLPÖ, 1913 NOTED LIVER INVOLVEMENT AND BILE (BILIRUBIN) HN IN THE CIRCULATION OF THE NEWBORN HIRSCH, 1913
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HYDROPS, FETALIS ANEMIA IN ALL CASES DIAMOND, 1932
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UNDERLYING ICTERUS, HYDROPS, AND ANEMIA
OF THE FETUS AND NEONATE LEVINE, 1939
POSTULATED NEW ANTIBLOOD GROUP
ANTIBODY IN SERUM OF MOTHER OF
STILLBORN THAT WAS NOT ABO

COOMBS, 1945 HN TEST TO DETECT WEAK AND INCOMPLETE Rh AGGLUTININS

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н HUMAN

UCED THE INTRAUTERINE TRANSF DIAGNOSTIC AMNIOCENTESIS

LIVING HUMAN FETUS LHF (INCLUDING MOTHER)

NONLIVING NEONATE OR SPONTANEOUS ABORTION (AUTOPSY)

ANIMAL

#### RESPIRATORY DISTRESS SYNDROME (RDS)

#### Medical Significance

Respiratory distress syndrome is a major cause of neonatal mortality and thus represents an important threat to a prematurely born infant. The condition as it is now recognized is a consequence of lack of sufficient pulmonary development in a prematurely born infant. Ninety-five percent of infants who die of RDS are premature. The overall incidence of RDS has been estimated by several different methods. In the most recent figures, it was estimated that during the years 1968 to 1970, the national incidence of RDS was 40,000 cases per year. A direct relationship is indicated between the frequency of RDS and the degree of prematurity, irrespective of whether estimated gestational age or birth weight is employed as a measure of prematurity. Frequencies as high as 80 percent are reported in the 1000 to 1250-gram group.

A very large variation in mortality rate from RDS has been reported in the literature depending upon risk factors and the methods of management. A summary of deaths in 1969<sup>100</sup> estimated that 1,000 infants per week born in the United States developed RDS and of this number, approximately 500 died. This would correspond to an annual mortality of 26,000 infants. The frequency of fatalities obtained from small populations of randomly selected cases have ranged from 20 to 95 percent. 9.49 A general clinical impression is that disease severity is strongly influenced by the degree of prematurity, and is corroborated by correlations of gestational age with mortality. Other estimates of national mortality also show a range from 12,000 to 40,000 cases per year. 6.60 In a compilation of deaths attributed to hyaline membrane disease in 1968, a total of 10,097 deaths were tabulated. If the incidence of RDS is 40,000 cases per year, this suggests an overall mortality rate of 28 percent in this country.

The majority of deaths from RDS occur in the first 72 to 96 hours after birth. The fatality rate for RDS declines nearly exponentially between the first and fourth 24-hour periods. 101 The typical clinical characterization of the RDS infant follows a progressive deterioration in the first 24 to 48 hours accompanied by a high mortality rate during this period. Infants who survive begin to recover from 72 hours onward. Of these survivors, a certain percentage will experience morbid sequelae, the two most important of which are neurologic impairment and chronic lung disease. In the past, data have indicated a rather high rate (20-27 percent) of secondary neurologic abnormalities resulting from RDS. 35 Because of recent advances in therapy and management of RDS infants, there is indication that neurologic sequela may be reduced. 3

In addition to prematurity, two other risk factors have been shown to lead to or aggravate the incidence of RDS. These are cesarean section and perinatal asphyxia. Usher and his co-workers 95,93 reviewed histories of over 10,000 vaginally delivered infants and 1,500 cesarean sections. They concluded that the procedure itself was the responsible factor in the higher incidence of RDS in the later group. This conclusion was in opposition to an earlier opinion 20 that

elective cesarean section in uncomplicated pregnancies did not lead to a higher incidence of RDS. The association of RDS with cesarean section was attributed to a history of maternal hemorrhage rather than to the procedure itself. However, several of the facts summoned by Usher and others indicate that cesarean section of itself is a predisposing factor to RDS. A comparison of 1,780 vaginal versus 334 abdominal deliveries performed at 35 to 38 weeks showed an eightfold greater incidence of RDS in the abdominally delivered infants. The incidence of RDS in emergency and elective cesarean sections is about the same when the two infants are compared at equal gestational age. The reason for the predisposition by cesarean section to RDS is not well understood, although a clue may be offered by the work of Fedrick and Butler 2 who found that infants delivered by cesarean section before initiation of labor had a 4-fold higher incidence of fatal RDS than those delivered by cesarean section during labor. It would thus appear that the onset of labor in some way prepares the infant's pulmonary system.

Another predisposing factor to the incidence of fatal RDS is the sex of the neonate. Ratios of the number of males to females who die with hyaline membrane disease range from 1.4 to 2.0.84 In a recent study, a ratio of 1.7 was reported.<sup>78</sup> The suggestion was made that the lungs of females mature at a faster rate than the lungs of males before birth. However, the higher death rate among the males may be attributable to the fact that males outnumber females in virtually all disorders leading to death in the neonatal period.<sup>76</sup> The ratio in neonatal mortality from all causes is from 1.62 to 1.76 for the period 1968 through 1970.<sup>101</sup>

Another factor which has long been implicated in predisposing the neonate to RDS is maternal diabetes. Several studies indicate that infants from diabetic mothers definitely do have a higher incidence of RDS. Ranges of 26 to 37 percent incidence have been reported. 37,55,57,91,99 However, it is difficult to assess the effect of maternal diabetes independently because of the very high incidence of cesarean section and premature births occurring in diabetic mothers. For example, in Hubbell's study, 55 cesarean sections were performed in 70 percent diabetic pregnancies. A subsequent study by Usher 95 indicates an almost equal incidence of RDS in infants delivered by cesarean section from diabetic and nondiabetic mothers when the results are compared according to gestational age. He thus attributes the high incidence of RDS in infants from diabetic mothers to the cesarean section procedure rather than to the diabetic condition of the mother. Irrespective of whether diabetes per se or the higher rate of cesarean section is the primary factor in the high incidence of RDS in infants from diabetic mothers, the fact remains that infants from diabetic mothers do have a higher incidence of RDS. A number of other factors have been associated with the occurrence of RDS in neonates which are thought to reduce the risk. For example, premature rupture of the membranes,82 heroin addiction in the mother, and two or more prior unsuccessful pregnancies 78 have all been associated with reduced risk of RDS in neonates.

In conclusion, the above facts establish that RDS is a major cause of death among neonates and that significant morbidity can result in survivors of this condition.

#### Historical Account

The first recorded clinical observation of the hyaline membrane associated Hochheim reported the existence of with RDS was reported in 1903 by Hochheim.52 a peculiar membrane which stained blue with hematoxylin which he termed myelin. Hochheim believed that this myelin was formed from desquamating cells of the alveolar epithelium. This myelin membrane was subsequently described in the lungs of newborn children by several German pathologists.\* The first description of the hyaline lesion in the English literature was in 1923 by Johnson,56 who associated the hyaline membrane with pneumonia in newborn infants. Hochheim originally postulated that the origin of the hyaline membrane could be from amniotic fluid aspirated by the infant. This hypothesis was given further credence by Farber in 1931,27 who showed that constituents of amniotic fluid could be found in neonatal lungs. Aspiration of amniotic fluid continued to be the most frequently hypothesized etiology for a period of almost 50 years after Hochheim's first report. In a summary of cases in the literature of 1903-1952 presented by Tra-Dinh-De,92 36 studies of hyaline-like membranes are reported. Of these, 24 ascribed the membrane to aspiration of amniotic fluid. Other etiologies are also suggested, and these include developmental or congenital abnormalities, degeneration of alveolar epithelium, oxygen poisoning, and intrauterine injury. Gluck suggests in a recent article47 that at least 50 etiologies were proposed during the first 50 years after the syndrome was recognized. These studies seemed to focus particular attention on the hyaline membrane, describing it as a distinctive coating of the alveoli by an irregular layer of homogeneous eosinophilic material. In a paper in 1950 by Potter,81 atelectasis of a newborn is divided into two categories, the first being those who die before respiration and the second, those who die after initial respiration. She also pointed out that the most important entity which causes hyaline membrane disease is prematurity. A detailed study of a large number of newborns in  $1950^{71}$  resulted in an excellent description of the clinical abnormalities associated with the formation of hyaline membrane disease.

In 1953, an important milestone in the diagnosis and, to some extent in the understanding, of the hyaline membrane was presented by Donald,<sup>24</sup> who described a reticulogranular pattern associated with neonatal atelectasis which appeared on radiographs. A very significant paper on understanding the etiology of RDS appeared in 1956 by Gitlin and Craig.<sup>42</sup> These authors showed that the lesions associated with RDS in the lung contained large amounts of fibrin. Since fibrinogen is not a constituent of amniotic fluid, its origin must lie within the infant itself rather than from aspirated amniotic fluid. The substantiation of these findings discounted the hypothesis of aspiration of amniotic fluid as leading to the formation of a hyaline membrane.

A major advance in understanding the etiology of RDS came in 1959 with the report of Avery and Mead<sup>5</sup> on the surface properties of lung extracts from infants with hyaline membrane disease. The surface tension properties of extracts from lungs of premature stillborns, live-born prematures, infants dying from hyaline

<sup>\*</sup>In more recent literature, the term "myelin" has been replaced by the word "hyaline."

membrane disease, normal children, and adults were measured and compared. results showed that a surface-active substance was found in large amounts in the lungs of infants over 1200 grams, in children, and in adults. In lung extracts of very small premature infants and infants dying with hyaline membrane disease, the surface-active material is deficient. Based on these findings, the authors suggested a pathogenesis of the disease which is still the basis of the current understanding. They suggested that the absence of the surfactant lining in the alveoli resulted in a higher surface tension and predisposed alveolar collapse after the first breath. This, in turn, would lead to a higher intraplural pressure at inspiration resulting in a higher intrathoracic blood volume. This could then account for the transudation of plasma proteins, which has been shown to exist in hyaline membrane disease. Thus, the presence of the hyaline membrane was postulated as being a secondary effect. The primary effect was atelectasis resulting from collapse of pulmonary alveoli. A subsequent paper 50 from this same group showed that excised lungs from infants who died from RDS had a greatly reduced compliance compared to lungs from stillborn infants and newborn infants dying from other causes. This low compliance was attributed to a reduction in the number of units participating in ventilation which, in turn, could result from collapse of alveoli.

Thus, at this juncture, attention was turned to the role of surfactant in the etiology of the respiratory distress syndrome. To understand the role of surfactant, one must go back to a paper published in 1929 by von Neergaard.96 Von Neergaard reported that the pressure/volume curves obtained by inflating and deflating lungs with air were not the same as those obtained from inflating and deflating with an aqueous solution. He postulated that the discrepancies in pressure necessary to extend the lung with air compared to water and the failure of the air-inflated lung to deflate along its own curve of expansion were due to surface tension forces in the lung. By quantifying the differences between the air and liquid volume/pressure curves, he concluded that approximately 2/3 to 3/4 of the retractive pressure of the lung was due to surface forces. He also postulated that a surface-active material must be present in the lung to account for these differences. Between the period of 1929 and 1955, a number of authors discussed the theoretical importance of the surface properties of the lung. However, no direct experimental evidence of surface properties in maintaining alveolar stability was obtained until 1955. In that year, Pattle 79 showed that foams taken from the inner spaces of edetamous lungs contained a potent surface-active material. Foam was obtained from lungs by producing acute pulmonary edema in animals and by washing lungs both in vivo and in vitro with a saline solution. The high stability and nearly constant size of the bubbles in the foam indicated to Pattle that they must have a very low surface tension. He suggested that the surface-active material was some form of mucous which was secreted by the lung. This suggestion originated from earlier work by Macklin,68 who stated that the Type II pneumonocytes (alveolar cells which constitute from 2 to 10 percent of the normal alveolar epithelial cells) contained granules which secreted a substance covering the air surfaces of alveolar cells. He did not at this time, however, identify this secreted substance as a phospholipid surfactant.

The next important advance in the understanding of the role of lung surfactant came in 1957 with the report of Clements. Using saline extracts from rat, cat, and dog lungs, the author showed on a Langmuir-Wilhelmy surface balance

that the surface tension was dependent upon the surface area. The tension varied from 46 to 10 dynes/cm as the surface area was decreased. He thus demonstrated hysteresis characteristics similar to the pressure/volume relationship found on the inflation and deflation of experimental lung samples. In a subsequent paper, Clements and co-workers began to develop a theoretical basis for the function of surfactant in lung alveoli. He showed that since the surface tension of the lung surface decreased as the surface contracted, the alveoli would be stabilized at low volumes.

Following the classic work of Avery mentioned above, investigations continued on the relationship of the surfactant to the properties of lung tissue. In 1961, Clements and co-workers<sup>17</sup> compared the pressure/volume relationships of human and rat lungs to the surface-active properties of extracts prepared from the specimens. The pressure/volume curves and the surface activity of the extracts showed wide variation among individual samples and yet a high correlation between these two properties was observed. The findings supported the hypothesis that the stability of the pulmonary alveolar structure was dependent upon the intrinsic surface-active material. The stabilizing activity present in lungs of newborn infants with hyaline membrane formation was apparently insufficient to stabilize units smaller than 90 microns in radius at a pressure of 5 cm of water. On the other hand, even the smallest units of normal lungs could be stabilized at this pressure. These findings were further corroborated in a subsequent paper by Gruenwald,51 who made pressure/volume measurements on postmortem lung specimens from 37 infants, and in addition, measured surface activity of saline extracts. A good correlation was found between the alveolar stability of the lungs and the surface activity of the extracts.

In line with these findings, the composition of the surface-active material was being investigated. Klaus and co-workers 58 analyzed foam obtained from beef lung and found it contained from 50 to 75 percent lipids and 5 percent nitrogen. The lipids were composed of 74 percent phospholipids and this portion of the lipid fraction produced the major effect on reducing surface tension. A number of subsequent studies indicated that the primary component of the phospholipids was dipalmitoyl lecithin. Interestingly enough, the presence of high amounts of this substance had been reported several years earlier by Thannhauser. 90 The physiologic significance of dipalmitoyl lecithin was not known at the time of this finding, however.

Subsequent to this, a great deal of work has been conducted up to the present time on the composition and properties of pulmonary surfactant. In a recent summary, Clements reports that surface-active material derived from lungs contains 41 percent dipalmitoyl lecithin, 25 percent monoenoic lecithin, percent protein, and 1 percent sphingomyelin, with the remainder consisting of a variety of lipids and phospholipids. The protein portion of the surface-active material is reproducible in extracts from several animals. This protein is believed to play an important role in the properties of lung surfactant in that it has been shown to increase the rate of adsorption of phospholipids on the surface. Lecithin by itself would be ineffective at the surface of the alveoli, although it is the principal component of the surface-active material which is largely responsible for the stability of the alveoli. Clements points out that a turnover of phospholipids at the alveolar surface occurs as the film collapses.

Therefore, the lung must continuously supply phospholipids to maintain stability. In the absence of an active synthesis of phospholipids, an infant's lung might be stable for a short period of time and subsequently degenerate because the rate of synthesis could not keep up with the phospholipid turnover.

In parallel with the studies of phospholipid composition, research efforts were directed to the methods of synthesis of phospholipids by the lung tissue. As mentioned previously, Macklin suggested the Type II alveolar cells were secretory. This work was followed up in 1961 by Klaus and co-workers, 59 who proposed that the surface-active lining of the mammalian lungs forms in the mitochondria of the Type II alveolar cells. In conjunction with this, Buckingham and Avery reported12 that the surface activity of extracts from mice lungs show very little surfactant activity until the nineteenth day. The appearance of the surfactant activity corresponds with the appearance of the inclusion bodies in the Type II alveolar epithelial cells. Thus, this work, as well as that of many others, showed the correlation between appearance of the Type II cells and the surfactant activity. A great deal of experimental work then followed on the development of surface activity in mammalian lungs. 43,44 These studies identified two main pathways of lecithin synthesis. The first, called the CDP choline pathway, was shown to be the major pathway in the rabbit and sheep fetus. The second pathway involves methylation of phosphatidyl ethanolamine. In the sheep and rabbit, this second pathway, designated the methylation pathway, is not significant until several days after birth. The story, however, is different in the monkey and human fetus, as shown by the studies of Gluck and co-workers. 46 In vitro studies on nonviable human fetuses demonstrated that the CDP choline pathway could be identified by 18 to 20 weeks' gestation. However, it was relatively inactive until the thirty-sixth week of gestation. The methylation reaction was identifiable by the twenty-fourth week of gestation but was evidenced only at a very low activ-Thus, the animal models which were studied intensively to elucidate the mechanisms of phospholipid synthesis had some differences when compared to the human. Following Gluck's work, a series of studies on the enzymes involved in the synthesis of lecithin in humans was performed by Zachman. 103 The details of the biosynthetic pathway are too numerous to be described in detail in this review. Suffice it to say that work with human tissue was essential to establish the biosynthetic pathway by which lecithin is synthesized in the human lungs. A recent report by Gluck and co-workers indicates that the rhesus monkey may serve as a good model for studying development of phospholipid synthesis.48

With the establishment that lecithin was synthesized by lung tissue and was the major component of the surfactant, the question arose as to how one could use this knowledge in the prediction of respiratory distress syndrome. An important step in this direction came in 1967 with the work of Scarpelli, 3 who showed that the lung was the source of tracheal fluid phospholipids. He demonstrated that the phospholipid content of tracheal fluid was similar to that of amniotic fluid and suggested that the former might be a source of phospholipids in the amniotic fluid. Demonstration of the validity of this concept was made in the classic work of Gluck in 1971,45 who showed that changes in phospholipids in amniotic fluid obtained by amniocentesis reflected those in the lung of the developing fetus. A sudden increase in the concentration of lecithin occurs at 35 weeks and this increase signifies the maturity of the pulmonary alveolar lining. The estimation of the lecithin concentrations was based upon the fact that the amniotic

fluid sphingomyelin concentration remained relatively constant throughout gestation and could serve as an internal standard. These results implied that the likelihood of RDS could be diagnosed antenatally by measurement of the lecithin/ sphingomyelin ratio in amniotic fluid. In the ensuing four years after Gluck's study, over a hundred reports have appeared in the literature. These reports have confirmed the clinical predictability of amniotic fluid phospholipids for the risk of RDS. A compendium of the results indicates that a properly determined amniotic fluid L/S ratio greater than 2.0 indicates with almost 100 percent probability that the infant will not develop RDS. The question remains open, however, about the probability of RDS occurring in L/S ratios less than 2.0. Another method of determining surfactant activity of amniotic fluid is the shake test described by Clements.18 A number of studies have been conducted on the value of this test in predicting the pulmonary maturity of an infant, and these indicate that this method can provide a good screening method. If the shake test is positive, there is a very high probability of pulmonary maturity. If the test, however, is negative, it is advisable to obtain an L/S ratio to determine more accurately the degree of fetal maturity.

The knowledge that a lack of sufficient surfactant synthesis led to RDS, coupled with the ability to predict pulmonary maturity by amniocentesis led to the desire to find a method of stimulation of fetal lungs antenatally in cases where premature delivery was a threat. Such an advance came in 1972 in work by Liggins and Howie.<sup>67</sup> These authors showed that the administration of glucocorticoids more than 24 hours before delivery decreased the likelihood of postnatal respiratory distress.

To understand the rationale for this work, it is necessary to review briefly past work on the effect of steroids on fetal stimulation. As early as 1953, Moog<sup>73</sup> had demonstrated that cortisone induced certain enzymes in the intestines of fetal mice. In 1961, Migeon et al.,<sup>70</sup> had shown that cortisol administered to mothers at midpregnancy could cross the placenta from mother to fetus. Because of the increasing use of cortisone in medical practice for conditions such as severe asthma, rheumatoid arthritis, and Rh sensitization, several studies were performed during this period and later to determine the danger or safety of administering cortisone during pregnancy. <sup>69,97,102</sup> Although caution was advised, this therapy did not appear to have an untoward effect on the infant, and long-term corticosteroid therapy was not felt to be a contraindication to pregnancy.

However, it was not until 1968 that the role of hormonal steroids in fetal lung maturation was suspected. Buckingham et al., were the first to suggest that fetal steroids may influence pulmonary epithelial cell maturation, just as Moog had found in the fetal intestine. The same year, Liggins in New Zealand reported that infusions of cortisol into fetal lambs resulted in premature parturition. This was followed by a second report by Liggins in 1969 that dexamethasone caused the same effect. More important, however, was his finding that dexamethasone administered directly to fetal lambs promoted lung maturation as determined by physiological parameters. He suggested that this may be the result of accelerated appearance of surfactant activity. It is also important to note that Liggins found that neither cortisol or dexamethasone induced parturition when administered to the pregnant ewe rather than directly to the fetus.

Dr. Mary Ellen Avery, while visiting with Dr. Liggins in New Zealand, quickly recognized the significance of his findings and initiated an intensive research program at McGill University-Montreal Children's Hospital Research Institute. By 1969, DeLemos et al., 21 reported preliminary findings which confirmed the accelerated maturation effects of corticoids and ACTH in fetal lambs, and in 1970, DeLemos et al., 22 were the first to demonstrate increased surfactant in the lungs of cortisol-treated fetal lambs. This classical report set off what amounted to an explosion in research into the role of steroidal hormones in fetal lung maturation. The effect of corticoids on general fetal lung maturation was quickly confirmed in lambs, rabbits, and rats, 57,61,62,63,74,80 and the effect on increased surfactant was confirmed in rabbits. 62,63,74

In 1971, Kotas and Avery<sup>62</sup> suggested that the administration of a glucocorticoid accelerated a normal sequence of differentiation in the fetal rabbit lung. This was quickly followed by a report by Wang et al.,<sup>98</sup> who observed that the Type II cells of cortisol-injected rabbit fetuses underwent rapid cytodifferentiation showing decreased quantities of glycogen and increased numbers of lamellar granules. The same effect was reported by other laboratories in the same year.<sup>57,80</sup> Also in 1971, Naeye et al.,<sup>77</sup> reported that anencephalic neonates with hypoplastic adrenal cortices had, in comparision with neonates without this malformation, less than half the mass of osmiophilic granules in Type II alveolar cells.

As a result of these key discoveries in the 1968-1971 period, several fronts were opened for further investigation. As would be expected, several laboratories began to probe deeper into the basic questions of pneumonocyte enzyme induction by steroidal hormones and glucocorticoid receptors in the fetal lung. Farrell and Zachman,<sup>29,30</sup> for example, reported in 1972 and 1973 that there was a marked enhancement of choline incorporation into surface-active lecithin in fetal rabbit lung after pretreatment with dexamethasone, and in 1973, Farrell and Blackburn<sup>31</sup> demonstrated an increase in choline phosphotransferase and lecithin synthesis in rat lungs from decapitated fetuses six hours after intraperitoneal injection of dexamethasone. Smith and co-workers extended these studies into cell cultures prepared from fetal rabbit lungs and midterm human fetal lung.85-88 Their studies suggest that cortisol may increase fetal pulmonary cellular growth in early gestation while enhancing maturation and slowing growth as term approaches. During this same period, Ballard and Ballard demonstrated first in rabbits 10 and then in the human fetus and neonate11 that the lung contains the receptor mechanism necessary for direct responsiveness to glucocorticoids. In a series of papers, Giannopoulos and co-workers 38-41 demonstrated large variations in the levels of lung glucocorticoid-binding protein (GBP) among different species as well as in the same species at different developmental stages.

While several other workers continued to demonstrate the role of steroidal hormones in regulating surfactant synthesis in animal models such as the lamb, rat, and monkey, 80,31,23 Liggins and Howie 67 in 1972 published the preliminary results of a controlled clinical trial in New Zealand. They reported that antepartum glucocorticoid treatment reduced the incidence of RDS in human infants born before 32 weeks of pregnancy. The same year, Baden and co-workers 8 in Montreal reported on a clinical trial of hydrocortisone therapy in neonates with RDS. They found no endogenous deficiency of corticosteroids in infants with RDS and demonstrated that the postnatal use of corticosteroids did not benefit the

infant with RDS. The following year, Howie and Liggins<sup>53</sup> reported on an extended clinical trial with antepartum betamethasone treatment. Reduced incidence of RDS was confirmed for infants born before 32 weeks of pregnancy and more than one day but less than seven days after the start of treatment. They cautioned that intrapartum fetal deaths were greater in the treated group than in controls in those patients with evidence of placental damage. While this difference was not at a significant level, preeclampsia would contraindicate betamethasone administration. The following year, Fargier and co-workers<sup>28</sup> in France reported on a similar clinical trial using betamethasone. They reported that the antepartum treatment reduced the incidence of hyaline membrane disease in premature infants from 20 percent in the control group to 4.4 percent in the infants born of treated mothers.

The significance of the findings of Bader et al.,38 who had reported that RDS infants had no endogenous deficiency of corticosteroids, was clarified by Murphy 75 in 1974, who demonstrated that the cortisol and cortisone levels in mixed cord blood, taken at delivery, was lower in infants which subsequently developed RDS than in normal infants. She suggested that pre- and postnatal stress increased cortisol levels; therefore, the stress associated with the RDS would quickly lead to a rise in cortisol in the distressed infant and the cortisol deficiency present at birth would be undetected in subsequent measurements.

In 1973, Spellacy et al., <sup>89</sup> reported that the rate of rise of amnionic-fluid L/S ratio in human pregnancies was significantly increased by the administration of a synthetic glucocorticoid to the mother. Similar findings were reported by Caspi et al., <sup>14</sup> the same year. While these studies were limited in scope and the significance of the findings needs to be carefully evaluated, they do illustrate the first use of amniocentesis in the steroid investigations. In January, 1975, Fencl and Tulchinsky<sup>33</sup> reported on a study relating total cortisol concentration in amniotic fluid with the L/S ratio at various stages of gestation in normal human pregnancy. They found a good rank correlation between cortisol and L/S ratio with a sharp increase in total amniotic-fluid cortisol after the thirty-fourth week of gestation which continued to rise as pregnancy progressed. They also noted that no occurrence of RDS was observed in the newborns when, 48 hours before labor, total amniotic-fluid cortisol was higher than 60 mg. per milliliter.

While the role of surfactants has occupied a central place in the last several years in the etiology and prenatal treatment of RDS, a number of other lines of investigation also shed some light on the other aspects of fetal development. One of these concerns the role of proteolytic enzyme inhibitors in the maturation of the lung. In 1970, it was first reported by Evans and co-workers that a correlation existed between the incidence of RDS and reduced alpha-l antitrypsin levels. This result was confirmed in a subsequent paper in which the same authors reported that total trypsin inhibitory capacity levels were significantly lower in the umbilical cord serum of newborn infants with RDS than in weight-matched control subjects. These results suggested that serum enzyme inhibitor levels could be of diagnostic value in the newborns for predicting the susceptability to RDS. The possibility of an antenatal diagnosis was also investigated by performing amniocentesis in 30 women in whom saline-induced abortions of presumably normal fetuses were to be performed. These were obtained at 12-22 weeks gestation and some relationship was found between alpha-l antitrypsin levels

and the gestational age. Further studies on this phenomenon 34 were performed by examining the lungs of 20 newborn infants whose death was attributed to RDS. Eight of the ten infants who had hyaline membranes also had alpha-l antitrypsin present in the lungs. This protein was not detected in infants who did not have hyaline membrane. The authors suggested that alpha-1 antitrypsin may play a role in the formation of hyaline membrane. The association of serum trypsin inhibitor capacity and RDS was independently confirmed by Kotas and co-workers.64 trypsin inhibitory capacity of umbilical cord serum was measured in 112 premature and 164 full-term infants to predict the subsequent development of fatal RDS. The activity of the trypsin inhibitor rose with weight in infants weighing between 1500-2500 grams. These authors concluded that umbilical cord trypsin inhibitory capacity measurement may be a useful test to identify newborn premature infants who are likely to develop fatal RDS. This finding, however, has been disputed recently by Francis and co-workers, 36 who stated they found no relationship between antitrypsin levles in infants with RDS. They felt the trypsin inhibitor levels were indicative of fetal development in general and were not specific indicators of RDS.

Another possible aspect of the etiology of RDS is the effect of the fibrinolytic system. As indicated previously, a major component of the hyaline membrane is fibrin which is formed from transudation of plasma proteins into the alveolar spaces. In 1963, Ambrus and co-workers¹ reported that the serum of premature infants had little or no plasminogen and associated this lack with the pathogenesis of RDS. They explored the therapeutic value of administering urokinase-activated human plasmin in cases of RDS.² A substantial increase in the survival rate was noted, however, because of the high cost of urokinase, practical application of this result remained somewhat questionable. An alternative to urokinase-activated plasmin is plasminogen itself. A study of the effect of plasminogen administration was recently reported.⁴ A double blind study was performed with 100 premature infants in which plasminogen or placebo was administered to the infants immediately after birth. The treated infants have a significantly lower incidence of severe RDS and death resulting from RDS. Thus another possible mode of prophylaxis of RDS may be indicated by these studies.

One of the most effective methods of therapy for RDS is the application of continuous distending airway pressure. The development of this method arose from the understanding of the lack of stability of the pulmonary alveoli due to lack of surfactant. By the use of a low continuous pressure at end-aspiration, the alveoli are, in essence, prevented from collapsing. This form of therapy results in better gas exchange than does conventional ventilation, and its early application may have some advantages in altering the course of RDS.

#### Contribution of Fetal Research to RDS

Fetal research played an important role in several key discoveries in the understanding of the etiology of RDS. After the classic work of Avery in 1959 in which it was demonstrated that the lung extracts of infants who died from RDS had very low surfactant levels compared to lungs of premature infants dying from other causes, the role of the development of the surfactant biosynthesis system

in the lungs assumed a central place in the etiology. The work in 1971 by Gluck in which he showed that the degree of maturity of the lung surfactant system could be predicted through amniocentesis was a landmark in the progress made toward conquering RDS. In Gluck's subsequent 1972 paper, he showed differences in the surfactant system of the human fetus compared to animal models. This, in turn, implied that research in the developing human fetus was essential for further understanding of the pulmonary surfactant system.

Prior to the initial clinical trial of antepartum glucocorticoid treatment conducted in New Zealand by Liggins and Howie, human fetuses had not been used in research on steroid function in lung maturation. Lambs, rabbits, and rats had been used to demonstrate the potential value of steroid treatment in accelerating fetal lung maturation. Of course, the early work of Migeon and others who had investigated the effect of steroidal hormone medication in pregnant women was very important. All of the animal studies had required direct infusion of the fetus for effective treatment because the corticosteroids did not cross the animal placenta. The fact that Migeon et al., had demonstrated that cortisol and corticosteroid did cross the human placenta allowed Liggins and Howie to administer the drug to the mother, a far less risky procedure. Therefore, the clinical trial in New Zealand was the first human experimentation directly related to the use of hormones in reducing the risk of RDS.

As previously discussed, this field of research is in its infancy with many lifesaving discoveries yet to be made. Human fetal research will be an important part of these continuing studies since it has already been demonstrated that major species differences exist. In past years there has been no satisfactory animal model for the mother-placenta-fetus system for studies aimed at unraveling the complex hormonal role in fetal lung development, although recent reports indicate that the rhesus monkey is promising.

# Effect of a Retrospective Ban on Fetal Research

As indicated previously, the ability to perform research involving the human fetus played an important role in understanding the etiology of RDS. The important work by Gluck in 1971 in which he followed the appearance of phospholipids in amniotic fluid was based on analysis of samples obtained by amniocentesis. Had he not been able to perform amniocentesis, this method for predicting fetal maturity and the resulting ability of the fetus to survive would not have been developed. Furthermore, understanding of certain aspects of the maturation processes of the human fetus would be lacking. As Gluck pointed out, the human is different from available animal models, and thus an accurate understanding of human fetal maturation processes must be obtained from human studies.

The method of antenatal steroid treatment to stimulate development of the fetal pulmonary surfactant system was, of necessity, evaluation in a human clinical trial. A large number of animal studies had indicated that administration of steroids could stimulate lung maturation of the fetus. However, the relevance and value of this treatment for the human could only be determined by studies in

the human. Admittedly, this treatment is still experimental, and its ultimate value still open to some questions. But if human studies had not been done, animal studies related to this would be merely of a laboratory finding reported in physiological journals.

#### Future Outlook

Despite the fact that significant advances have been made in understanding the etiology of respiratory distress syndrome, a great many questions still remain unanswered. In the broadest sense, a complete understanding of the process of human fetal development is still lacking. Although a great deal of work has been done with the development of the pulmonary system in laboratory animal models, the relevance of these models to the human fetus is not well established. In fact, it has been shown that the phospholipid biosynthetic pathways in animal models are different from those in humans. A great deal remains to be learned about the biochemical messengers that prepare the fetus to survive when birth is imminent.

Stimulation of the phospholipid biosynthetic pathway of the fetus by administration of glucocorticoids to the mother offers an attractive route for the prophylactic prevention of RDS. However, much remains to be learned about this before antenatal steroid administration can be considered an acceptable clinical method. In the first place, the reasons for its lack of effectiveness after 32 weeks gestation need to be determined. Secondly, the effect of glucocorticoids on other biosynthetic and metabolic pathways in the fetus has not been elucidated. The report of Liggins and co-workers of a higher intrapartum death rate in the treated infants from toxemic mothers as compared to the controls needs to be investigated further for its statistical significance. Another question which remains to be answered is the long-term effect of administration of glucocorticoids on the child. It is possible that a child treated through the mother with glucocorticoids may have sequelae several years subsequent to birth. As stated above, the biochemical messengers which prepare the fetus for survival in the outside environment when delivery is imminent are not well understood. A long period of labor appears to induce maturation in a premature fetus's pulmonary system. It is well established that delivery of a premature infant by cesarean section before the onset of labor results in a much higher risk of RDS. The reasons why the lack of a labor period causes this predisposition need to be clearly elucidated.

Further work also needs to be done on the efficacy of plasminogen treatments of infants who have a high risk of RDS. The clinical trials performed thus far indicate a statistically significant benefit from plasminogen treatments, but larger numbers of cases need to be done to establish overall efficacy. Since achieving an understanding of RDS involves an understanding of the overall process of the human fetal maturation process, further research in this area should have implications over a very broad range. An understanding of the nature of hormone receptors and the induction of biosynthetic pathways could be a result of these investigations. Contributions are likely to be made in understanding of the etiology of such important diseases as emphysema and cancer. An effective armamentarium of treatment methods, both antenatal and postnatal, for RDS can be expected from the lines of investigation now underway and hopefully can lead to a very large saving of human life in the future.

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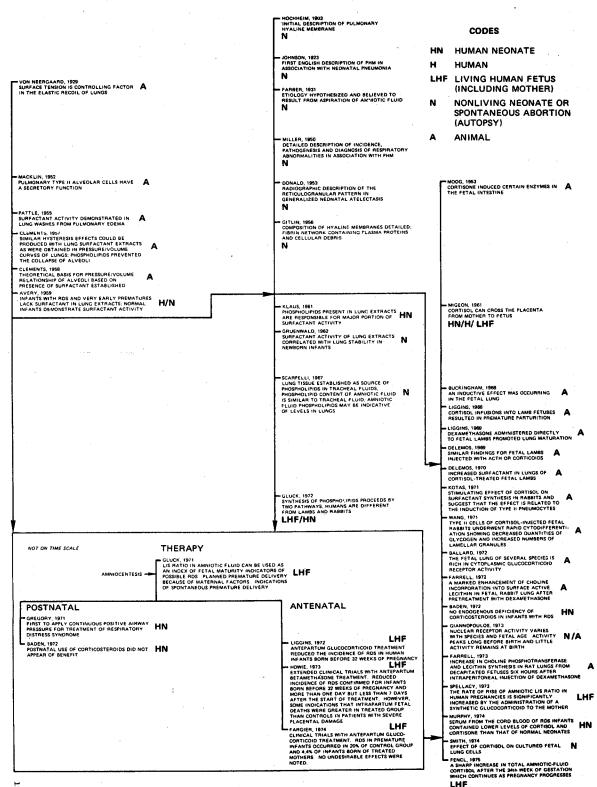
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ANIMAL MODELS

#### ANIMAL MODELS

#### Introduction and Summary

Because the objectives of this study included the identification of the role of research involving living human fetuses in the four cases, and estimation of the effect of a retrospective ban on such fetal research, the adequacy and availability of animal models were considered. The foregoing descriptions of each of the cases include information on animal models, but because of the importance of possible animal models to the conclusions drawn, this section of the report has been prepared to centralize and expand on the information on animal models for the research on living human fetuses. Summaries of the findings are presented below.

#### Congenital Rubella Syndrome (Rubella Vaccine)

In the research that established the association of congenital rubella syndrome with rubella in the mother, research on living human fetuses was not involved, and therefore the question of possible animal models is irrelevant. The association was established by studies on stillborns or neonates, which do not fit the definition of research on living human fetuses as used in this report.

Establishment of the efficacy of the vaccine in preventing rubella and therefore preventing congenital rubella syndrome again do not involve fetal research—humans including nonpregnant women were used. In the determination of the safety of vaccinating pregnant women, human fetuses were used. Studies with animal models had shown that the live attenuated virus would not cross the placental barrier. The inadequacy of these models became apparent after vaccination of presumed nonpregnant women. Examination of the fetuses after induced abortion showed the presence of the live attenuated virus. A study involving pregnant women planning abortions was then done to verify the findings of the few accidental vaccinations.

## Amniocentesis

As a procedure, no record could be found of animal experimentation before its suggested use in humans for therapy of hydramnios in 1882. Since that time there has been considerable animal work, but differences in the amniotic fluid, pelvic structure, trauma resistance, fluid barrier and placenta location exclude animals as good models for the procedure. This conclusion was also reached by the Yale group in the concurrent but separate study (Contract No. NO1-HU-5-2112).

As has been described earlier, amniocentesis played an important role in characterizing and detecting Rh hemolytic disease and in the determination of the degree of fetal lung maturation. It also allows the detection of sex and of

a number of genetic defects in the fetus. These methods depend on the study of the fluid or of the cells either directly as harvested from the fluid or after cell culture. Although animal models for most of these abnormalities are not available, the harvesting and growth of cells can be demonstrated from animal amniotic fluid. However, had not the amniocentesis procedure been available, study of the human amniotic cells would not have been possible.

#### Isoimmunization (Rh Vaccine)

In this case, fetal research was vital in antenatal characterization and detection of the disease. Detection of the disease in the fetus allowed the determination of the need for antenatal transfusions, which drastically reduced the number of in utero fetal deaths. No adequate animal models for Rh hemolytic disease were available in the 1950s when these studies were begun. Intensive study of immune diseases in primates was begun in the middle 1960s, and it now appears that adequate models may exist, except for the problems of animal availability.

It must be pointed out that the fetal research necessary for the eradication of this disease depended on amniocentesis. In antenatal transfusion therapy, the need for the transfusion is dictated by examination of the amniotic fluid. Actual in utero fetal transfusions were preceded by animal studies.

Development of the Rh vaccine, once an understanding of the disease process was gained, did not involve fetal research and the efficacy of the vaccine was proved through use of male volunteers.

# Respiratory Distress Syndrome

The role of surfactant in RDS was established by the study of neonate victims of hyaline membrane disease. Methods to measure lung maturation (which is predictive of RDS) were developed by both animal and human fetal research. Because of interspecies differences in the rate of lung maturation, the latter was necessary at the time it was done, since an adequate animal model did not exist at that time. Fetal research was necessary for definitive conclusions to be made.

In the development of antenatal glucocorticoid therapy, the effect of the drug was established in animal studies. With animals, the glucocorticoid had to be delivered directly to the fetus because the drug did not pass the placental barrier. Thus fetal research was necessary to establish that maternal administration of the drug in humans resulted in fetal uptake and consequent lung maturation.

#### Congenital Rubella Syndrome

Since the isolation of the etiologic agent of rubella and its definitive association with the congential rubella syndrome, considerable effort has been directed to establish an animal model for congenital infection by rubella virus. In this regard, several animal species have been investigated. Congenital infection with natural "wild" rubella virus has been achieved in ferrets, rats, and rabbits. 5, 6

Avila et al., <sup>7</sup> studied rubella virus induced congenital abnormalities in the rat. Intramuscular inoculation of rubella virus into pregnant rats did not have an effect on the developing embryo. Direct intrauterine injection of live virus, however, caused an increase in resorption rate and retardation of postnatal growth. These effects are also found in congenital rubella infection of humans, <sup>8,9</sup> monkeys, <sup>10-13</sup> and rabbits. <sup>5</sup> In addition, ocular abnormalities in 3 of 64 offsprings of dams given direct intrauterine injections were observed. However, repeated attempts to isolate virus from the offspring, from resorption sites, and from retained placenta in mothers who failed to deliver were uniformly unsuccessful.

The results from several laboratories indicate that the rabbit may be a useful model for studying congenital rubella.<sup>5,6,14-16</sup> Kono described eye defects, including cataracts and microophthalmia in congenitally infected rabbits.<sup>17</sup> London et al.,<sup>16</sup> have demonstrated that rubella virus caused congenital infection when pregnant rabbits were inoculated on the sixth day of gestation. However, there were no gross malformations in any fetuses, newborns, or babies.

In a study designed to determine the effect of vaccination on the transplacental transmission of rubella virus in rabbits, Cohen et al., 18 demonstrated that the effect of vaccination on congenital rubella in rabbits corresponds in general to the observations in man<sup>19-22</sup> in that rubella infection occurred in preimmunized animals. Further similarity in rubella infection in rabbit and man was seen in the HAI response. The response in adult rabbits to vaccine was varied and relatively poor in comparison with that following the injection of low passage virus as noted in children with HPV-77 virus by Meyer et al., 23 and in rabbits with HPV-77 (duck embryo) by Oxford and Potter. 24

The virus recovered from young rabbits of dams immunized with vaccine virus and challenged with "wild" virus appeared to be "wild" virus. This is consistent with the failure of Kono et al., to isolate vaccine virus from off-spring of immunized dams, indicating lack of passage of vaccine virus across the placenta. As will be pointed out later, the human situation regarding transplacental passage of vaccine virus is different from that of the rabbit. Further differences in placental behavior were shown by the finding that IgM will not cross the human placenta but will transverse the rabbit placenta.

In addition, a number of nonhuman primates have been evaluated for use as model systems. These include baboons (Papio spp)<sup>25,26</sup> chimpanzee (Pan troglodytes),<sup>25</sup> rhesus monkeys (Macaca mulatta),<sup>27-33</sup> African green monkeys (Cercopithecus aethiops),<sup>34-35</sup> cynomolgus monkeys (Macaca fascicularis),<sup>36</sup> and patas

monkeys (Erythrocebus patas).<sup>37</sup> These animals are susceptible to rubella virus infection; however, fetal abnormalities similar to congenital rubella in the human<sup>38</sup> are rarely seen.<sup>27,29,32,33</sup>

Recently, Patterson et al., 39 used marmosets to investigate susceptibility to rubella virus infection. Marmosets were susceptible to infection by intranasal inoculation. Infected animals began to excrete virus 12 days after inoculation and continued to shed virus for 6-7 days. Significant hemagglutination—inhibition antibody developed by 3-7 weeks postinoculation. The infection was shown to spread naturally; one uninoculated animal of three exposed to the infected group developed rubella HAI antibodies. However, there were significant differences in rubella infection in marmosets compared to natural rubella in humans. The infected animals did not develop clinical signs of infection. Further, congenital rubella virus infection or anomalies were not present in the fetuses of two female marmosets infected during early pregnancy. The value of the marmoset model for congenital rubella, therefore, remains to be established.

Sever et al., 33 reported on experimental rubella infection in pregnant rhesus monkeys. Five pregnant monkeys were inoculated intravenously with rubella virus during day 25 and 28 of gestation. None of the animals developed clinical disease; however, virus was recovered from the nasopharynx of 4 of the 5 animals, and the blood of 2 animals. Further, neutralizing antibody was detected on day 14 and complement-fixing antibody was present at six weeks. At the time of delivery, 1 stillborn and 4 live offsprings were studied; there was no evidence of infection or congenital malformation. However, 1 of 3 offsprings had antibody at six months of age, suggesting active antibody production due to undetected transplacental infection.

Parkman et al., 32 reported that after rubella virus inoculation of 6 pregnant rhesus monkeys in the fourth week of gestation, virus was found in 3 of the fetuses 10 to 31 days later.

Hopps et al., 40 reported on a comparison of virulent low passage rubella virus (LPV) and attenuated high passage rubella virus (HPV-77) infection in 12 pregnant rhesus monkeys. The animals were inoculated parentally during the fourth week of gestation, 6 animals received HPV-77, and 6 were inoculated with LPV. All of the animals developed antibodies. The animals were sacrificed 10 to 33 days after inoculation and specimens of maternal and fetal tissue were collected for virus isolation. Rubella virus infection was transmitted to the products of conception in 5 of the 6 animals inoculated with the virulent LPV strain. However, in those 6 animals inoculated with the attenuated HPV-77 strain, no rubella virus was isolated from maternal or fetal specimens taken 17, 21, and 28 days after inoculation.

From what has been reported for the animal model systems evaluated, it is clear that the experimental animals behave differently when exposed to rubella virus. With most animals, congenital infection with natural "wild" rubella virus can occur, but in many cases, congenital malformations are absent. Where congenital defects have been reported, they primarily involve the eye. The spectrum of congenital abnormalities in animal model systems does not approach that found in humans.

A most important consideration when discussing the appropriateness of animal models is that vaccine virus did not cross the placenta and infect the fetus. Based on this, the vaccine could be considered safe for use in pregnant women. This, however, was not the case in humans where it was shown that vaccine virus did cross the placenta and did infect the fetus.

To quote from testimony given by Dr. Michael Oxman, Harvard Medical School, before the Massachusetts State Legislature, "When rubella vaccine was first developed, an important question was its safety for the fetus--in other words, would the vaccine virus behave like the natural 'wild' rubella virus and, after infecting the mother, cross the placenta to infect and damage the fetus? Tests were done in pregnant monkeys and whereas the 'wild' rubella virus did cross the placenta and did infect the monkey fetus, just as it does in the human, the vaccine virus did not. This suggested that administration of rubella vaccine to pregnant women might not be hazardous to the fetus. Fortunately, however, physicians in several medical centers then performed the same study in women scheduled for therapeutic abortions. After a full explanation of what was involved, a number of women volunteered and received rubella vaccine 11 to 30 days prior to their abortion. Subsequent examination of the aborted fetal tissues showed that, in contrast to the results in the monkey, the vaccine did cross the human placenta and did infect the human fetus. On the basis of this information, the administration of rubella vaccine to pregnant women or to women who might become pregnant within 60 days of vaccination is prohibited."

Based on these considerations, it is clear that animal models have been inappropriate for congenital rubella and in some cases, misleading in terms of vaccine safety.

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#### Amniocentesis

When considering an alternate animal model in lieu of amniocentesis on humans and fetal research, one should differentiate between the amniocentesis procedure per se, and the diagnostic and therapeutic procedures performed via amniocentesis. In both situations the possibilities of an alternate animal model must be considered for the procedure per se or as a model for developing a diagnostic or therapeutic procedure. Thus, this section will attempt to outline the possible alternate animal models for each situation.

# Alternate Animal Models for Developing Amniocentesis Procedure

Various animal models have been considered for evaluating amniocentesis, but unlike the human, the embryos of domestic animals (sheep, cattle, horses, pigs, and cats) have large allantoic vesicles and, as a result, contain large volumes of both allantoic and amniotic fluids. Marsh et al., indicate in their paper that the amniotic volume patterns do differ from animal to animal. In the cat and guinea pig, amniotic fluid shows a slight fall in volume followed by a climb to term. The rat, hamster, mouse, and rabbit show a very rapid decrease to virtual disappearance near term while moderate to rapid decreases near birth are characteristic of the sow and cow. Sheep and human beings show a stationary volume or slight decline near birth once a maximum is attained. A hair saturation factor may affect the amniotic volume in some animals because the amniotic fluid attaches more and more to fetal hair as term approaches.<sup>2</sup> Thus, it is apparent that many of the potential animal models are unsatisfactory because they show a distinct difference from humans in the volume of amniotic fluid present during the gestational period. In addition, the only animal models which might be suitable for developing the technique of transabdominal amniocentesis should be monovular and possess a unicornuate uterus.3 This statement is based upon the fact that the technique could not be satisfactorily evaluated either in uteri containing multiple fetuses or in a bicornuate uterus because of structural differences relative to humans. These restrictions reduce the potential animal model to higher primates, e.g., monkeys, chimpanzees or baboons.

In considering a higher primate, one must examine the similarities and differences between it and humans. Some of the similarities, although not necessarily related to the procedure per se, would include the following:

- (1) Access to the rhesus monkey fetus in utero is possible and samples of fetal body fluids can be obtained throughout gestation.<sup>4</sup>
- (2) The embryological studies of Heuser and Streeter<sup>5</sup> and Streeter<sup>6</sup> have demonstrated that the anatomical and temporal aspects of morphological development in the macaque is similar to the human embryo in most respects throughout the critical period of differentiation.

- (3) It has been shown that there is a similarity in the rhesus monkey and humans as regards embryotoxity, i.e., identical teratological manifestations as seen in humans have been produced in rhesus monkeys regarding radiation, androgenic hormones and thalidomide syndrome.<sup>7</sup>
- (4) Placental structure in rhesus monkeys is highly analogous to the human during the later stages of pregnancy. 7.8
- (5) The virtual identity between female human and monkey reproductive physiology has been established by many investigators.

As a result of human amniocentesis, some investigators are now routinely performing amniocentesis in subhuman primates. This would lead one to believe that indeed the higher primates could have been used as models to perfect the technique. However, the reasons cited below are also considered valid by some investigators for not employing primates in developing amniocentesis as a procedure. These include the following:

- (1) Significant difference in the amniotic fluid: fetal size ratio relative to humans leading to invalid extrapolation of a technique developed in these animals to humans, especially for late second and third trimester amniocentesis.
- (2) Difference in skin and subcutaneous tissue composition such that development of skill by the operator would not be applicable to humans.
- (3) Difference in boney pelvis structure to the extent that this hard tissue, in many cases, would not allow invasion of the uterus at the desired human site.<sup>3</sup>
- (4) Placental position in some of these species is characteristically anterior so that transabdominal entry into the uterus would always be through the placenta.<sup>3</sup>
- (5) Size of the uterus is always smaller at equivalent stages of pregnancy.
- (6) Size differences also introduce the problem of needle diameter and length. Properly sized needles for humans could not be determined without direct evaluation on humans.
- (7) The simian uterus is resistant to trauma<sup>10</sup> which suggests that premature delivery might occur if the techniques developed in primates were extended to humans.
- (8) There is a fluid barrier around the amnion in some monkeys which provides a self-sealing mechanism to prevent losses of amniotic fluid from the puncture site. Loss of amniotic fluid

following amniocentesis has been implicated in various anomalies. One case of Potter's facies has been reported in a human newborn after prolonged leakage of amniotic fluid. 11

(9) During the later stages of gestation the volume of amniotic fluid available would be decreasing due to the hair saturation factor as mentioned earlier.

In the evaluation of amniocentesis in mice and rats, numerous anomalies including malformation of the extremities, microstomia, short umbilical cord and particularly cleft palate were reported after the procedure was performed. 12-22 These animal experiments in mice and rats showed that cleft palate could be produced with 100 percent frequency if amniocentesis was carried out in a certain stage of pregnancy prior to palate closure. The similarities between the defects produced by amniocentesis in rats and mice and human cases of cleft palate led Poswillo to suggest that amniocentesis might produce the same effect on human fetuses during the first trimester of development. It must be remembered at this time that only a very limited number of amniocenteses have been performed during the late first trimester period.

Poswillo 9 has shown that a suitable animal model, the Macaca irus monkey, does exist for demonstrating closure of the posterior palate at day 46 of development, and, according to Kraus et al., 23 the human palate closes at day 47. There results showed that the congenital defects produced in the lower species (rats and mice) by amniotic-sac puncture were not reproduced in the M. irus monkey. Thus, it would appear on the basis of these limited data that the hazard of inducing congenital malformations, e.g., cleft palate, is far less than that predicted by the rat and mouse studies. Furthermore, thousands of amniocenteses have been performed in humans during the second and third trimester of pregnancy and the complications noted are less than one percent. This would be additional proof that amniocentesis per se does not cause congenital malformations as observed in the rat and mice studies.

Although Poswillo<sup>9</sup> has demonstrated an animal model which closely parallels the human embryo during the first trimester of development, it is very doubtful if this animal model can be adequately extrapolated to cleft palate formation in human embryos. The reasons for this conclusion are as follows:

(1) The most significant reason is the fluid barrier surrounding the amnion in M. irus which provides a self-sealing mechanism to occlude puncture wounds of both the amnion and chorion. This self-sealing mechanism has not been demonstrated in humans, and, if Trassler et al., 22 are correct in their assessment of the malformations caused in rats and mice, i.e., a loss of amniotic fluid resulting in oligohydramnios induces the abnormalities seen in rat and mice fetuses, such a loss of amniotic fluid during the first trimester of development could prove disasterous to human embryos.

- (2) It has not been demonstrated that a correlation exists between the volumes of fluid in the chorionic cavities of both species, because this would be the only practical method of obtaining fluid prior to 50 days of development.9
- (3) Most investigators agree that the earliest acceptable time that amniocentesis should be performed in humans is 14 weeks, almost twice the length of time that cleft palate could be detected.

In conclusion, a ban on human fetal research with regard to developing improved techniques of amniocentesis would have resulted in its nonutilization due to inadequate or inappropriate alternate animal models with which to develop and perfect the method. The ramifications of the unavailability of this technique are overwhelming considering the multitude of highly useful and desirable diagnostic and therapeutic procedures which rely on amniocentesis.

# Alternate Animal Models for the Diagnostic and Therapeutic Techniques Developed as a Result of Amniocentesis

If it is accepted, as in the preceeding section, that the development of amniocentesis was dependent upon research involving living human fetuses, the effects of a ban on human fetal research in the antenatal diagnosis and therapy via amniocentesis would have been far reaching indeed.

The diagnostic and therapeutic methods developed via amniocentesis include the following:

- (1) Analysis of components in amniotic fluid
- (2) Detection of genetic defects
- (3) Detection of Rh isoimmunization
- (4) Detection of fetal maturity
- (5) Providing relief from polyhydramnios
- (6) Induction of a therapeutic or elective abortion.

An important question in determining the effect of a ban on human fetal research is whether or not an animal model could have been substituted for the advances made to date regarding prenatal diagnosis and therapeutic procedures developed as a result of amniocentesis. Each of the above indications for performing amniocentesis will be considered. The development of alternate animal models for Rh isoimmunization and the respiratory distress syndrome will be discussed in those sections.

# Analysis of Amniotic Fluid

In comparing the materials found in amniotic fluid of humans and other species, it is apparent that some materials are found in both while in other instances there is a distinct difference. For instance, the amniotic fluid of foetal lambs contains lecithin, sphingomyelin, and phosphatidyl ethanolamine the as does human amniotic fluid. In addition, observations show that both human fetal and monkey fetal liquors contain many of the major protein components of serum. However, the fact one particular protein was shown to be present in three species of monkeys but was absent from human liquor suggested a difference in fetal metabolism.

Further indications of a possible difference in the metabolism of compounds, i.e., lactic acid, has been demonstrated.<sup>27</sup> The transfer of lactic acid from the human fetus to the mother indicated a turnover rate of 1.4 minutes while the turnover rate from the monkey fetus to the mother was in excess of fifteen minutes. As a result, Friedman et al.,<sup>27</sup> concluded that lactic acid is not a major end-product of fetal metabolism in primates.

Other animals have afforded valuable information concerning the source of amniotic fluid and the maternal-fetal relationship to various components found in amniotic fluid. Both the fetal lamb  $^{28}$  and the monkey fetus  $^{29}$  have been demonstrated upon sodium depletion to respond to the deficiency like a sodium deficient adult by restricting sodium losses in the urine and by excreting water. The rhesus monkeys as well as the guinea pig, rabbit, calf and rat demonstrate selective absorption of antibodies and of radioactive labeled plasma proteins but the mechanism of absorption differs. Heterologous albumin has been shown immunologically to reach the fetus in the rabbit, but Whipple et al., found that some labeled serum proteins were taken up in rabbits but not in the dog while labeled serum albumin,  $\beta$ -globulin and  $\gamma$ -globulin were transferred to the guinea pig fetus.

The anatomical membrane concerned with selective transmission in orders other than primates has been considered to be the endoderm of the gut or the yolk sac. On the basis of the evidence of the above comparative studies it was postulated that transmission in man and other primates was also by way of the amniotic fluid and the fetal gut. However, the anatomy of the placental systems and fetal membranes vary widely among different orders of animals. The human being possesses a specialized haemochorial placental system quite unlike that of other orders, and the yolk sac in mid and late pregnancy is entirely vestigial. A comparable placental system is again found only among the catarrhine monkeys and anthropoid primates (apes) with the placenta of the rhesus monkey resembling the human placenta very closely in later stages of pregnancy.

The experiments of Bangham <sup>30,41</sup> with radioactive labeled proteins injected into pregnant rhesus monkeys provide evidence that there is a selective transfer of certain maternal serum proteins across the placenta and that the amniotic fluid plays an unimportant part, if any, in the transmission of proteins to the primate and human fetus. There is also evidence using labeled lactic acid injected into the fetal circulation of the rhesus monkey that the maternal and fetal organisms freely exchange metabolites <sup>27</sup> in both directions across the placenta.

Thus, these few correlations with regard to amniotic fluid concentrations of certain metabolites and proteins should caution against too great a tendency to interpolate results in one or several species or orders to the human situation.

## Detection of Genetic Defects

Knowledge of the mitotic and meiotic behavior of chromosomes is one area where animal models have contributed to the present state of advanced techniques which permit visualization of the chromosomes both in human lymphocytes and in cells cultured from amniotic fluid obtained by amniocentesis in human pregnancies. The mechanisms leading to abnormal behavior of the chromosomes as seen in nondisjunction and in balanced and unbalanced chromosome translocations have long been known both in lower forms and in mammals.42-45 Nondisjunction (failure of members of a chromosome pair to separate equally at meiosis in ovum and sperm) is the primary cause of the trisomies which are the major type of chromosome aberration producing gross malformation in human concepti and newborns. Down's syndrome (mongolism) is the most common trisomy in human births and consists of three members of chromosome pair number 21, instead of the normal pair. A more rare but inheritable abnormality of the human chromosomes which can lead to an unbalanced condition of chromosome number and to congenital malformation is known as a translocation. The most common translocation in humans is D/G (one chromosome of the D type is permanently attached to one of the G type). Unlike the true trisomy which is an "accident" of cell division in meiosis and therefore is not inheritable, the translocation can be carried in a balanced state in a normal human "carrier" and can be inherited from the "carrier" in an unbalanced form which produces congenital malformations.

Models of the aneuploidies, of which trisomies like Down's syndrome are but a type, have also been known for the domestic cat, mouse, and hamster. Although these chromosome aberrations have models, the models cannot give us any clinical indications of what specific additions, losses or translocations a given human chromosome will present. This is because the gene content of the human chromosome differs from that of its model.

Recent advances in inducing banding of specific chromosomes and in formation of mouse/man somatic cell hybrids have brought about rapid advances in assigning specific human genes to specific chromosomes and in establishing groups of genes which are linked (closely located) on the same chromosome. This information has long been available in corn, tomato, wheat, and the fruit fly, mouse and hamster. The knowledge of gene location on specific chromosomes and of groups of genes which are closely linked will enhance the value of amniocentesis in human pregnancies. With this additional knowledge it is possible to combine biochemical studies of the amniotic fluid contents or cultured amniotic fluid cells with specific chromosome patterns or known genes to which the congenital malformation may be linked.

The above technique has been postulated as an aid in detecting fetuses affected with sex-linked diseases where accurate sex-determination may be made from studies of presence or absence of both the X and Y (F body) chromosomes, while biochemical determinations of a linked gene such as the ABH secretor or

G6PD status are made in families or subpopulations where these genes are common. These techniques can be refined in an animal model such as a mouse in which amniotic sex chromatin and fetal sexing are demonstrable 46 and, in which much information concerning gene location and linkages are already available, but will have to be adapted to fit the specific gene defect of the human subject.

In summary, there are no known animal models for identifying the X-linked diseases presently detectable by amniocentesis in the human which include the Lesch-Nyhan and Hunter's syndromes, and Fabry's disease. The same situation would prevail for the cytogenetic studies used to detect chromosomal aberrations since the chromosomal number and gene content is different. Thus, a suitable animal model does not exist for detecting chromosomal aberrations. In addition, there is no animal model for the various inborn errors of metabolism which have been identified by antenatal diagnosis.

Diagnosis of the major congenital malformations of the central nervous system such as anencephaly and spina bifida (open spine) have been the most difficult to predict from family data and from amniotic fluid since there has been no specific biochemical or cytological change associated with this category of human malformation. Attempts have been made to determine the presence of anencephaly with or without spina bifida by increase in optical density of the amniotic fluid at 450nm ( $\Delta$  OD450) provided the pregnancy is not complicated by Rh sensitization. Attempts have been made to determine the previously cited sensitization. The general it may be concluded from the previously cited work that in the last trimester of pregnancy, an antenatal diagnosis of upper intestinal obstruction may be made if there is an increase in  $\Delta$  OD450, and not associated with Rh sensitization.

Another approach to diagnosis of central nervous system malformations from amniotic fluid is the reduction in 5-hydroxy-indoleacetic acid (5HIAA) levels as reported by Emery et al.<sup>52</sup> Reduction of 5HIAA was observed, but no change was observed in a number of other substances present in amniotic fluid nor was reduction of 5HIAA levels observed in cases of polyhydramnios where the fetus was normal.

A new approach to the diagnosis of central nervous system malformations has been postulated by the detection of a specific biochemical substance in amniotic fluid and demonstrated in fetuses of the Lewis rat who were affected with spina bifida. The presence of specific proteins ( $\beta$ -trace and  $\gamma$ -trace) in human cerebrospinal fluid (CSF) has been well established and their study was undertaken to investigate whether closure malformations of the central nervous system (spina bifida) would cause a rise in amniotic fluid alpha-foetoprotein levels. It has been suggested that leakage or transudation of fetal blood components or CSF directly into the amniotic fluid would cause a rise in the alpha-foetoprotein concentration. The authors demonstrated that a  $\beta$ -trace-like protein of rat CSF could be demonstrated in the amniotic fluid of embryos exhibiting spina bifida.

These results clearly point to the development of an antenatal diagnosis for spina bifida, but the authors are aware that a true communication between the central nervous system and the amniotic fluid is a prerequisite for the detection of  $\beta$ -trace-like protein. While the preceding article postulates an

animal model in the much needed area of human malformation with hitherto unknown biochemical relation to composition of amniotic fluid, its usefulness in predicting closure malformation in human pregnancy has yet to be demonstrated.

## Detection of Fetal Maturity

A common problem in clinical obstetrics is the precise determination of gestational age and fetal maturity. Peterson et al.,54 have shown that the rhesus monkey can be used as a model for the ultrasonic measurement of the biparietal diameter of the fetal head. After approximately 120 days gestation in the rhesus monkey (Macaca mulatta), a noticeable decline in the rate of growth of the fetal skull was observed via these biparietal measurements, data which are in agreement with trends noted in similar studies of the human fetus.

In addition to the above observation, amniotic fluid creatinine levels in the last third of pregnancy in Macaca mulatta are comparable to values in humans, but no clear relationship exists between the creatinine concentration and the duration of pregnancy. Similarly, the bilirubin concentration in the amniotic fluid does not show a change with reference to gestational age nor does osmolality appear to be a predictor of fetal age and growth in the rhesus monkey. All these latter determinations have proven of value for estimating human gestational age and fetal maturity. Thus, there is a clear separation between the two species and the monkey is not considered a totally satisfactory model for detecting fetal maturity.

<u>Polyhydramnios</u>. The polyhydramnios condition has been observed in diabetic monkeys, <sup>54</sup> and, as a result, amniocentesis could therefore be performed on such a species to demonstrate the effect of fluid removal. However, a primary disadvantage in using monkeys as a polyhydramnios model would be the difficulty in breeding primates which are in captivity, developing a colony of diabetic monkeys and, the effect of diabetes on the fetal development of the monkey.

Induction of Abortion. Any of the higher primates presumably could be used for developing the abortifacients to be used for inducing an abortion in conjunction with amniocentesis. However, regarding the amniocentesis procedure itself, the higher primates are considered an unsatisfactory model for reasons cited earlier.

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#### Isoimmunization

It became apparent soon after Rh incompatibility was postulated to be responsible for the hydrops, anemia, jaundice, and brain damage associated with the disease process designated erythroblastosis that methods of early detection were the only possible means to predict the probability of disease in these fetuses. Tests to assess the presence of Rh antibodies in the circulation of the sensitized gravid female, and the presence and quantity of fetal erythrocytes in the maternal circulation led to the development of prompt exchange transfusions for neonates with erythroblastosis fetalis.

The principle method of early detection of Rh hemolytic disease of the fetus in utero is based on the detection of bilirubin in amniotic fluid. It was shown that in the fetus, high levels of bilirubin pigment in the amniotic fluid correlate with the severity of the hemolytic disease in utero. Therefore, many of the animal models pertaining to erythroblastosis involve various aspects of bilirubin metabolism. Guinea pigs, rats, and rhesus monkeys were used in these studies. A study in guinea pigs 1 demonstrated a bidirectional transfer of radioactive carbon labeled unconjugated bilirubin across the placenta from the fetal to maternal side and vice versa. Conjugated bilirubin injected into the fetal circulation demonstrated only trivial passage of the conjugated pigment into the maternal circulation. A later study 2 using radioactive tagged conjugated bilirubin and labeled water soluble BSP demonstrated that high molecular weight water soluble substances do not diffuse readily across the placental membrane. Similar studies of bilirubin disposition in fetal monkeys 3,4,5,6 supported the results previously obtained in guinea pigs. These data suggest that in both guinea pigs and primates, the placenta is virtually impermeable to conjugated bilirubin and that both the monkey and guinea pig fetuses may exhibit an impairment of hepatic excretion of conjugated bilirubin. In both the guinea pig and monkey, unconjugated bilirubin readily entered amniotic fluid from the maternal but not the fetal circulation. In contrast to the results of the studies in the guinea pig and monkey, investigations using tritiated bilirubin in rats 7 were unable to demonstrate transfer of unconjugated bilirubin from fetus to mother. While these differences may be due to species variability, it is evident that there is a need for further data on the disposition of bilirubin especially in primates. The correspondence of greater concentrations of bilirubin pigments to progressive severity of in utero fetal involvement of the human have led to the use of  $(\Delta A_{450})$  spectrophotometric studies of human amniotic fluid in the management of The fact that bilirubin pigment concentrations in amni-Rh isoimmunization.8,9 otic fluid follow increased sensitization of the Rh(D) mother as reflected by rising antibody titres in her circulation, would seem to indicate that the maternal-fetal distribution of bilirubin in the human closely approximates that which was later demonstrated to exist in the monkey and guinea pig.

Some clinical symptoms associated with hemolytic disease of the newborn, namely jaundice, failure to thrive and positive Coombs test, were reported in consecutive litters of piglets from a sow mated to a boar with incompatible antigens associated with his red cells. Although some clinical signs of hemolytic disease were present in these piglets, the pig is not a true model for human hemolytic disease, because there is no *in utero* involvement of the fetuses.

Involvement of the piglets only occurs if during the suckling period they are exposed to the maternal antibodies contained in the collostrum. 10

An animal model which is useful in studying methods of treatment for the jaundice of hemolytic disease is a genetic strain of rat (j/j) which is bred to carry a recessive genetic disorder of hyperbilirubinemia. This type of mutation in the rat was initially described by Gunn. As a consequence of the demonstration by Haddock and Nadler that bilirubin toxicity is modified by blue light treatment in cultures of human fibroblasts, hyperbilirubinemic j/j rats have shown less neural injury when exposed to blue light. The photodecomposition of bilirubin has also been successfully used in human newborns who are at risk for central nervous system damage due to bilirubin toxicity from a variety of causes. The latest and the strain of the photodecomposition of causes. The latest area of the photogeneous system damage due to bilirubin toxicity from a variety of causes.

In the case of severe in utero involvement of the fetus, it has often been necessary to carry out intrauterine transfusion of the human fetus. As early as 1922, experiments with uptake of India ink from the peritoneal cavity to the circulating blood by lymphatic channels were carried out on fetal kittens by Cunningham. 20 He found that the entry of material into mediastinal lymph nodes only occurred in association with respiratory activity which he observed in older fetuses. Since then the validity of his assumption from this model has been confirmed and the role of diaphragmatic movement in accelerating the rate of absorption of particulate matter (i.e., red cells) from the peritoneal cavity has been established. 21 Thus it was postulated that uptake of blood might be slow and less efficient in the fetus owing to the absence of respiratory activity under normal intrauterine conditions. In recent years, further interest in the mechanism and fate of red cells transfused by the intraperitoneal route to the fetus in utero has been stimulated by its use for administration of blood to the human fetus in severe erythroblastosis fetalis. Pritchard and Weisman $^{23}$  had determined the usefulness of absorption of erythrocytes from the peritoneal cavity of humans in 1957. In 1967, the use of the fetal lamb as a model gave retrospective confirmation to the relative efficiency of this method of administering red blood cells. 22 The results obtained from the experiments in the fetal lamb support the contention that, in the human fetus, the majority of red cells administered by the intraperitoneal route reach the fetal circulation intact. Thus uptake of at least 80 percent of the labeled cells by the fetal lamb is in close agreement with the data obtained by Taylor et al., in 1966, using tagged adult red cells injected into the peritoneal cavity of two erythroblastotic human fetuses. The total uptake of donor blood was calculated to be as high as 93 percent in one fetus and 77 percent in the other.

Information is now accumulating that marked isoantigen differentiation is a feature of various species of animal as well as of man. <sup>24, 25, 26</sup> By use of the isoimmunization method, antigens have been detected in the red blood cells of chimpanzees, gibbons, yellow baboons, hamadrayas baboons, mandrills, rhesus monkeys, and marmosets. Of these the hamadrayas baboon <sup>27</sup> appears to be most promising for use in developing a model of hemolytic disease of the newborn and in devising a method of antenatal treatment of that disease. Although use of anti-Rh serum is preventing onset of sensitization in humans, it is still necessary to look for new methods of devising ways of protecting the rhesus-positive fetuses of rhesus-negative women who are presensitized through a variety of

mechanisms. Verbickij 27 presents data that indicate success in setting up a breeding colony of hamadrayas baboons that represent a sufficiently faithful model of hemolytic disease of the newborn in man. The author failed to find complete parallelism between the titre of isoimmune antierythrocyte antibodies in the blood of the female baboon and the severity of the disease in the fetus. However, the model is sufficiently similar to that of man that he has been able to devise new methods of antenatal treatment of the disease (at least in the model system). The method devised by Verbickij is based on the principle of forming a barrier in the amniotic fluid consisting of haptenes which bind maternal isoimmune antibodies and thus do not allow them to penetrate to the erythrocytes and fixed cells of the fetal tissues and organs. The author used erythrophosphatides isolated from the blood of hamadrayas baboons of corresponding phenotype as haptene. This model holds promise for use in the human situation; however, its usefulness in the human can never be brought about without biochemical definition of human haptene and controlled experimental use of the haptene-binding technique in Rh-sensitized pregnant women.

In summary, the availability of animal models and their applicability as models in the various phases of this research has been considered. During the course of the research which led to the ultimate prevention of erythroblastosis fetalis a number of animal models were considered based on several criteria.<sup>28</sup>

- (1) Dog availability, breeding ease, gestational period and the existence of canine erythroblastosis.
- (2) Rodent species (rat, guinea pig, mouse, rabbit) availability, breeding ease, and inducibility of hemolytic disease.
- (3) Donkey or mule large size of fetus and presence of pathologic erythroblastosis manifestations.
- (4) Primates (chimpanzee and baboon) system of comparable blood group isoantigens and isoimmune hemolytic disease.

These models were employed in selected phases of the research but ultimately rejected as models for Rh isoimmune hemolytic disease in humans for the following reasons: 28,29

- Dog dissimilar placental construction compared to humans, there is no placental transfer of antibodies.
- (2) Rodent species small fetal size was prohibitive for surgical procedures comparable to human situation and disease manifestations were highly variable even within the same litter.
- (3) Donkey or mule disease pathology is similar but there is, no placental transfer of antibodies.

(4) Primates - the advent of intense research on the isoantigens of primates and the mechanism of isoimmune disease in these animals is a recent event. Although these animals may ultimately prove to be good models for the study of isoimmune hemolytic diseases similar to erythroblastosis fetalis, the availability of the primate species, cost, and a lack of knowledge of the blood group isoantigens in these species did not make them ideal models for the type of research required to rapidly solve the Rh problem.

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# Respiratory Distress Syndrome

The report on the respiratory distress syndrome traces the understanding of RDS from its early stages to the present knowledge of the diagnosis and treatment. From the historiograph, it can be seen that the present-day understanding of the disease and its treatment evolved through several stages which we identify as follows:

- (1) Understanding the role of surfactant
- (2) Composition of surfactant
- (3) Elucidation of biosynthetic pathways
- (4) Stages of fetal lung development
- (5) Effect of glucocorticoids on lung development.

In each of these areas of research activity, animal models played a significant role in the development of the present-day knowledge of RDS. In most of these areas, the animal studies have been very extensive, and it is not the intent of this report to assemble a detailed review of the work. Rather, we shall examine the role of animal models in several of the significant advances made during the last several years. We shall address the question of the usefulness of the animal models and where the animal models failed with respect to their relevance to the human.

#### Role of Surfactant

The early work in elucidating the role of surfactants in lung mechanics was done almost entirely with animal models. In fact, most of the work cannot justifiably be designated as work with animal models in that it was done with excised lungs taken from animals, and in some cases from man. In the first paper identified in the historiograph, von Neergaard used lungs excised from dog, pig, and man to measure surface/volume relationships. The next significant work, that of Pattle in 1955, lung washes were obtained from both excised animal lungs in vivo to show the presence of surfactant in these washes. The studies of Clements on the relationship of the pressure/volume curves of lungs to the surface tension properties of lung extracts were performed mainly with excised dog lungs.

It should be pointed out, however, that the key work which related the respiratory distress syndrome to lack of surfactant was not performed with animal models but with autopsy specimens obtained from humans. The question of whether animal models could have been used in this discovery is not relevant since pathology specimens were used. Once the relationship between RDS and lack of pulmonary surfactant was made, then the role of animal models in understanding pulmonary surfactant synthesis became important.

### Surfactant Composition

As in the case of establishment of the importance of pulmonary surfactant for lung stability, studies on the composition of the surfactant were performed mainly on excised animal tissue or autopsy specimens from humans. The early work of Klaus <sup>7</sup> utilized beef lung for the determination of the composition and properties of the pulmonary surfactant. Similarly, the work of King and associates <sup>8-10</sup> was based on the analysis of extracts from excised dog lung. A recent report by Clements <sup>11</sup> summarizing the current state of knowledge in the overall composition of lung surfactant is based mainly on data obtained from dog lung but states that the overall composition is quite similar for most mammalian species.

## Biosynthetic Pathways for Fetal Lung Development

The study of the process of lung maturation and the biosynthetic pathways of phospholipid synthesis relied heavily upon animal model experimentation. It should be pointed out that through the course of the investigations, frequent cross comparisons were made with humans, most of which were taken from autopsy specimens. The work by Klaus and co-workers 12 which linked the mitochondrial of Type II alveolar cells to the secretion of phospholipids was performed with guinea pigs. The work of Buckingham and Avery 13 showing that the appearance of phospholipids in lung extracts was linked to the appearance of inclusion bodies in Type II alveolar epithelial cells was performed with mice.

Studies on the biosynthetic pathways for synthesis of phospholipids have centered mainly upon lecithin biosynthesis since this is the main constituent of the surface-active material. Two pathways for biosynthesis of lecithin have been identified in mammalian species, and these are designated as the choline incorporation pathway in which CDP choline reacts with a diglyceride to form lecithin. In the second pathway, ethanol amine is phosphorylated, activated, and linked to diglyceride to form phosphotityl ethanol amine. This is then successively methylated to ultimately form lecithin. As indicated in the report, a great deal of experimental work has been performed on elucidating the biosynthetic pathways for lecithin production in fetal lungs. In a series of papers, Gluck and co-workers investigated the biosynthetic pathways using rabbit and sheep animal models. 14-16 Gluck's subsequent studies showed that the biosynthetic pathways in the sheep and rabbit were different from those in the rhesus and human fetus. 17 The biosynthetic pathways of lecithin in the human have been elucidated in a series of papers by Zachman. 18

It should be pointed out that the animal models possess a distinct advantage in determining biosynthetic pathways in that radioactive precursors can be utilized in these studies. This enables the investigator to follow directly the pathway of a particular compound through several synthetic steps. In human studies, pathways must be elucidated indirectly. Recently, the rhesus monkey has been shown to be a good animal model for studying fetal lung development and the biosynthesis of lecithin. The group of Farrell and Epstein, using rhesus monkey fetuses, both in vitro and in vivo, followed the synthesis of lecithin using

radioactively labeled precursors. 19-21 They found that the first pathway (choline incorporation) was responsible for almost all of the lecithin synthesized by the lung tissue. An abrupt increase in the activity of this pathway occurred at the time when gestation was 90 percent complete. This increase in the Path I activity allows a surge in total lung lecithin and furthermore correlates significantly with the rise in amniotic fluid lecithin. 22

The historiograph in the report identified the work of Gluck in 1971 23 as being a critically important factor in the present-day medical armamentarium against RDS. In this work, Gluck and co-workers studied phospholipid levels in amniotic fluid from 302 amniocenteses and showed that these levels reflect those in the lung of the developing fetus. Comparing the lecithin concentration to the sphingomyelin concentration, a ratio can be obtained and Gluck's results showed that a sharp increase in this ratio occurred at 35 weeks of gestation. Determination of the lecithin/sphingomyelin (L/S) ratio was shown to be diagnostic of the state of pulmonary development of the fetus and thus could have a predictive value of the likelihood of RDS occurring. This work was based on the suggestion of Scarpelli in 1967 24 who studied tracheal and amniotic fluid phospholipids in sheep and suggested that the lung was the source of amniotic fluid phospholipids. Gluck's amniocenteses were performed in women with normal pregnancies. At that time, a human study seemed indicated because the relevancy of the abnormal model was not established until later. Gluck and co-workers made several assumptions about biosynthetic pathways in humans based upon indirect evidence obtained from the composition of the fatty ester composition of lecithin samples. These are in disagreement with the above-cited studies in the rhesus monkey in which the pathways were obtained directly to radioisotope study. From a pragmatic point of view, however, the human studies were necessary at the time Gluck performed them to demonstrate that one could accurately assess the maturity of the fetal pulmonary system before birth.

# Effect of Glucocorticoids on Lung Development

One of the most significant developments in RDS therapy is the antenatal treatment of the fetus through administration of steroids to the mother to stimulate pulmonary development of the fetus in utero. The historical developments for this treatment are outlined in the report and will not be discussed in detail here. The history of this development represents a rich interplay between animal models and studies in humans. Basis for the development was the demonstration in 1953 that cortisone induced certain enzymes in the intestines of fetal rats. The experimental demonstration of the stimulatory effect of steroids upon lung tissue was performed in 1969 by Liggins the showed that the administration of steroids to fetal lambs resulted in premature parturition and accelerated lung maturation. In 1970, DeLemos administered cortisol to fetal lambs and demonstrated increased surfactant production in the treated animals. The effect of corticoids in general on fetal lung maturation was subsequently confirmed in lambs, rabbits, and rats. 28-32

The clinical study in 1972 by Liggins was based on the animal studies showing the stimulatory effect of steroids on lung maturation in the developing fetus. More importantly, his mode of treatment was based on a clinical study

in 1961 by Migeon<sup>33</sup> which showed that cortisol administered to mothers at midpregnancy crossed the placenta from mother to fetus. An estimation of the probable safety of administration of cortisol to the mother was based upon further clinical studies performed in 1966 and 1967 <sup>34,35</sup> which studied the effects of steroid therapy during pregnancy.

The animal model studies which led to Liggins' work demonstrated the efficacy of steroid administration in promoting lung maturation but were inadequate because steroids administered to the mother did not cross the placental barrier in the sheep. Human studies were essential at this point to determine whether or not lung maturation could be stimulated in infants with a high risk of developing RDS. It should be emphasized at this point that the administration of steroids must still be considered as an experimental rather than an accepted clinical practice.

After Liggins' initial clinical demonstration of the stimulatory effects of steroids in humans, animal studies on the mechanism of steroid stimulation continued. Ballard and Ballard in 1972  $^{36}$  showed that fetal lung tissue of several species contained glucocorticoid receptor sites. This was followed by work in 1974  $^{37}$  which showed receptor activity for glucocorticoids in lungs of human fetuses and neonates.

The effect of glucocorticoid administration to the mother on the amniotic L/S ratio in humans was studied in 1973 by Spellacy.<sup>38</sup> These clinical studies showed that the L/S ratio increased after a glucocorticoid was administered to the mother. In another clinical study reported in 1975, <sup>39</sup> the levels of amniotic fluid cortisol with relation to gestational age was measured. The results showed that a sharp increase in the cortisol levels occurred after the 34th week of gestation. This increase in cortisol corresponds to the increase in lecithin content of the amniotic fluid. The relevance of the rhesus monkey as a model for human lung development was recently demonstrated in a report by Gluck.<sup>40</sup> He shows that the biochemical pathways for surfactant are the same and the rise in L/S ratios corresponds to those found in the human. The relevance of the rhesus as an animal model will be important in future studies on the safety and efficacy of the antenatal administration of steroids.

#### Conclusions

We believe the results show that both animal and human studies were essential in the present-day status of prevention and therapy of RDS. In particular, two clinical studies were essential for this development. These are the study of Gluck in 1971 showing the predictive value of the L/S ratio and the clinical study of Liggins in 1972 showing the stimulatory effect of antepartum glucocorticoid administration. Relevant animal models had not been demonstrated at the time of these studies, and thus clinical studies were a logical, essential step. In a larger sense, in any therapeutic procedure, the time comes when a human study must be undertaken if the technique is to find use in the human. It appears from our study of RDS that the clinical trials cited above came at an appropriate time in the development of the diagnostic and therapeutic procedures.

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GLOSSARY

#### GLOSSARY\*

- A-Antigen. A substance, or blood factor, on the surface of some individuals' red cells, that provokes an immune reaction from anti-A antibody.
- ABO blood groups. See human blood groups.
- ABO-Compatible. One person is ABO-compatible to another if his red cells do not carry A or B antigen that will provoke a reaction from antibodies in the other's serum.
- ABO-Incompatible. One person is ABO-incompatible to another if his red cells carry A and/or B antigen that will provoke an immune reaction if transfused into the other, due to the presence in the other's serum of anti-A and/or anti-B antibody.
- ABO protection. The immunologic phenomenon through which a fetus that is ABO-incompatible with its mother as well as Rh-incompatible with her appears to be less in danger of erythroblastosis than one which is Rh-incompatible but ABO-compatible with her.
- Agglutinate (verb). To bring together in an aggregate, or clump, as some antibodies do to red cells.
- Agglutination. Immune reaction in which red cells carrying a specific antigen (for example, A) are stuck together in clumps, or aggregates, by the corresponding antibody (anti-A).
- Alveoli (pulmonary). Small sac-like structures through the walls of which gas exchange takes place.
- Amniocentesis. Passage of a hollow needle into the amniotic fluid that surrounds the fetus in the womb, and the removal of a specimen of the fluid.
- Amniotic fluid. Fluid within the amniotic sac surrounding the fetus.
- Anemia. A deficiency state of blood in which there are too few red cells or the red cells are of too poor quality to fulfill their oxygen-transporting function in the body.
- <u>Anencephalic</u>. Congenital absence of the cranial vault with the brain partially or completely missing.
- Anti-A antibody. An antibody naturally present in individuals of groups O and B that will attack and destroy red cells of persons in groups A and AB.
- Anti-B antibody. An antibody naturally present in individuals of groups O and A that will attack and destroy red cells of persons in groups B and AB.
- Antibody. A substance produced by the body in response to a specific foreign material, or antigen. An antibody acts, in an immune reaction, to defend the body by destroying or nullifying the antigen against which it is made.

<sup>\*</sup>Adapted from Dorland's Illustrated Medical Dictionary, (Twenty-Fifth Edition), W.B. Saunders Co., Philadelphia, 1965; and Zimmerman, D.R., Rh. The Intimate History of a Disease and Its Conquest, Macmillan Publishing Co., Inc., New York, 1973.

Antigen. A substance on or in a red cell that is antagonistic to a human or other organism in such a way that it forms an antibody against it. The blood factors A, B, and Rh are antigens. Chemically, most antigens are proteins.

Anti-Rh antibody. An antibody that may be formed in Rh-negative individuals, in response to antigenic challenge by the Rh factor, which will attack and destroy red cells of persons who are Rh-positive.

Anti-Rh gamma globulin. See Rh vaccine.

Antitrypsin. A substance having an inhibitory action on the enzyme trypsin.

Ascites. Accumulation of serous fluid in the abdominal cavity, also called hydrops.

Atelectasis. Incomplete expansion of the lungs at birth.

Autosome. Any ordinary paired chromosome as distinguished from a sex chromosome.

<u>B-Antigen</u>. A substance on the surface of some individuals' red cells that provokes an immune reaction from anti-B antibody.

Betamethasone. A synthetic glucocorticoid.

<u>Bilirubin</u>. A breakdown product of hemoglobin released when red cells are destroyed; it is made by the liver. Some forms of this bile pigment are highly toxic, and may stain and injure brain tissue (kernicterus), causing death.

Biopsy. The removal and examination of tissue from the living body.

<u>Blood factor</u>. An inherited antigen present on the surface membrane of red cells of some individuals but not on others.

Blood groups. See human blood groups.

CDE. Alternative nomenclature for the Rh blood group system.

<u>Challenge</u>. In immunology, the administration of an antigen to awake an immunologic response in a previously sensitized person.

Choline. A vitamin and basic constituent of lecithin.

Chromosome. A structure in the cell nucleus which transmits genetic information.

<u>Compatibility</u>. A person is compatible with another if his red cells can be transfused into him without provoking an immune reaction, or transfusion reaction.

<u>Complement.</u> A series of enzymatic proteins that interact and combine with the antigen-antibody complex producing lysis when the antigen is an intact cell.

Complement fixation test. A test used to determine the presence of complement. It is the basis of many serological tests for infection.

Congenital. Existing at or present before birth.

Cortices. Plural of cortex, the outer layer of a body structure.

Cortisol. A steroid hormone.

Cytodifferentiation. In cells, to distinguish on the basis of differences or to develop specialized form, character, or function.

Decidua. The mucous lining of the uterus thrown off after parturition.

- Dexamethasone. A synthetic glucocorticoid.
- ECG. Electrocardiogram a graphic tracing of the electric current produced by the excitation of the heart muscle.
- Eclampsia. Convulsions and coma occurring in a pregnant woman.
- Swelling of body tissues due to fluid retention.
- Embryopathy. A morbid condition resulting from interference with normal embryonic development.
- Encephalography. A graphic tracing of the potentials on the skull emanating from nerve potentials in the brain.
- Enzyme. A protein capable of producing or accelerating a change in (often a specific) compound.
- Epidemiology. A study of the relationships of the various factors determining the frequency and distribution of a disease.
- Epithelium. The covering of the external and internal surfaces of the body including the lining of vessels and other small cavities.
- Erythroblast. An immature red cell. It is identifiable under the microscope because, unlike adult red cells, it still retains a nucleus. Too rapid destruction of adult red cells leads to compensatory overproduction of immature ones; hence, the disease name, erythroblastosis, which signifies the presence of and excess of erythroblasts.
- Erythroblastosis fetalis. Disease of fetal and early newborn life. Usually occurs when red cells from Rh-positive fetus cross the placenta and provoke immune response in Rh-negative mother. Her anti-Rh antibodies then enter fetus, destroying its red cells, and stimulating abnormally high production of immature red cells, or erythroblasts.
- Erythrocyte. See red blood cell.
- Etiology. The study or theory of the factors that cause disease and the method of introduction to the host.
- Exanthem. An eruptive disease or fever, a rash.
- Exchange transfusion. In newborn erythroblastic infants, total or near-total removal of the baby's Rh-positive blood, which is vulnerable to attack by maternal antibodies brought from the womb, and its simultaneous replacement with invulnerable Rh-negative blood.
- Fetoscopy. Examination of the fetus by means of an endoscope inserted through the abdomen.
- Fibrin. An insoluble protein formed from fibrinogen during the normal clotting of blood.
- Fibrinogen. A soluble blood protein involved in the clotting process.
- Fibroblast. A tissue connective cell.
- Gamma globulin (GG). That part of the serum of which antibodies are made. The gamma globulin is separable into several parts on the basis of their molecular weight. Two of these parts are designated 7S and 19S.

- Genetics. The biologic science that deals with heredity, and change and similarity between organisms through time.
- Gestation. The period of development of the young until birth, the fetal period.
- Glucocorticoid. Any corticoid that increases the rate of formation of carbohydrates from molecules such as proteins or fatty acids.
- Gravid. Pregnant.
- Group A. A person whose red cells carry the A antigen but not the B belongs to group A.
- Group AB. A person whose red cells carry the A antigen and the B antigen belongs to group AB.
- Group B. A person whose red cells carry the B antigen but not the A belongs to group B.
- Group O. A person whose red cells carry neither the A antigen nor the B belongs to group O.
- Hemagglutination. Agglutination of red blood cells.
- Hemoglobin. The stuff of red cells, which gives them their color and which binds oxygen so that the cells can transport it from the lungs to all body tissues.
- <u>Hemolysis</u>. Destruction of a red cell by an agent that eats through its outer membrane, spilling the contents. Some antibodies are hemolysins.
- Hemolytic anemia. Anemia caused by the destruction of red cells. Antibody against an antigen on a red cell's surface may hemolyze the cell. Erythroblastosis fetalis is a hemolytic anemia.
- Herd immunity. When the number of immune members of a group is sufficient to reduce greatly the spread of infection.
- Hormone. A chemical produced in the body which has a specific regulatory function on the activity of an organ.
- Human blood groups. Usually designates the four groups of individuals--A, B,
  O, and AB--identified by the ABO system discovered by Landsteiner. For
  clarity, other systems, like Rh, are said to define blood types, rather than
  groups. Each blood group or type is based on a blood factor, or antigen, that
  is present on its members' red cells.
- Hyaline membrane. A layer of material lining the alveoli and alveolar ducts of infants having respiratory distress syndrome - the membrane is composed of fibrin.
- Hydrops. The most severe form of erythroblastosis fetalis, in which the baby is born waterlogged, swollen, and, usually, dead.
- Hypoplastic. Marked by incomplete development of an organ.
- Icterus. Yellowing of the skin. It occurs when excessive destruction of red cells leads to a backup of their breakdown products in the body.
- <u>Icterus gravis neonatorum</u>. A form of erythroblastosis found in newborns who are unable to excrete bilirubin and other breakdown products of fetal cells destroyed by anti-Rh antibody from the mother.

IgG antibody. One of the classes of antibodies (see antibody).

IgM antibody. One of the classes of antibodies (see antibody).

Immune reaction. The self-protecting production of antibody against an antigen, and the antibody's interaction with the antigen. Also called immune response.

Immunization. The formation by an individual of antibody against a particular antigen. Once the individual has reacted immunologically to a given antigen, he will respond, quickly, with antibody production whenever that antigen is again present. This individual thus is immunized, or has developed an immunity, to that antigen.

Immunology. The science that studies the immune reaction.

Incompatibility. A person is incompatible with another if his red cells will provoke an immune reaction, or transfusion reaction, when transfused into the other.

Intrapleural. Within the membrane lining the thoracic cavity.

Intrauterine transfusion. A transfusion of red cells into an erythroblastic fetus, usually through a thin tube stuck through the mother's abdominal wall, uterus, and into the fetal abdominal cavity.

In utero. In the uterus, e.g., a fetus.

In vitro. In glass, i.e., in a test tube or lab vessel rather than in a living
body (in vivo).

Ischemic. Having a deficiency of the blood supply.

<u>Isoantigen</u>. An antigen that exists in alternate forms in a species and thus can evoke an immune response in a member of that species lacking that form of antigen.

<u>Isoimmunization</u>. Development of antibodies against an antigen derived from a genetically dissimilar individual of the same species (see isoantigen).

Jaundice. Yellowing of the skin. It occurs when excessive destruction of red cells leads to a backup of their breakdown products in the body.

Kernicterus. Condition with severe neural symptoms associated with high levels of bilirubin.

Kleihauer test. A laboratory method for identifying fetal red cells present in a specimen of the mother's red cells. The hemoglobin of the adult cells is washed away, while the hemoglobin in the fetal cells remains.

Lecithin. Any of a group of phospholipids found in animal tissues.

Lidocaine. A topical (local) anesthetic.

<u>Lipids</u>. A group of fatty substances including fatty acids, neutral fats, waxes, steroids, and phosphotides.

Lymphocyte. A white blood cell that plays a role in antibody production.

Mitochondria. Small spherical to rod-shaped particles in cells - principal site of energy production - they are the portion of the cells with genetic continuity.

Mitotic. Pertaining to mitosis - a method of indirect division of a cell in which the two daughter nuclei normally receive identical complements of chromosomes.

Mongolism. Down's syndrome - a genetic abnormality in which the genetic material of a chromosome (21) is triplicated instead of duplicated.

Myelinization. Formation of the lipid (myelin) sheath of certain nerve fibers.

Osmolality. A property of a solution which depends on the concentration of the solute.

Parturition. The process of giving birth.

Passive antibody. Antibody that has been injected into an individual, as contradistinct from active antibody, which is made by the individual's immune system in response to an antigenic challenge.

<u>Pathogenesis</u>. Development of a morbid condition or disease - more specifically on a cellular level.

<u>Pathology</u>. The science of disease and its causes. Pathologists conduct autopsies and render diagnoses on the basis of tests and analysis of specimens removed from patients. In American hospitals, a pathologist often runs the blood bank.

<u>Pharyngeal</u>. Pertaining to the pharynx - the membranous sac between the mouth and nose and the esophagus.

<u>Phospholipid</u>. A lipid composed of fatty acids, glycerin, phosphate, and nitrogenous components.

Phototherapy. Use of blue light to lower bilirubin levels in the neonate. Bilirubin is susceptible to chemical breakdown when exposed to specific wavelengths of light.

<u>Placenta</u>. Tissue structure at the fetus' point of attachment to the uterine wall. It is richly endowed with blood vessels. Maternal and fetal circulations are separated by a very thin membrane, through which nourishment passes into the fetus.

Plasma. The clear liquid portion of blood after the red cells have been removed.

<u>Plasmin</u>. A soluble blood protein derived from plasminogen - acts to lyse fibrin clots (see plasminogen).

Plasminogen. The blood soluble protein precursor of plasmin.

Polyhydramnios. Excess of amniotic fluid.

Postpartum. After delivery of a baby.

Preeclampsia. A toxemia of late pregnancy.

Prophylaxis. A prevention of disease, preventative treatment.

Protection. See ABO protection.

Proteolytic. Capable of splitting proteins by hydrolysis.

Red blood cells. Dish-shaped cells whose stuff, the hemoglobin, gives them their reddish color. Red cells carry oxygen from lungs to all body tissues. Red cell covering, or membrane, carries A, B, Rh, and other blood factors or antigens.

- Rh-compatible. One person is Rh-compatible with another if his red cells cannot provoke an immune reaction, due to anti-Rh antibodies, when transfused into the other. Individuals who are Rh-negative are Rh-compatible with everyone. Individuals who are Rh-positive are Rh-compatible with other Rh-positive individuals.
- Rh factor. An antigen found on the red cell membrane surface of about 85 percent of humans. It is named after a similar antigen on rhesus monkey red cells; its chemical composition is unknown. The Rh factor is responsible for erythroblastosis fetalis and some transfusion reactions.
- Rh hemolytic disease. Disease of fetal and early newborn life. It occurs when red cells from an Rh-positive fetus cross the placenta and provoke an immune response in an Rh-negative mother. Her anti-Rh antibodies then enter the fetus, destroying its red cells, and stimulating abnormally high production of immature cells, or erythroblasts.
- Rh immunization. The immunization of an Rh-negative individual to the Rh factor through deliberate or inadvertent transfusion of Rh-positive blood, or (in pregnant women) through transplacental passage of fetal Rh-positive red cells into the maternal circulation.
- Rh immunoglobulin. See Rh vaccine.
- Rh-incompatible. A person is Rh-incompatible with another if his red cells can provoke an immune reaction, due to anti-Rh antibodies, when transfused into the other. A person is Rh-incompatible with another only if he is Rh-positive and the other is Rh-negative.
- Rh-negative. A person whose red cells do not carry the Rh factor is Rh-negative.
- Rh-positive. A person whose red cells carry the Rh factor is Rh-positive.
- Rh vaccine. Potent anti-Rh antibody, in the form of the 7S fraction of gamma globulin. The vaccine is administered to a woman unsensitized to the Rh factor when she delivers a baby in order to prevent her from developing an immunity to the Rh factor that could cause sickness or death in the next Rhpositive baby she conceives.
- RhoGAM. Ortho's registered trade name for Rh vaccine.
- Sensitization. See immunization.
- Seroconversion. Development of antibodies in response to the administration of a vaccine.
- Serological. Pertaining to the study of the antigen-antibody reactions in vitro.
- Serum. The clear, liquid part of blood which remains after the red cells and clotting elements have been removed. The clear liquid which separates from a clot.
- 75. A part of the gamma globulin in which antibodies may exist. The 7S gamma globulin molecule is relatively small, has two armlike appendages, and will pass through the placenta from mother to fetus.
- Sphingomyelin. A group of phospholipids occurring primarily in nervous tissue and membranes.

- Spina bifida. A defect involving hernial protrusion of the spinal cord and/or brain.
- Temporal bone. The lateral region of the head above the cheek bone the temple region.
- Teratogenic. Tending to produce anomalies of formation of the fetus.
- Titer. The measure of an antibody's strength. An antibody with a low titer, 1:2, is less potent than one with a higher titer, 1:64, or 1:64,000.
- <u>Transfusion reaction</u>. The destruction of incompatible donor blood in a transfusion recipient's bloodstream may quickly produce discomfort, anxiety, difficulty in breathing, rapid heartbeat, and other distressful symptoms. Kidney failure and death may follow.
- <u>Transplacental passage</u>. Passage through the placental membrane from mother to fetus or fetus to mother.
- <u>Urokinase</u>. A soluble enzyme that promotes the conversion of plasminogen to plasmin.
- <u>Uterus</u>. The female organ in which the young develops from just after conception to birth.
- Vaccine. A substance introduced into the body to prevent disease immunologically.
- <u>Vaginal fornix</u>. The recess formed between the vaginal wall and the vaginal part of the cervix.
- <u>Virus (wild and attenuated)</u>. One of a group of minute infectious agents.
- Zepherin. A germicidal compound.

APPENDIX

#### APPENDIX

# DISCUSSION OF THE PROCEDURE AND COMPLICATIONS OF AMNIOCENTESIS

### Technique

The transabdominal approach for purposes of amniocentesis is now the method of choice based on previous experience with severe complications (e.g., induced premature labor, sepsis and severe hemorrhage) associated with the transvaginal (through the vaginal fornix, either anterior or posterior) and the transcervical approaches.<sup>2, 29, 35, 45, 50, 85, 108</sup> The actual technique used to enter the amniotic sac and withdraw fluid has been refined and most clinicians are in agreement on the steps required to safely obtain a sample of amniotic fluid through the abdominal wall.

### Preliminary Procedures

The bladder should always be voided prior to the operation. In most cases, this can be done voluntarily without catheterization.

### Abdominal Preparation

Strict aseptic procedures must be adhered to throughout the operation to avoid sepsis. The abdomen should be thoroughly prepared with an antibacterial solution. Solutions used include alcohol, Zepherine, iodine, and Phisohex. The abdomen is then draped with sterile towels.

#### Local Anesthesia

There are differences of opinion regarding the use of local anesthesia. Many believe that if the midline is selected carefully or as a general rule, a local anesthesia is not required.<sup>4,31,34,45</sup> Others recommend the injection of local anesthetics such as lidocaine at the anticipated puncture site.<sup>6,17,50,108</sup> There is a strong indication for use of local anesthesia if the patient exhibits an undue amount of anxiety.

<sup>\*</sup>References are to be found at the end of the section on Amniocentesis.

## Location of the Puncture Site

There is no accepted agreement on the puncture site for amniocentesis. Many have reported that the puncture site should be 2-3 cm above the symphysis pubis, 31,34 while others reference from the umbilicus down by as much as 5 cm. 17,41 The puncture site should, in fact, be determined by previous manual palpation so that site of entry into the amniotic sac avoids the placenta and is in the area of fetal small parts. 2,35,59,75,101 The recent introduction of ultrasonography allows the obstetrician to safely determine the position of the placenta and the fetus so that puncture of either is minimized. 12,31,33,35,53,54,85,119,124 Placentography and amniography have also been used for this purpose, 2,9,10,50,81 but they are generally not recommended during the second trimester.

### Puncturing Procedure

The apparatus used to enter the abdominal cavity has varied from an 18-gauge needle <sup>17,75,101</sup> to a 3- to 5-inch long, 21- to 22-gauge spinal needle <sup>50,52</sup> It has been suggested that a needle with a relatively obtuse angle which is not well honed will allow the operator to more readily determine the layers of tissue being penetrated. An ACOG Bulletin has recommended that an 18-gauge needle be inserted through the skin and subcutaneous tissue followed by insertion of a 20-gauge needle through the larger needle into the amniotic cavity. This presumably reduces the possiblity of sepsis.

#### Obtaining Amniotic Fluid

For diagnostic purposes, amounts of fluid withdrawn range from 5 to 30 or 40 cc. Procedures performed during the second trimester should not withdraw more than 20 cc. The fluid should be withdrawn very slowly to avoid upsetting the intrauterine environment and to avoid placental separation. Indications for repeated procedures are obvious if the sample is grossly contaminated with blood, or if only blood is obtained when withdrawing the specimen. In addition, hemolytic disease and fetal distress cases may call for several repeat procedures throughout the pregnancy. It should be noted that plastic syringes are recommended since amniotic fluid cells more readily collect on the walls of glass syringes.

#### Postoperative Observation

Many clinicians indicate that fetal heart rate and maternal vital signs should be monitored from 1-5 hours following the procedure to detect any fetal distress.<sup>6,17,34,35,108</sup> The mother is generally advised to report any fever, abdominal pain or cramping including suspected labor, fluid leakage from the puncture site, or vaginal bleeding after the procedure.

### Timing of the Procedure

The timing of the procedure is based on the type of diagnosis and/or therapy to be performed. These can be broken down into various categories and are listed below.

### Diagnosis of Genetic Disease

Ideally, the timing for this procedure should be as early as possible in the second trimester because in certain cases, three to four weeks are required in order to obtain results from the diagnostic procedures. In such cases, the parents may elect to induce a therapeutic abortion where a significant genital defect is diagnosed. Timing is of the essence in this regard since abortions beyond the 20th week of gestational age are associated with an increase in maternal complications. Unfortunately, there is insufficient amniotic fluid for purposes of amniocentesis prior to at least the 13th week. It has been reported that amniocentesis to detect genetic defects should be performed at or before 14 weeks; because of the consensus seems to be that amniocentesis should be performed no later than 16 weeks so that if the parents desire, therapeutic abortion can be performed at or prior to the 20th week of gestational age.

### Hemolytic Disease

In this case the fetus may show signs of anemia as early as the 32nd week of gestation in severe cases. However, others feel that the 34th week is most desirable for optimum accuracy in determining fetal anemia under these circumstances. It has also been reported that little information is gained after the 36th week, although in severe cases, this is not necessarily true.

As far as the mother is concerned, monitoring of Rh antibody titer in her blood may require amniocentesis as early as 20 to 22 weeks if there is a history of prenatal death from erythroblastosis. Timing of repeat amniocenteses depends on the initial results and the previous history. Optical density suggesting severe disease or history of a previous erythroblastosis prenatal death indicates repeat amniocentesis at 7 to 10 day intervals. If there is no decrease in fetal activity or less than a 2-tube rise in the antibody titer, and if the initial reading was in the mid or low zone, repeat amniocentesis may be deferred for 2 to 3 weeks.

#### Respiratory Distress Syndrome

This situation is not genetic in origin but occurs as a result of premature delivery. That is, the fetus's lungs are not sufficiently mature to allow exchange of oxygen and  ${\rm CO}_2$  in order to survive. The timing for amniocentesis is based on several maternal factors which would lead to premature delivery.

These include toxemia, diabetes, incompetent cervix, or a past history of premature deliveries. Amniocentesis in this situation is usually performed in the third trimester and can be performed at any time during this period when incipient premature labor is diagnosed.

## Complications

It is important to recognize that complications to both the mother and the fetus have been reported. However, the incidence of severe complications is extremely small. It is estimated that over 4,000 midtrimester amniocenteses have been performed for diagnostic purposes and at least four times that number during the third trimester for diagnostic and therapeutic purposes. Reports of isolated severe complications involving death or severe trauma should not cloud the overall view of the complications of amniocentesis. Complications are minimized by adhering to the procedures described above and by skill of the operator. The importance of this latter requirement cannot be overemphasized, and an experienced obstetrician should always perform the procedure.

### Maternal Complications

The most frequently reported maternal problems associated with amniocentesis are sepsis which include peritonitis and amnionitis (the latter also affects the fetus), hemorrhage which can result from perforation of the placenta or umbilical cord (these complications also affect the fetus), or puncture of a blood vessel in the myometrium or abdominal tissue. In the case of an Rh-negative mother and Rh-positive fetus, isoimmunization can result if the fetus, umbilical cord, or placenta are punctured and fetal blood subsequently enters the maternal circulation. The complications of induced abortion will not be discussed here, even though the classic method of withdrawal of amniotic fluid by amniocentesis is used prior to introduction of abortifacients such as hypertonic glucose or hypertonic saline.<sup>72</sup> The risks to the mother as a result of the amniocentesis in conjunction with abortion are identical to those in amniocentesis used for most other purposes; however these can be complicated and added to by the abortion procedure itself.

Table 5 lists the frequency of maternal as well as fetal complications reported by various investigators. A brief discussion of the major maternal complications is included below.

Many papers indicate that sepsis to both the mother and the fetus should not occur with rigid sterile techniques. It has long been accepted that the transvaginal or transcervical approach has a much higher risk of introducing sepsis.

The most frequent cause of hemorrhage is perforation of the placenta by the needle. It has been reported that passage of the needle through the placenta is not uncommon, with no consequent damage to the mother or the fetus.<sup>26</sup> However,

severe problems have been reported due to hemorrhage and are shown in Table 5. Another possible problem with hemorrhage is that the amniotic fluid becomes contaminated with maternal blood and in the case of sex determination, improper diagnosis has resulted. Other sources of bleeding involve puncture of the umbilical cord or a blood vessel in the myometrium which can result in contamination of the amniotic fluid also. Some cases of abdominal bleeding have been reported but are relatively rare.

It has been reported that ultrasonic localization of the placenta virtually eliminates puncture of the placenta. 12, 31, 35, 53, 85, 108, 124 Others 2, 9, 10, 80, 91 have used placentography and amniography for the same purpose.

Various clinicians have reported on the induction of abortion or premature labor, depending on gestational age, following amniocentesis. The reasons for onset of premature labor leading to abortion or delivery of a premature infant are not well defined. In many cases, the situation has been confirmed not to have been caused by the amniocentesis procedure. 53,60,90

There is a possibility of trauma to other areas of the abdomen such as the bowel and bladder. This type of complication is extremely rare and when it does occur, is generally a result of improper procedure.

Abruptio Placenta affects the fetus as much as it does the mother but it should be considered an extremely infrequent complication. The placenta may separate as a result of agitation of the intrauterine environment and can generally be eliminated by not puncturing the placenta and withdrawing the amniotic fluid at a very slow rate.

Fluid leakage after the procedure has been reported several times. In most cases, the problem is transient and no sequelae result. Rare cases of amniotic fluid embolism as a result of fluid leakage have been reported. Fluid leakage may be a result of utilizing a needle with an oversized diameter and this reinforces the use of a 22-gauge or smaller needle.

Rh isoimmunization is limited to those mothers with Rh negative type blood and a fetus with Rh positive blood. Rh isoimmunization can occur if the fetus, umbilical cord, or placenta is punctured and its blood enters the maternal circulation. Such a situation can affect future pregnancies of the mother. This should be considered a significant potential risk in all Rh-negative mothers and appropriate means to treat the situation should be available when the mother is Rh negative.

Failure to obtain amniotic fluid is not a complication per se, but presents some unique problems which should be discussed. An inability to obtain amniotic fluid may indicate that the fetus or the placenta has been punctured. It may also indicate that the needle has not entered the amniotic sac and consequently the needle should be advanced further. The incidence of not obtaining amniotic fluid and requirement for repeated procedures is relatively high as shown in Table 5. Repeated procedures obviously increase the possibility of all other risks, and this problem is probably the most important which currently exists. The routine use of ultrasonography in order to locate appropriate puncture sights where amniotic fluid can be obtained should alleviate most of these situations.

Fetal Complications. The most common fetal complications associated with amniocentesis are injury, hemorrhage associated with puncture, errors in diagnostic procedure due to twinning or multiple fetuses, death as a result of amnionitis, and abortion. Prematurity without death as a result of induced labor should also be considered a complication. As with the maternal complications, there are isolated reports of severe trauma and/or death to the fetus attributable to amniocentesis. These cases should be maintained in proper perspective with relation to the total number of amniocenteses performed. Such cases can be avoided with proper skill and knowledge of the operator. Table 5 includes fetal complications and a discussion of those of significance are included below.

Cases of injury to the fetus are most frequent when amniocentesis is performed prior to the 14th week of gestational age or very late in the third trimester. The former is a result of a lack of an adequate amount of fluid, about 50 to 60 cc, as compared with about 350 cc at 17 weeks. The problem at or near term is that the size of the fetus relative to the overall volume of the amniotic sac is quite large compared with earlier stages of gestational age and thus the risk of injury at this time is much greater. Even though there is an increased volume of fluid at 16 to 17 weeks when the procedure is normally performed to detect genetic defects, there is still a fairly high risk of puncturing the fetus. However, unless there is severe hemorrhaging, it has been reported that such suspected punctures do not affect the fetus whatsoever and, in particular, do not induce malformations, 20,35,69 as they do in mice or rats. 28,114,118

Hemorrhage has been reported in a few cases of amniocentesis and is of particular importance if the mother is Rh negative and the fetus is Rh positive. In this situation, the fetus may already be anemic and hemorrhage could be fatal. Ultrasonographic location of the fetus should minimize the risk of perforating major blood vessels in the fetus since this allows introduction of the needle into an area where the small parts of the fetus are located. It has been observed that if a normal fetus is touched with the point of a needle, he will move away from it. Many cases of fetal puncture have been attributed to a hydropic fetus. And the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the s

Abortion and premature labor, as discussed in the section above on maternal complications, is often not attributable to anniocentesis and, even when it is, it is difficult to fully describe the reasons. Induction of premature labor is not a result, in most cases, of injury to the fetus due to the amniocentesis procedure. It should still, however, be considered a risk when performing the procedure and is perhaps the most serious risk to the fetus because of lack of knowledge regarding the causes for induction of labor following amniocentesis.

Errors in diagnosing due to twins or multiple fetuses is a situation which has been reported on several occasions (e.g., Ref. 27) and all investigators agree that the routine use of ultrasonography or fetal ECG prior to the procedure would virtually eliminate this problem.<sup>50,68,79</sup> The problem consists of withdrawing fluid from the amniotic sac of only one twin in the case of a double sac and using that fluid for diagnostic purposes.

# Amniography, Ultrasonography, Amnioscopy and Fetoscopy

These three areas are discussed since they have been widely utilized in conjunction with amniocentesis or in the case of amnioscopy and fetoscopy, evolved as a result of information gained from amniotic fluid by the procedure of amniocentesis. 107

Amniography. Amniography was first performed in 1930 in order to assess fetal age. Modern use of amniography is invariably restricted to the third trimester due to associated knowledge of the possibility of induction of fetal malformation due to exposure to X-radiation earlier in pregnancy. Amniography can be used to determine fetal age, fetal distress, and fetal death. With the advent of the introduction of ultrasonography in the middle 1960s, however, the use of amniography is not generally recommended in conjunction with amniocentesis due to certain risks associated with it in addition to exposure to X-radiation. These include the possibility of injection of radioopaque dye into the fetus, and possible allergic reactions to the dye. Ultrasonography as described below provides much of the same information with no apparent side effects.

Ultrasonography. Ultrasound has been shown to be safe in obstetrical diagnosis 7,57,100 and is suitable for use prior to amniocentesis in the second and third trimesters to ascertain the gestational age, location of the fetus, location of the placenta, and the occurrence of twinning or multiple fetuses.

The value of having this information has been discussed previously and its importance cannot be overemphasized. The use of ultrasonography prior to amniocentesis is fast becoming a routine procedure in order to avoid certain complications.

Amnioscopy and Fetoscopy. Transcervical amnioscopy and fetoscopy were introduced due to an increased interest in obtaining knowledge of the intrauterine environment and the fetus during pregnancy. This valuable diagnostic tool has been refined to the point where endoscopes can be introduced through the abdominal wall (now generally referred to as fetoscopy). The procedure is now relatively safe, and it can provide information regarding fetal malformations and other anomalies in utero, such as fetal distress, and location and condition of the placenta.

Table 5. Complications of Transabdominal Amniocentesis

,								Based on No.	
	Author	Patients	Taps	Successful Taps, Percent (or number)	Indications for Amniocentesis	Site of Puncture	Number of Complications	of Taps, Percentage of Complications	Comments on Complications
Diekm	Diekman and Davis	1	25	100	Volumetric determination of amniotic fluid	1	None	0	
Kerr	Kerr and MacKay	t	20	001	X-ray diagnosis of Placenta Previa	1	ĸ	£	3 fetal deaths following amniography.
Rivelt		ı	20	1	Polyhydramnious	1	None	0	
8	Cornell and Case	1	ဖ	001	Amniography	i	None	0	
Burke	<b>.</b>	ı	75	1	Amniography	1	None	0	
Bevis	· s•	69	158	I,	Fetal hemolytic disease	ţ	None	0	
Bevis	. <u>s</u>		205	ť	Fetal hemolytic disease	i I	None	0	
8	Savignac	1	<b>6</b>	1	Diagnostic amniography	1	None	0	
Bevis	. <u>s</u>	1	1,7	l .	Fetal hemolytic disease			t. 4.	Abortion 2 days postamniocentesis.
1957 Walker	ker	l 	134	1	Fetal hemolytic disease	1	None	0	
1958 Par	Parrish et al.	1	8	95	1	ı	(1 minor)	(2) 0	1 Abdominal pain; 9 bloody taps without sequelae.
1958 Sig	Sjostedt et al.		45	. 1	Determine oxygen tension of amniotic fluid.	1	(1 minor)	(2.2) 0	Abdominal pain.
1960 Mc	Moncriell and Browne	ı	250	ı	Fetal hemolytic disease	1	None	0	
4		-							

× se	Author	Patients	Taps	Successful Taps, Percent (or number)	Indications for Amniocentesis	Site of Puncture	Number of Complications	Based on No. of Taps, Percentage of Complications	Comments on Complications
1963	Fairweather et al.	1	145	20 patients	Immunological implications of amniocentesis	1	See comments		11 percent stillbirths, causes not fully defined.
1963	McGaughey et al.	1	200	ı	Fetomaternal exchange at term in normal pregnancies	<b>1</b>	None	•	
1963	Reddin and Brown	ı	6	1	Studies on amniotic fluid	i	None	0	
1983 1983	Zipursky et al.	l ·	5	8	Transplacental fetal hemorrhage after placental injury during delivery or armiocentesis	1	0	1	Fetomaternal transfusions.
1964	Alvey	I	200	8	Fetal hemolytic disease	2" below umbilicus at midline	None	0	
1964	Fairweather and Walker	<b>6</b>	171	5	Fetal hemolytic disease	1–2" below umbilicus on side of fetal limbs	•	23	Fetal blood obtained in 4 taps; 2 macerated hydropic infants delivered, 2 required exchange transfusion. 40.5 percent maternal bloody taps without sequelse. 3 patients with febrile which subsided without treatment.
1964	Robertson	ı	252	ı	Feral hemolytic disease	1		0.4	Fetal death after bloody tap.
1964	Lewis et al.	1	78	ı	Fetal hemolytic disease	í	· •	13	Questionable placental abruption.
1982	McLain	1	75(?)	1	Amniography	3-4cm below umbilicus in midline or toward fetal small perts	None	•	
26 28	Walker et al.	1	217	1	Fetal hemolytic disease		None	0	

Comments on Complications	7 fetomaternal transfusions with 1 still- born and 1 neonatal death after trau- matic taps; 20 failed or bloody taps.				Severe amnionitis and maternal peritonitis.		5 fetomaternal hemorrhages; 22 failed or bloody taps.	40.5 percent maternal bloody taps and 13.5 percent fetal bloody taps without sequelae.	Amnionitis with premature labor	Amnionitis.			1 failed or bloody tap.
Based on No. of Taps, Percentage of Complications	1.7	0	0	0	۸.		1.6	ı	9.0	<del>-</del>	0	0	0
Number of Complications	7 .	None	None	None	+-	None	us	See comments	<b>-</b>	-	None	None	None
Site of Puncture	Placental localization using Cr51	1	i	1 -	1	1 -		ı	I	Caudal and anterior to fetal anterior shoulder	. · · · · · · · · · · · · · · · · · · ·		Placental localization w/RISA132
Indications for Amniocentesis	Fetal hemolytic disease	Fetal hemolytic disease	Fetal hemolytic disease	Fetal hemolytic disease	Evaluation of amniocentesis	Use of Teflon catheter in technique	Assessment of fetomaternal hemorrhage from amniocentesis	Fetal hemolytic disease	Fetal hemolytic disease	Fetal hemolytic disease	Determine amniotic fluid volume	Fetal hemolytic disease	ı
Successful Taps, Percent (or number)	1	1	1	92	t	8		96	1	1.76	1	ı	ı
Taps	402	75	42	006	٧	8	35	74	166	101	22	1000	48
Patients	2	1	ı	I	~	1	83	1	ļ	6	l	400	į
Author	Bowmen and Pollack	Cherry	Crosby and Merrill	Freda	Goodlin	Mann et al.	Jensen and Sorenson	Queenan and Adams	Westberg and Margolis	Alpern	Charles and Jacoby	Freda	Hibbard
Year	1965	1965	1965	1965	1965	1965	1965	1965	1965	1966	1966	1966	1966
												_	

Table 5 (Continued)

Comments on Complications		Feromaternal transfusion resulting in fetal death from anemia and shock at birth.		Needle marks on infant, 1 developed sub- cutaneous infection.	Injection of radiopaque dye into fetal arm.	29 failed or bloody taps.	10 fetomaternal hemor*hage, 28 bloody or failed taps.		1 premature labor; 289 failed or bloody taps, 59 taps with fetal blood.	Fetomaternal transfusions with increased maternal sensiligation and fetal death in 2 cases, 14 failed or bloody taps.	1 severe intrauterine infection following glucose abortion; 2 ruptured membranes; abdominal pain in some cases. 20 failed or bloody taps.	1 definite fetal vein rupture by needle causing fetal death; 2 other fetal deaths after polyhydramnous treatment; 1 placental trauma; 1 failed or bloody tap.
Сош		Fetomaterns fetal death f birth.		Needle marks on infecution.	Injection of arm.	29 failed or	10 fetomatern or failed taps.		1 premature taps, 59 tap	Fetomatern maternal ser 2 cases, 14	1 severe intraut glucose abortio abdominal pain or bloody taps.	1 definite for causing feta after polyhy cental traun
Based on No. of Taps, Percentage of Complications	0	<b>G</b> .	0	σ	~	1	18.5		0.2	10.8	9.0	~
Number of Complications	None	8	None	<b>м</b>	<del></del>	None	10	None	<b>-</b>	<b>co</b>	3 Major	. 4
Site of Puncture	ł	Side of fetal small parts	1	Nucleal tap on side of fetal small parts	4	Placental localization w/radioisotope and thermogram	ı	1	I	1	Fetal small parts	<b>I</b> .
Indications for Amniocentesis	1	Assessment of fetal hemorrhage and amniocentesis	Amniography	Amniography	Amniography	1	t	Genetic defects	1	Fetomaternal hemorrhage from amniocentesis	Evaluation of amniocentesis	ŧ
Successful Taps, Percent (or number)		l	I.	1	ı	·	I	ı	l	I	1	l
Taps	1500	4.	75	20	~	2000	54	. 88	604	74	200	۸.
Patients	i	i i	ı	. 1	47	ı	t		1	I	1	ı
Author	Mandelbaum and Evans	Misenhimer	Schwartz et al.	Witchick	Berner	Freda	Cassady et al.	Jacobsen and Barter	Queenan	Wang	Asensio	Burnett and Anderson
Year	1966	1966	1966	1966	1967	1967	1967	1967	1967	1967	1968	1968

Comments on Complications	i feral hematoma of thorax, I pneumothorax of fetus; I subdural hematoma and brain demege due to needle puncture – stillborn. First two cases treated and development to normal.		All fetomaternal hemorrhage.	1 case of major fetal vessel lacerated causing fetal death; i placental trauma.	4 failed or bloody taps.	Severe fetal anemia at birth with evidence of erythroblastosis; 4 failed or bloody taps; 1 tap with fetal blood.	Spontaneous rupture of membranes and premature labor in 2.2 percent; feto-maternal hemorrhage in 38 percent, 2 intrauterine deaths after amniocentesis (1.1 percent), 15 failed or bloody taps, 1 with fetal blood in taps.		2 annionitis responded to treatment, 1 premature labor at 20 weeks, 2 intrauterine deaths in severely ansitized mothers, 1 maternal sensitivity to radiopaque material. 69 samples contaminated with meternal or fetal blood (2,3 percent).	Spontaneous abortion 1 month after procedure with evidence of recent minimal choricemnionitis. Cause for abortion listed as incompetent cervix.
Breed on No. of Taps, Percentage of Complications	No startistical significance due to lack of adequate number of cases	•	11.2	<b>qua</b>		0.2	See comments	0	0.2	(9.0)
Number of Complications	<b>m</b>	None	46		None	•	1	None reported	<b>w</b>	(1) See comments
Site of Puncture	Anterior abdominal well	Suprapubic, no longer performs placentography	I	i		Placental localization using radioisotope and thermogram	ı	Placental localization using ultrasonography	Area of fetal small parts	Midline toward middle of uterus
Indications for Amniocentesis	Assessment of fetal complications	1	ŀ	1	Genetic defects	Evaluation of armiocentesis	Fetal hemolytic disease	i	Various	Genetic defects (13–18 wk)
Successful Taps, Percent (or number)	I	1	ì	1	į	i	88.7	ı	1	8
Taps	ı	0009	410	×200	25	416	185	107	3000	162
Patients	3 case histories	1	1	is I	1	161	1	1	1	155
Author	Стеветтел	Haworth	Peddle	Stenchever and Cibils	Butler and Reiss	Crystle	. <b>§</b>	Hinselmenn et al.	Mondelbaum	Nacker
į	896	988	988	986	1970	1970	1970	1970	1970	1970

Table 5 (Continued)

Based on No. of Taps, Comments on Complications of Complications	0.05 Fetal death attributable to fetomaternal hemorrhage.		0 1 failed tap attributed to anterior placenta.		Petal bleeding leading to 3 intrauterine deaths, 1 intrauterine transfusion, and 1 Caesarian section before fetal bleeding	was significant. I questionable amnionities in conjunction with premature rupture of membranes.	2.4 1 fetomaternal hemorrhage, 1 failure at 14 weeks.		See comments 15 percent fetal erythrocytes.	See comments 6 percent transplacental hemorrhage.	1 abortion and 1 extrasystole.	4 spontaneous abortion w/clear fluid taps; 2 transient leakages of fluid with no sequelae.	
Number of of Complications of Com	-	None	0	None attributable to amniocentesis	CD .		-	None reported	See comments See com	See comments See con	2 significant	4 significant	
Site of Puncture		1	Placental localization using ultrasonography	1	1		·	i	25 percent of cases used ultrasonography	Ultrasonography used to locate site on all cases	1		-
Indications for Amniocentesis	1	Genetic defects	Genetic defects	Genetic defects (13-18 wk)	Assessment of amniocentesis		Risks in routine use of procedure	Genetic defects (14-16 wks)	Prior to 20th week, genetic abnormalities	After 20th week, fetal hemolytic disease	Genetic diagnosis	Genetic diagnosis	
Successful Taps, Percent (or number)	100	100	1	1 patient	I	x		1	1		ı	5 patients (failed culture)	
Taps	2000	170	92	256	291		42	80	<b>5</b> 6	113	<b>~.</b> .	~	
Patients	1	ı	1	231	ı		ı	. 1	23	101	8	73	
Author	Walker	Emery et al.	Ferguson-Smith et al.	Gerbie	Ryan		Scringeour	Turnbull	Blajckman (a)	Blajckman (b)	Allen	Doran	
Year	1970	1971	1971	1971	1972		1972	1973	1974	1974	1974	1974	

CRITIQUE OF BATTELLE REPORT Robert E. Cooke, M.D., Commissioner

# CRITIQUE OF BATTELLE REPORT Robert E. Cooke, M.D., Commissioner

One of the most critical questions put to the National Commission on the Protection of Human Subjects is that of the necessity for research utilizing the living human fetus in utero or ex utero when the research is not for the benefit of that particular fetus.

Testimony has been given and denied as to the necessity for such research in solving important practical problems affecting significant numbers of persons in the near future.

The integrity of the Commission in the minds of groups of different views—all heavily emotionally involved—laity, clergy, scientists—will depend upon the objectivity and impartiality of the answers provided to the issue posed.

The only true objective approach beyond question, since scientists make this analysis, is to collect information and analyze past research accomplishments with the intention of <u>disproving</u>, <u>not proving</u> the hypothesis that research utilizing the living human fetus nonbeneficially is necessary.

In the neurosciences, for example, the presumption (without laws or bans) has existed that invasive nonbeneficial research on the human brain is out of the question. With that presumption great progress has been made in understanding a very complex organ or collection of organs by highly creative animal research, by study of human pathological material synthesized with clinical and therapeutic research.

An analysis of the understanding of human brain function could either emphasize superficially living human research or could show by very detailed and painstaking analysis the enormous contribution made by animal studies—the latter being closer to the facts.

In general in relation to the problem of nonbeneficial research on the living human fetus, the Battelle Report in part because of time constraints, but probably also because of orientation, does not challenge sufficiently the stated hypothesis.

The emphasis in the report is placed:

- On what some would consider relatively trivial contributions sharpness of needle, etc., in amniocentesis.
- On contributions from human therapeutic research—in the premature infant in hyaline membrane disease.

- 3. On living tissues from the dead fetus--rubella.
- 4. On fluid (and cells therein) from around the fetus or fetal membranes, placenta, placental vessels, etc., in prenatal genetic disease detection.
- 5. On fetal therapeutic research as in hydrops fetalis associated with Rh disease rather than on nonbeneficial research on the living human fetus in utero or ex utero.

The report is written as though human research is in question and substantial credibility of the report as regards fetal research is thereby lost.

In fact most of the research cited was done before any significant number of legalized abortions were being carried out and practically none of the work in Rh disease or hyaline membrane disease used abortuses. Abortuses were used in rubella and amniocentesis but the necessity for their use is addressed below.

The biased orientation appears throughout. In the introduction, page 15-5, the statement is made that "amniocentesis is central to research leading to an understanding, characterization, and detection of the disease (congenital rubella syndrome)." That statement is utterly false. Minimal information has or is being gained in rubella from amniocentesis. Living human fetal research or nonbeneficial nature played essentially no role in Rh disease. Transfusion therapy was for the benefit of that fetus. Rh vaccine required maternal blood samples—not fetal research. The introduction, page 15-5, further implies that without amniocentesis and/or fetal research there would be "no basis for successful research toward prevention or cure" in RDS or hemolytic disease. These statements are gross exaggerations as well. Animal research or research on lungs of dead prematures shed enormous light on RDS and exchange transfusion in living newborns was the giant step in Rh disease.

Such a bias vitiates the claim (page 15-5) that "dependence must be placed on the judgement of qualified persons that proceeding to research involving living human fetuses is justified on the basis of research/benefit considerations."

In RDS--the major fetal contribution has been the L/S ratio as an indicator of lung maturity. Now its use is strictly therapeutic. The earlier collection of amniotic fluid to establish normative data could have been collected opportunistically from amniotic fluid at caesarean section and correlated with other indicators of maturity and survival. However, even the amniotic fluid studies cited as fetal research were noninvasive to the fetus per se and probably acceptable to most religious groups. The study of lung inflation curves, of surfactant levels, of steroid induction of biochemical maturation of the lung did not require living human fetuses.

The study of transplacental movement of steroid near term to induce lung maturation did not require abortuses and elective caesarean section would suffice.

In the development of the rubella vaccine, the report indicates that use of animals to study transplacental passage of the vaccine virus was misleading. The initial studies utilized only six rhesus monkeys. No other animals were used. A positive take in any one should have been enough to raise serious doubts as to its use in pregnant women.

Likewise, the use of pregnant women--intentionally vaccinated prior to abortion is said to have been essential to discover the threat to future fetuses. However, despite this report accidental vaccine infection of the fetus was reported shortly thereafter thereby vitiating the original intent to avoid accidental infection.

On page 15-14 the sensitivity of the reporters must be further questioned. The report suggests that women who are to be aborted and who are presumably vaccinated might be challenged by wild type virus intentionally to show fetal protection by the previous immunization procedures. No concern is expressed regarding possible illness in the mothers from wild type rubella--a not totally benign illness in adult females.

In rubella, then, epidemiologic investigations clearly established and characterized the congenital rubella syndrome. Maternal serologic studies and clinical follow-up established the frequency of damage. The danger of the vaccine to the human fetus was learned accidentally despite in utero fetal research. Retrospectively in utero fetal research might have been justified before any use of the vaccine so that accidental infection would have been avoided, however, in fact such research did not prevent later accidental infection.

In the discussion of amniocentesis, the bias of the report continues. In the benefit to cost calculation, for example, the average age of Down's Syndrome used in the calculation is 50 years. Penrose, in his book, gives the correct average longevity of DS as 16 years. The report, therefore, increases benefit by a factor of 3. Present longevity may be closer to 20 years.

In discussions of the technique of amniocentesis most of the "advances" are minor technical ones, "the type and degree of sharpness of the needle," not substantive research and such information could have been gained as part of therapeutic research for Rh disease, etc., or probably from animal studies. The use of ultrasound could be developed in animals readily.

The assertion that the techniques could not have been developed in animals is unreasonable. Certainly the Blalock-Taussig procedure for cyanotic heart disease is conceptually and technically far more complex than amniocentesis. Yet, all details of the surgery were worked out not in humans but in dogs that do not even have tetralogy of Fallot.

In the discussion of amniocentesis, detection of defects through tissue culture utilized living cells shed into fluid--not the living fetus. Normative values for enzymes were obtained in significant numbers from the use of amniotic fluid obtained at the time of abortion not from the living fetus.

In the discussion of Rh disease--"three major phases are cited as requiring human fetal research."

- 1. Fetal cells in the maternal circulation. Maternal sensitization and antibody coating were already well known; hence "fetal research" was not fetal research. It required small samples of maternal blood.
- Maternal anti-Rh antibodies found on fetal (newborn more exactly) cells by Coomb's test. Fetal research not required.
- 3. The postnatal CNS effects of bilirubin and the lack of damage to the fetus was known without live fetal research and the prevention of hernicterus by exchange transfusion which was an enormous achievement (Diamond and Allen) required no fetal research.

Likewise, Rhogam development to prevent Rh sensitization at delivery or abortion did not require studying of the living fetus.

Indeed, the three areas cited, pages 15-62 and 15-63, were very minor in the picture of the solving of the Rh story.

The same effort to justify fetal research comes through on page 15-63. The large number of stillborns referred to from E. F. with hydrops implies that the major advances in Rh disease were fetal. That is incorrect just as is the summary statement, page 15-63, "It was through this sequence of critical advances in human fetal research that the Rh vaccine was conceived and the threat of Rh disease brought under control."

On page 15-64 a list of so-called critical questions is presented to suggest that the ban on fetal research would have affected most of the discoveries. The answer to all are "yes" not "no" (except 3 - "the same") without beneficial research on the living human fetus in utero or ex utero.

The statement that a "ban on fetal research would not have allowed this understanding of the mechanism of Rh disease in humans to evolve over the short span of 15 years" is simply not true. The understanding came without the research which is now banned.

The RDS story is similar to the other areas cited. Fetal research was necessary—namely, research on dead premature infant lungs, fetal fluid obtained by amniocentesis near term to guide therapy of that infant and fetal research on animals. Thus, a ban on research on the living human fetus obtained by abortion would not have prevented the present advances. Therapeutic efforts aimed at the near-term or premature infant with hyaline membrane disease are not prevented by any such ban.

In conclusion, the Battelle Report has erred as many scientists have done in trying to justify the importance of human research by failing to challenge

objectively the need for nonbeneficial research on the living human fetus in utero or ex utero. As a scientist, I feel the evidence must be exhaustively searched to show absolutely unequivocally, not subject to dispute by anyone, that some vital link in the chain that led to the solution of a problem that all men of good will would agree was important required the nonbeneficial nontherapeutic use of a living human fetus in utero or ex utero.

The Battelle Report has not done so in my opinion and unfortunately has been presented unchallenged in the press as authoritative.

The revised final report unfortunately can not dispel the earlier impressions. The distinction between therapeutic and nontherapeutic is helpful. The discussion of animal models is more objective. The basic problem, however, still exists.

RESPONSE TO THE COOKE CRITIQUE

#### RESPONSE TO THE COOKE CRITIQUE

From reading the critique, it appears that the primary difficulty arose from differences in the definition of "fetal research." Our working definition, as stated in the Introduction and the Overall Conclusions, was "any experimentation on either the pregnant woman or the fetus in which either drugs or surgical procedures are involved." Thus we included numerous examples which Dr. Cooke, using a more restricted definition, does not consider fetal research.

For clarity, his comments are discussed by individual cases.

#### Congenital Rubella Syndrome

Our report agrees with him that fetal research played no part in establishing the association of CRS with rubella or in the development of the vaccine. As to the fetal research involved in studies of vaccine transmission transplacentally to the fetus, we agree that the first study did involve some women who were unknowingly pregnant. It and subsequent studies did delineate the risk of the vaccine to fetuses and establish the proper time for vaccination. While only six rhesus monkeys were used in the transplacental study that led to the abovementioned fetal research (vaccination of pregnant women before planned abortions), we agree with a number of investigators that the fetal research was necessary. To have waited for the vaccination of pregnant women to show the vaccine passage across the placenta would have meant either the birth of infected infants or unwanted abortions. As to the intentional challenge by wild virus to vaccinated women, we did not "suggest" it. We merely pointed out that such an experiment would represent the ultimate test of the effectiveness of the vaccine.

#### Amniocentesis

Here especially the problem of the definition of fetal research appears. By our given definition, withdrawal of amniotic fluid to determine the status of a fetus is fetal research until the diagnosis involved is regarded as an established procedure. Thus, the studies involving amniocentesis in Rh-immune disease, respiratory distress syndrome, and the determination of genetic defects, at the time they were done, qualified as fetal research. As to the adequacy of animal models for the procedure of amniocentesis, there is obviously a difference of opinion. We gave our assessment of the evidence. The Yale report reached the same conclusion.

Dr. Cooke also criticized our use of 50 years as the life expectancy of children with Down's syndrome. Our reference for this figure is Milunsky in *The Prenatal Diagnosis of Hereditary Disorders*, 1973, Charles C. Thomas publisher. A reproduction of the relevant pages is attached.

#### Rh Vaccine

As to the areas given on pages 15-62 and 15-63, we stand on our statement that their definition was necessary to the understanding of the mechanism of erythroblastosis. Under the given definition of fetal research, study of the pregnant woman's blood qualifies as fetal research. Mengert in 1955 used amniotic fluid, thereby qualifying the study as fetal research. The work of Diamond and Allen was described in the report as not involving fetal research. It should be noted however, that the postnatal transfusions perfected by Diamond and Allen of course did nothing for the fetuses dying in utero. The intrauterine transfusion procedure was a result of fetal research.

As regards Dr. Cooke's comments on the questions on page 15-64, unfortunately we did not give explicit answers in a 1, 2, 3, . . . series. The pages following, however, do show that not all research was fetal and that some was fetal by our definition, though not by Dr. Cooke's.

#### Respiratory Distress Syndrome

Here again, the definition of fetal research has caused problems. We consider the studies on L/S ratio via amniocentesis to be fetal research; Dr. Cooke does not. Antenatal therapeutic studies, as with corticosteroids, are fetal research by the definition used; Dr. Cooke does not consider these as fetal research.

To summarize, the conclusions we reached in our study were based on a given definition of research on living fetuses. Using Dr. Cooke's definition, many, perhaps even most, research studies described in the report would not have been classified as fetal research. Had we used his definition, our conclusions would have been drastically altered.

R. I. Leininger Battelle's Columbus Laboratories April 21, 1975 From A. Milunsky, The Prenatal Diagnosis of Hereditary Disorders (Springfield, Ill.: Charles C. Thomas, 1973, pp. 166 to 167)

If the risk of bearing a chromosomally abnormal child in the thirty-five to thirty-nine year age range is about 1:60 (see Chapter 11), then an estimated 4,667 defective offspring will be born in this group. Similarly, with a risk of about 1:40, about 3,000 defective offspring will be born in the group of mothers aged forty or over. Together this represents a total of 7,667 seriously defective offspring born each year to 400,000 mothers over thirty-five years of age in the U.S.A.

If amniocentesis and prenatal genetic studies were routinely provided for women over thirty-five years of age, then the cost of 400,000 cases would be about \$60 million. To this would be added the cost of therapeutic abortion by the generally preferred technique of hypertonic saline induction or the 2 to 3 percent of cases which require termination of pregnancy by hysterotomy.

This computed cost would be about \$3,250,400 for terminating the 7,667 pregnancies with defective fetuses, assuming all couples requested such action and that the cost of saline induction does not exceed \$400 (known range for outpatient to inpatient saline induction is \$100 to 400) and hysterotomy, \$800. Hence, the cost of prenatal diagnosis and therapeutic abortion when necessary for 400,000 mothers over thirty-five years of age would be about \$63 million.

The cost of care for the 7,667 defective offspring that would otherwise be born is not easily assessed. For the majority of these patients the defects would be serious enough to result in institutionalization sooner or later. Current figures at the Walter E. Fernald State School for Retarded Children in Waltham, Massachusetts, indicate that the average cost of residential care for outpatient is \$6,100 per year. Assuming an average life expectancy of fifty years, it would cost an estimated \$305,000 for the life-time care of one patient. For 7,667 patients the conservative figure for care in one year would therefore reach the astronomical figure of \$460 million, and for the projected life-time care \$2,338,435,000. Hence, the birth of 7,667 chromosomally defective offspring in one year could ultimately cost society in excess of 2 billion dollars—about thirty—two times the cost of prevention through prenatal diagnosis and therapeutic abortion.

Each year with the birth of a similar number of chromosome-defective offspring (mainly with mongolism) a future committment in excess of 2 billion dollars is created. In twenty years of present costs (which of course will not apply) the commitment will have grown to about 40 billion dollars, a figure not very dissimilar to the recent calculations of Swanson (853).

These estimates have been made with the full realization that the tendency to institutionalize early or at all is said to be changing. (Admission ages to the Walter E. Fernald State School has not changed significantly over the past decade, with one-fourth of the patients admitted between zero to five years, five-twelfths between six to fifteen years and one-third over fifteen years of age.) The significant death rate in the first five years of age for children with Down's syndrome is known (155) but is rapidly decreasing. The life expectancy for increasing numbers of patients . . .

16 THE STABILITY OF THE DECISION TO SEEK INDUCED ABORTION Michael B. Bracken, M.P.H., Ph.D.

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# The Stability of the Decision to Seek Induced Abortion

#### INTRODUCTION

This paper focuses on the stability of the decision to seek an induced abortion. Three areas are considered: (a) the available literature has been reviewed, and some previously unpublished data are presented, in a manner which sheds a little light on the frequency with which women change their mind about seeking induced abortion; (b) evidence suggesting possible characteristics of women who might be at higher risk of changing their mind about deciding to abort is reviewed; and (c) some psychological and situational factors which might contribute to a change in the decision to abort are examined.

In addition to attempting to collect and integrate currently available material in a manner which contributes to our knowledge of the problem of decision-making stability prior to seeking induced abortion, the reviewer has attempted to limit his observations to issues of particular pertinence to the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The review, therefore, has two further restrictions.

First, the literature published before 1970 has not been generally considered although in at least one case 1 the data presented were collected prior to that time. While there is some evidence from other countries to suggest that restrictive abortion laws have less than total impact in preventing women from seeking abortion 2-5 studies from Britain and the United States show a considerable increase in the number of women obtaining abortions following liberalization of abortion laws. In Britain, since the 1967 Abortion Act, the rate of abortion per 1000 resident women ages 15 to 44 has risen from 3.5 in 1968 to 10.0 in 1971.6 In the United States approximately 200,000 legal abortions were performed in 1970, 745,400 in 1973 (a rate of 16.5 abortions per 1000 women aged 15 to 44) and it has been projected that in 1974, 892,000 legal abortions were performed.7 These data also show that the United States Supreme Court Decision in 1973,8 which liberalized abortion laws, did not have a particularly marked effect on what has been a steady annual increase in the rate of abortion, in the United States, since the late 1960s when several states enacted less restrictive abortion codes.

The second restriction in the current review is that only one aspect of the stability of the abortion decision—the change from a decision to abort to one in favor of delivery—has been considered. As we shall see below, decision making during unwanted pregnancy may include periods in which a woman continually revises and re-revises the options open to her. While a decision to deliver may later be changed to a decision to abort 9,10 (or regret that abortion can no longer, for medical reasons, be performed), this change in decision is not considered further in this paper.

# THE RATE AT WHICH WOMEN CHANGE THEIR MIND ABOUT ABORTION

In reviewing the available information on the rate at which women change their mind about abortion we will consider three aspects of the source of evidence: (1) the period in the individual's own decision making when the change in decision was ascertained, (2) the location—clinic, hospital, county and socio—legal conditions in effect when the data were collected, and (3) the nature of the statistic itself—including factors influencing the numerator and denominator which may effect the computed rate.

## The Period of Decision Making During Which Indecision May Occur

All women who experience pregnancy may consider the possibility of abortion and, therefore, are at risk of changing their decision from abortion to delivery. Nonetheless, it is clear that many women who become pregnant unequivocally wish for the pregnancy to lead to delivery and for them abortion is not a serious option. Other women, however, variously described as having an unwanted or unplanned pregnancy, give abortion considerable consideration. It is convenient to examine the stability of the decision process, in these women, for two periods: (a) the time between suspecting pregnancy and making an appointment at an abortion facility, and (b) the time between visiting an abortion facility and actually having the abortion. While such a dichotomy helps us to examine the decision process on an empirical level, however, it does not necessarily conform with the psychological reality of the decision process itself.

Evidence from studies of the first period of decision making may be most useful in predicting the characteristics of women who will change their decision to abort after reaching the clinic, and in predicting the psychological and situational correlates of such a change. Decisions which occur after the abortion client has made personal contact with an abortion facility are of acute interest to the Commission since this is the time when a woman is most likely to be asked to participate in medical studies.

# The Time Between Suspicion of Pregnancy and Personal Contact at the Clinic

In a study carried out at Yale-New Haven Hospital and also at a private New York Clinic women who aborted were asked to retrospectively report how frequently they changed their mind about the decision to abort. Approximately one third of the respondents had changed their minds about the decision to abort at least once (Table 1). $^{11}$ 

Table 1. Distribution of Variable-Indecision About Abortion and Association with Gestation Group\*

	New York			New	Haven	
Times changed mind about abortion	No. Percent		<u>Black</u> No. Percent		White No. Percent	
Never	197 62.3		74 71.8		126 72.0	
Once or twice	83 26.3		17 16.5		35 20.0	
Many times/all the time	36 11.4		12 11.7		14 8.0	
Gestation group (weeks)	Percent changed mind about abortion	No.	Percent changed mind about abortion	No.	Percent changed mind about abortion	No.
< 9	27.5	80	20.0	10	25.8	31
9-12	32.5	83	42.8	28	23.9	71
13-18	48.2	85	21.3	47	32.2	59
> 18	40.0	75	27.9	18	35.7	14
**p < 0.01	γ = .19**		γ = .15		γ = .14	

\*Source: Table is reprinted from Bracken.11

A less direct way of considering the frequency with which women may change their mind about the abortion is to examine the difficulty in making the decision. Women aborting at the State University Hospital in Syracuse, New York, between July 1970 and June 1971, were asked about their decision to abort and reported that it was: not difficult 56 percent; mildly difficult 20 percent; considerably difficult 24 percent. Similar results were found in the New Haven and New York Study in which abortion clients were asked to rank, on a 7-point scale, whether their decision had been extremely easy (scored 1) or extremely difficult (scored 7). The mean scores for women aborting in both New Haven and New York were 3.3 indicating that almost half the women had experienced some difficulty in making their decision. In another New York study at Park East Hospital, carried out between December 1971 and April 1972, one-fourth of the women aborting found the decision "difficult to make."

Another way of obtaining some estimate of the risk for a change in the decision to abort is to measure the degree of conflict during the decision

process. When this was done in the New Haven and New York studies mean levels of conflict of 2.5 were found (measured on a 7-point scale where l = low and 7 = high conflict).

Yet another way of estimating the level of indecision during this period is to determine the number of women who make appointments at abortion facilities but fail to keep them. The results of a small, ad hoc survey designed to collect data on the frequency of missed appointments are shown in Table 2.

Inspection of Table 2 suggests that roughly 10 percent of appointments made for first trimester abortion are not kept. It would be wrong, however, to interpret this figure as anything other than a maximum estimate for women who have decided not to abort. It was mentioned at all clinics surveyed that an appointment might be missed because a woman had elected to abort at another clinic, or that the appointment was inconvenient and might be rescheduled (much, but probably not all, of duplicate scheduling was avoided in computing clinic statistics), or that the client found she was not pregnant, or had spontaneously aborted.

Table 2. Proportion of Women Failing to Keep Clinic Appointments for First Trimester Abortions

	<u> </u>	Number of	Number of	Percent
Source	Year	Women Making Appointments	Women Missing Appointments	
Eastern Women's Center, New York <sup>20</sup>		11,765	1,360	11.6
Eastern Women's Center, New York <sup>20</sup>	1973	9,830	1,493	15.2
Nathanson <sup>15</sup>	Jul 1970 to Aug 1971	29,696	1,848	6.2
Preterm, Boston <sup>27</sup>	Dec 1974 to Feb 1975	2,758	237	8.5
Erie Medical Center, Buffalo,	1973	7,061	646	9.1
New York <sup>28</sup>	1974	5,041	369	7.3

## Decision Changes Following Personal Contact with Abortion Facility

The essential information collected for this section is presented in Table 3. In order to determine the rate at which women change their decision to abort after making personal contact with the abortion clinic, an attempt has been made to standardize the rate as follows:

Rate of women deciding to deliver after visiting abortion clinic  $\frac{\text{deciding to deliver}}{\text{after visiting abortion clinic}} = \frac{\text{Number of women reported}}{\text{deciding to deliver}} \times 100$  for abortion in same time period

The reported rates range from a low of 0.06 percent to 9.7 percent, a 162-fold difference! In order to weight the evidence in Table 3 we will review the sources of data in more detail in the following two sections.

#### The Type of Abortion Facility from Which Rates were Obtained

The effect of different types of abortion facility on the rate at which women change their decision to abort is highlighted by contrasting the two facilities showing the extreme differences in rate. Grady Memorial Hospital, at the time of the study, 18 was a 1,100 bed hospital serving medically indigent people from Atlanta. In 1970, in order for a woman to obtain an abortion, three licensed physicians and two out of three members of a hospital committee had to agree that an abortion was necessary. This system continued in the hospital even after a Georgia Federal District Court had ruled, in July of 1970, that established specific indications for abortion were unconstitutional. During 1970, 341 women applied for abortion of whom 139 were found to be "ineligible" or withdrew before they could be presented to the abortion committee, 43 women who were presented were refused abortion and 134 women were aborted. The median time for the abortion work-up was reported to be 15 days. In this, rather formidable, institutional and psychosocial environment, 31 women were reported to have changed their decision to abort (Table 3).

Eastern Women's Center<sup>20</sup> is typical of many large clinics specializing in abortion and reproductive health found in the United States at the present time and a description of the routines for obtaining abortion at other clinics<sup>15,22</sup> could equally apply there. Most appointments are made by telephone after the abortion client has, in many cases, already been counseled by a family planning or other agency counselor. When the abortion patient visits the clinic she is examined, counseled and aborted on the same day. Counseling at free standing abortion clinics provides emotional support prior to, sometimes during, and often following the abortion.<sup>23-26</sup> In 1973, at Eastern Women's Center, 553 women were denied abortion because of advanced gestation, 3 women were found on medical examination to have medical contraindications, 7 women decided not to abort and 7,770 women had an abortion.

Table 3. Description of Studies Providing Rates for Women Who Decide Not to Abort After Personal Contact With Abortion Facility

	V6D.4	S				
Source	Year of Data Collection	Patients Referred Patients Referre		Time When Decision to Abort was Changed	Rates*	
Newton et al. 16	1972	General practitioners and family planning clinics	Abortion Counseling Clinic, King's College Hospital, London	After first contact with Abortion Clinic**	26/1,173 (2.2%)	
Bracken and Swigar <sup>17</sup>	1970–1971	Family planning clinics, referral agencies and physicians	Yale-New Haven Hospital, Connecticut	After first contact with Abortion Clinic**	31/474 (6.6%)	
Bracken <sup>11</sup>	1972–1973	Initial visit at Yale-New Haven Hospital Clinic	Yale-New Haven Clinic for abortion	Between initial visit and abortion— on same day for first trimester cases	2/395 (0.5%)	
Yale-New Haven Hospital <sup>21</sup>	Jan 1972 to May 1973	Clinic visit for abortion	Abortion at same clinic	During the clinic visit	30/3,887 (0.8%)	
Baker and Freeman <sup>18</sup>	1971	Private physicians and direct applica- tion to hospital	Grady Memorial Hospital, Atlanta, Georgia	Between contact with abortion "coordinator" and abortion procedure	33/341 (9.7%)†	
British Pregnancy Advisory Service (BPAS) <sup>19</sup>	1971	BPAS counseling and approval for abortion	BPAS Clinic for abortion	Between consultation with 2 MDs who signed a certificate approving the abortion and the procedure	248/16,088 (1.5%)	
Preterm Boston <sup>27</sup>	Aug 1, 1973 to Dec 31, 1974	Clinic visit for abortion	Abortion at same clinic	During the clinic visit	31/10,858 (0.3%)	
London Pregnancy Advisory Service (LPAS)††	Probably 1969–1970	Initial LPAS interview	LPAS Clinic for abortion	Between initial interview and abortion	42/3,000 (1.4%)	
Pare and Raven <sup>1</sup>	1962-1968	Psychiatric interview and recommended for abortion	St. Bartholomew's Hospital, London	Between psychiatric approval and abortion	2/130 (1.5%)	
Eastern Women's Center <sup>20</sup>	Feb 1 to Aug 1, 1972	Clinic visit for abortion	Abortion at same clinic	During the clinic visit	6/9,820§ (0.06%)	
Eastern Women's Center <sup>20</sup>	1973	Clinic visit for abortion	Abortion at same clinic	During the clinic visit	7/7,777§ (0.09%)	

<sup>\*</sup>Number of women changing mind over total number of women referred for abortion. For some studies rates have been recomputed for the current report.

<sup>\*\*</sup>It is unclear what proportion of those women who decided not to abort did so following a telephone appointment but before visiting the clinic versus those women who visited the clinic and then changed their mind.

<sup>†</sup>An additional two women were listed as "rejection of system" and nine as a "minor unwilling or unable to obtain (parental) consent." Inclusion of these women in the rate of those listed as "changed mind" increases it to 12.9%. At follow-up only 27 of the 44 women not "aborting" were found to be pregnant (see text for details).

 $<sup>\</sup>dagger\dagger$ These data were reported as evidence to the Committee on the Working of the Abortion Act.  $^6$ 

<sup>\$</sup>These data exclude women not aborted because of advanced gestation and other medical contraindications.

Several of the reported studies are from Britain 1,6,16,19 and these data show a more uniform rate for changes in decision which range from 1.4 percent to 2.2 percent. Even though abortions are performed under liberal laws in Britain a woman must have the consent of her physician before an abortion may be performed. Contact with the physician may be a relatively uniform institutional process which, in effect, filters out women who might otherwise be candidates for later changing their decision to abort. Moreover, this process may account for the similarity of the rates from the British data. In other respects, particularly their counseling and medical procedures, the larger scale British abortion facilities, the London<sup>6</sup> and British<sup>19</sup> Pregnancy Advisory Services, are not unlike free standing abortion clinics in the United States. One wonders, then, why the rates in changing the decision to abort are not more alike. For example, the lowest available rate from the United States, 0.06 percent, is 23 times lower than the lowest British rate of 1.4 percent. One explanation may be that data from the free standing facilities includes only women aborting in the first trimester whereas the British data included second trimester patients. The possible influence of gestation on changing the decision to abort will be discussed in a later section.

# Problems in Computing the Change in Decision Rate

The formula used to compute the rate for women who change their decision to abort has been presented above. It is, of course, essential in computing the rate to ensure that all the women in the numerator have also been listed in the denominator and this has been done in Table 3. In comparing rates from different abortion facilities one would like to be assured that criteria for entering the numerator are the same across studies, as are criteria for entering the denominator.

Typically, women are identified who have "changed their mind" or who are "having the baby." There has been no systematic attempt to adequately define what is meant by a change in the decision, indeed there is no specific study of the phenomenon of decision changes prior to abortion anywhere in the literature. Some of the data presented in this report have been culled from clinic statistics and one can have little assurance that correct criteria for collecting research data were completely followed. Other data have been determined from reports of methodology and sampling in studies which were essentially dealing with other research questions. Several studies <sup>16,17</sup> include an unknown proportion of women who changed their decision to abort prior to reaching the clinic among those women who did so after the clinic visit. In a sample from Yale—New Haven Hospital some women who changed their decision to abort before visiting the clinic are included <sup>17</sup> whereas these women are not included in service statistics from the same hospital which show a much lower rate<sup>21</sup> as does information from the sampling frame for another study at the same hospital. <sup>11</sup>

In one study  $^{18}$  women who "rejected the system" and minors "unwilling or unable to obtain (parental) consent" were not included with those who "changed

their mind." One cannot be confident, however, that such women would not have been included in the numerator of other studies.

As we have seen, the characteristics of women entering the denominator, that is women referred for abortion, have been influenced by different social, legal and clinic policies. Women who are prescreened by physicians, excluded because of advanced gestational age, or disinclined to request abortion because of institutional policies, have been disproportionately excluded from some studies rather than others.

# CHARACTERISTICS OF WOMEN WHO MAY BE AT HIGHER RISK OF DECIDING NOT TO ABORT

Again it is useful to consider the period during which a woman might decide not to abort in two stages; the time between suspicion of pregnancy and contact at a clinic, and the period following personal contact at the clinic. There is no evidence in the literature, nor from clinical impression, that tells us which women have been more likely to change their decision to abort after making contact with the abortion facility. Nonetheless, it is possible to paint some picture, albeit an incomplete one, of women who are more likely to report, when they finally do obtain an abortion, that they went through a period of indecision. This evidence will be reviewed in the remainder of this section.

# Evidence From Studies of Delayed Decisions to Abort

Indecision, increased conflict over the decision to abort (Table 1), and delayed decisions to abort (1,13,29) have been shown to be related to abortion obtained in the second trimester. Women who have been shown to be significantly more likely to delay in seeking abortion, therefore, might also be similar to those who are more likely to change their decision to abort. There is a growing body of information on the phenomenon of delayed abortion and only the major correlates of delay will be reported here.

Women delaying in seeking induced abortion have been generally found to be young, 13, 17,31,32 single, 13, 17, 29, 31-33 primigravidas, 13, 29, 32 and experiencing their first abortion. 34, 35 Black women have been found to be later presenters for abortion, 13, 17, 31 as have women from lower socioeconomic groups, 32, 33 those with lower levels of completed education, 17, 32 and women who are unemployed. 13, 17, 32

These observations should not suggest that the delay in seeking an abortion results entirely, or even principally, from changes in the decision to abort. Many of the women who delay in seeking abortion have been reported to at least be partially delayed because of institutional hurdles in obtaining abortion 13, 17, 29, 33, 36-38 or because of an unstable relationship with the partner 13, 32, 39 or parents. 40 Yet another contributor to delayed abortion has been reported to be delay in recognition of pregnancy 11, 13, 17, 29, 32, 40, 41 or denial of pregnancy. 14,40

# Evidence from Unpublished Data

In a study of the decision to seek induced abortion among samples of women in New York and New Haven<sup>11</sup> respondents were asked "How many times did you change your mind about having the abortion?" The responses have been shown in Table 1. Indecision over the decision to abort was used as a dependent variable (dichotomized as never changed mind versus changed mind once or more) in order to reanalyze data from the study to examine the correlates of indecision prior to the abortion.

When simple socioeconomic factors were considered, women who were younger, less well educated and nulliparas were significantly more likely to report indecision prior to abortion. In order to obtain a more complete picture of the socio-demographic and psychological milieu in which indecision occurs the New York data were analyzed using a stepwise multiple regression technique. The first step in the regression analysis selected the single variable with the greatest prediction on the dependent variable based on the simple correlations. The second independent variable put into the regression equation was that which provided the best prediction of the dependent variable in conjunction with the first variable. Only independent variables making a significant contribution (as measured by an F-test) when added to the other independent variables have been presented in Table 4.

Table 4. Stepwise Multiple Regression Analysis of Changes in the Decision to Abort by Selected Independent Variables, New York Sample (n = 345)

Step	Variable*	В	s.e.B	F	R	R <sup>2</sup>	r
1.	Difficulty in making the decision to abort	.1220	.0246	24.70	.622	.387	.622
2.	Initially rejected idea of abortion	.1148	.0282	16.59	.665	.442	.569
3.	Initially happy about pregnancy	.0860	.0271	9.97	.692	.479	.437
4.	Nonsupportive relation- ship with partner	.0829	.0393	4.46	.698	.487	.127
5.	More people know about abortion decision	.0527	.0306	2.97	<b>.</b> 704	. 495	.212
6.	Low ego resilience	.4544	.2715	2.80	.709	.503	.158

<sup>\*</sup>Variables are described to indicate prediction of more frequent indecision over decision to abort.

The six independent variables first entering the regression equation were able to explain 50 percent of the variance in the dependent variable. None of the demographic measures entered the regression equation, indeed the most powerful variables predicting indecision are ones reflecting the woman's psychological reaction to the pregnancy and abortion, the level of support she is likely to receive from her partner, the influence of many people knowing about the abortion and the woman's ability to cope with conflict during the decision process as measured by her ego resilience.

This analysis suggests, then, that changes in the decision to abort prior to visiting the clinic are associated less with simple demographic variables and more with psychological attributes which are less easily measured. Thus any attempt to develop measures which would enable clinicians to improve their ability to identify women who might change their decision to abort would have to include factors operationalizing the kind of psychological parameters shown in Table 4.

The evidence presented above may be summarized as follows. There is fairly substantial agreement, in the literature, on the demographic characteristics of women who have delayed abortion procedures. There has been less success in identifying women who delay making decisions to abort independent of other factors which may cause delayed abortion. Furthermore, there is some evidence that delayed abortion is associated with indecision to abort and this will be discussed more thoroughly in the next section.

It is quite obvious that a good deal of further investigation is required to confirm the rather tenuous relationships which emerge out of the currently available research findings. Moreover, it is important to emphasize that there is nothing in the available literature to indicate that women who are indecisive about their abortion prior to reaching the clinic will also continue to be indecisive after visiting the clinic. It could be argued that women who are indecisive during the earlier stages of their decision to abort might be more likely to continue to be indecisive until the abortion is performed, and, indeed, even after the abortion. Alternatively, women who pass through an indecisive period prior to visiting the clinic and then resolve the decisional conflicts may be least likely to change their decision to abort after visiting the clinic. There is evidence in the psychological literature for both points of view and few, if any, clinical reports speak to the issue.

Possibly other parameters, such as the woman's ability to cope with conflict, her self-esteem, feelings of powerlessness, and so on, will be more important indicators of late changes in the decision to abort than will a simple measure of how indecisive a woman was during her pre-clinic decision making. In one study<sup>14</sup> women of low ego resilience delayed relatively less in seeking abortion when the decision was highly conflictful than women of higher ego resilience. One explanation of this unexpected finding is that women who are better able to cope with the distress of having to decide to abort (the high ego resilience group) delay with increased conflict because they use the time to resolve conflicting issues which may produce indecisiveness. Women who cannot cope with the conflict of decision making may have truncated their decision processes in order to avoid the stress and anxiety of decisional conflicts and thus they will not resolve their indecisiveness. Such women are much more likely to be prone to changing their abortion decision after arrival at the clinic and when

they are faced with new considerations in their decision for which they were not prepared. Some of the possible factors which may change the woman's decision at this stage are discussed below.

# PSYCHOLOGICAL AND SITUATIONAL FACTORS WHICH MIGHT CONTRIBUTE TO A CHANGE IN THE DECISION TO ABORT

Here we consider a number of factors which might contribute to a change in the decision to abort. In the previous section it was postulated that an important determinant of late changed decisions could be the failure to resolve conflicting issues (rather than simply the presence of conflict) in the earlier decision—making stages. When late changes in the decision to abort occur the full ramifications of the decision to abort may not have been thought through making the decision vulnerable to new (possibly, even trivial) pieces of information which change the decisional "balance sheet" in favor of the delivery option.

The concept of "balanced decision" hints at a psychosocial concept of decision making which has been more fully developed by Janis and Mann<sup>44,45</sup> and described in terms of decision making during unwanted pregnancy elsewhere.<sup>30</sup> It has been proposed that during the decision to abort a woman passes through five stages. She must (1) acknowledge that she is pregnant, (2) consider the options, abortion or delivery, which are open to her, (3) consider the advantages and disadvantages of abortion or delivery by scanning and weighing the pros and cons of each alternative, (4) commit herself to one particular option, and (5) adhere to the decision.

Stage 3, when the pros and cons of abortion are considered, is of particular relevance to the Commission's interest since the degree of effort put into considering all information pertinent to the decision at this stage will "influence the long-run stability of the decision."<sup>45</sup> Thus a new piece of information during Stage 5 is only likely to result in a changed decision if it has not been anticipated and if contingency plans (both utilitarian and psychological) have not been prepared during Stage 3. For example, women who have sought information about abortion techniques, say by asking their physician, friends or by reading, are less likely to decide not to abort when the abortion procedures are described at the clinic. Improvement in the early decision-making process, according to this formulation, will reduce the risk of later indecision.

This brief description of the psychosocial concept of decision making under conflict does violence to a rather complicated theory based on a considerable amount of psychological evidence. It is sufficient, however, to make the point that the process of decision making is likely to be a more powerful predictor of later changes in the decision than is any one particular group of variables. Thus the search for situational factors which might contribute to a late decision not to abort is likely to be an elusive one.

The above discussion notwithstanding, four issues will be considered as having some likelihood of influencing the probability that a woman might change her decision to abort. These are (1) the gestational age of the pregnancy, (2) social and psychological considerations, (3) abortion counseling at the clinic, and (4) participation in a research project at the clinic.

## Gestational Age of Pregnancy

There is some indication that increased gestational age is correlated with increased conflict during the decision process prior to arriving at the clinic (Table 1)<sup>11</sup> and a more difficult decision to abort.<sup>11, 13, 14, 29, 32</sup> Here, however, we are more concerned with the influence of gestation on a change in the decision to abort after visiting the clinic. Three considerations might contribute to late changes in the abortion decision. First, with later gestation, the abortion client may have experienced fetal movement which results in an increased emotional investment in the fetus. While the experience of fetal movement would be more likely to influence preclinic decisional change than it would be to produce a change in decision during the clinic visit itself, experience of fetal movement might be an important factor in influencing other considerations that do occur during the clinic visit.

Second, it would seem reasonable to propose that the principal influence of later gestation is on the change in the abortion procedure demanded by a second trimester pregnancy. It is likely that most women are unaware of the different abortion procedures for first and second trimester abortion until they arrive at the clinic. The second trimester procedure (usually saline instillation) has an approximately four-fold increased risk of major complications <sup>31</sup> and a seven- to nine-fold increased risk of death <sup>46</sup> and, on being confronted with a more serious procedure than expected, women who have not made a firm decision to abort may decide to deliver. Furthermore, the second trimester abortion procedure is more expensive <sup>47,78</sup> and requires an overnight hospital stay--considerations which might also be sufficient to change the decision in favor of not aborting.

Very few of the studies reported in Table 3 indicate the proportion of first trimester abortion patients who change their decision versus those in the second trimester. However, samples with the larger proportion of second trimester women are also those with a larger rate of decisional change. At Grady Memorial Hospital<sup>18</sup> 26.7 percent and at Yale-New Haven Hospital<sup>21</sup> 24.2 percent were in the second trimester. The data from the British Pregnancy Advisory Service<sup>19</sup> and King's College Hospital<sup>16</sup> indicate that 20 percent and 14.5 percent respectively were referred for abortion in the second trimester. Both of the women in the Yale-New Haven study sample<sup>11</sup> who decided to deliver were in the second trimester. The three large free-standing abortion clinics represented in Table 3 only include first trimester procedures. <sup>15, 20, 27</sup>

The third consideration results from the fact that women who present for abortion between the twelfth and fifteenth week of gestation are often asked to return beyond the fifteenth week because that is the optimal period for instillation procedures. There is neither empirical nor clinical documentation of the number of women who may, during this potentially vulnerable period, decide not to abort. Women who are refused abortion (many during the first telephone contact) because of advanced gestation at first trimester abortion clinics must often reregister for a second trimester abortion at another hospital. Records of the outcome of denied applications have not been maintained.

Of acute interest is the final pregnancy decision of women who visit a clinic or hospital abortion facility and who are only told following a medical examination that they are too advanced in pregnancy for a first trimester

procedure. These women are at risk of being asked to participate in research projects. While many first trimester abortion clinics maintain very close relationships with hospitals performing second trimester procedures, no data have been found which indicate what proportion of women denied first abortion do go on to abort in the second trimester. Some estimate of the prevalence of denied abortion because of advanced gestation is indicated by the data in Table 5.

Table 5. The Number and Proportion of Women Refused First Trimester Abortions Because of Advanced Gestational Age

Source	Year	Number Refused	Total Refused X 100 Total Keeping Appointment
Erie Medical Center Buffalo, New York <sup>28</sup>	1973	658	9.7
Bullato, New Tolk	1974	658	6.8
Eastern Women's Center New York <sup>20</sup>	Feb 1 to Aug 1,1972	454	18.6
	1973	553	15.1
	Jan 1 to Oct 31,1974	294	15.0

#### Social and Situational Factors

In this section a number of issues which emerge from the literature and which have not been previously considered are briefly discussed in terms of their implication for a change in the decision to abort.

A number of factors have been considered to contribute to conflict during pregnancy. Much of this research has dealt with "wanted" pregnancy and the factors include: hyperemesis, 48 common antenatal problems, 49 attitudes toward feminine role, 50,51 sexual attitudes toward mother, father, and husband, 52 "sick role" expectations in pregnancy, 53 and rejection of the pregnancy by the father and experience of having a previously defective or deformed child. All of the above factors might be considered, if they occur during a pregnancy which is not unequivocally wanted, to contribute to an unchanged decision to abort. Evidence from studies of the reasons for seeking induced abortion also suggest situations in which the abortion decision is likely to remain firm. Among the more important are: social sanctions faced by single women who do not renounce motherhood, 51,55 inability to manage another child, 55-57 and anxiety over deformity of the child.55

The same body of literature suggests a number of situations which, in the absence of hard data can only lead us to speculate, may be associated with a changed decision to deliver and not abort either before or during the clinic visit. These include: deviant scores on psychological tests, 58 emotional immaturity, 59 attempts to involve the partner in marriage, 56,57,60 inadequate emotional supports, 55 mental abnormality, 56,61 previous psychiatric difficulty, 56,57 and anxiety of the abortion procedure itself 62 or surgery in general. 63

#### Abortion Counseling

Much of the early literature was written at a time when abortion "counseling" consisted of an interview during which the abortion applicant had to convince a psychiatrist that abortion was necessary for her mental, if not physical health. Reviewers of this literature 64-66 have pointed out the biases inherent in findings from that research. In this section we are concerned with the influence of abortion counseling as it currently is practiced in many abortion clinics in the United States. 23-26, 67-69

The essential feature of abortion counseling, as expressed by almost all writers and most pertinent for this inquiry, is that aspect of counseling in which the counselor determines the nature of the abortion client's decisionmaking process. The review of the pros and cons of the decision to abort, including an examination of any conflicts in the decision and how they were resolved, enables the counselor to assess the "quality" of the decision process. Particularly important, is whether the abortion client denied, negated or used other ego defense mechanisms leading her to ignore areas of conflict during the decision making which might result in an increased risk of postdecisional regret after the abortion. This type of counseling rarely leads to a unilateral decision on the part of the counselor to deny the client an abortion but, most frequently, the abortion client herself realizes during counseling that she is not yet prepared to commit herself to having an abortion. It was reported that the 31 women who decided not to abort while at Preterm in Boston (Table 3),27 did so during extensive individual counseling with trained abortion counselors.

Abortion counseling, then, is a crucial process for screening out applicants for abortion who might be at higher risk for changing their decision to abort prior to the procedure itself.

## Participation in Research Projects

In order to gain some insight into the possible effect of participation in research prior to abortion on the decision to abort it is again useful to consider the "balance-sheet" model of decision making. At least two issues must be considered: (a) the extent to which a decision to abort is balanced in favor of abortion, and (b) the nature of the research activity itself.

Women who are firmly committed to aborting (either because the factors in their decision were heavily weighted toward abortion or because decisional conflicts were successfully resolved in favor of abortion) are unlikely to change that decision because of participation in a research project. For these women, participation in research is most likely to become yet another component in their decisional balance sheet which either reinforces an existing decision to abort or (for some types of research discussed below) favors delivery but is not a powerful enough cognition to counterbalance other factors favoring abortion.

What, however, of the woman who is less certain of her decision to seek abortion? In the absence of empirical data on the issue we must turn to some of the psychological literature for guidance. A woman who is generally disposed against abortion and yet finds herself in a clinic preparing for an abortion procedure is experiencing cognitive dissonance. The speculating on the effect of participation in research on this situation it would seem reasonable to expect that the nature of the research activity itself would influence the decision. Research which emphasized the viability or "humanity" of the fetus might be sufficient to induce a change in the decision to abort. Other research, which had some element of risk to the fetus and therefore of giving birth to a deformed baby, would reduce the likelihood of a change in the decision to abort.

In one Hungarian study 74 327 women were examined by ultrasonic Doppler technique within one hour of a requested first trimester abortion. The study sought to determine the efficiency of the Doppler technique, which has no risk to the fetus, in detecting fetal heart beats at various stages of pregnancy. While patients were not told the purpose of the ultrasonic Doppler examination, over 90 percent of the patients associated the audible sounds with the fetal heart. The reaction of the patients, especially the multigravidas, on listening to the fetal heart sounds is of interest here. Among the multigravidas 60 percent were reported very disturbed by the sounds and immediately went into a long explanation rationalizing their decision to seek abortion to the medical staff. A further 16 percent changed their minds about the abortion and decided to bear the pregnancy to term. Among primigravidas 30 percent were disturbed by the experience and an additional 2 percent decided not to abort.

The report of this study does not indicate whether women were counseled prior to their abortion. Nor, beyond knowing that patients were not told to expect fetal heart sounds, are the consent procedures described. However, irrespective of steps taken to obtain informed consent, one must deplore the callous disregard shown the patient by leaving the instrument within such close proximity to her that it could be overheard.

The Hungarian study primarily emphasizes the importance of ensuring that all patients asked to participate in research projects have been independently counseled to provide assurances that a firm decision to abort has been reached. The study also indicates the need to avoid research maneuvers which violate the particular sensibilities of preabortion patients. The Hungarian study neither sheds light on the effect of fetal research which does not raise conflict over the decision to abort nor on research which, because of increased risk to the fetus, further supports the decision to abort.

Participation in research which has some risk to the fetus might be considered to reduce the choice which still remains for abortion or delivery. Evidence from psychological laboratories 73,75,76 suggests that the reduction of choice in a decision also reduces cognitive dissonance. These data imply, then, that participation in a higher risk fetal research project would incline the more ambivalent abortion patient toward a firmer decision to abort. Additionally, it might be argued, that only a relatively severe threat, such as fetal research involving drugs, would enhance an existing decision to abort. Less innocuous procedures, say the completion of questionnaires, might simply increase cognitive dissonance in the ambivalent patient 77 and act as an additional factor against the abortion decision.

#### SUMMARY

- Little available research has directly confronted the question of change in the decision to abort which is reviewed in this paper. All the evidence is drawn, second hand, from a variety of sources in which other issues were the object of interest. There is a clear demand for hard empirical data in this area.
- Among women who abort as many as one third report having changed their decision to abort at least once prior to reaching the clinic. Difficult decisions and conflict during decision making are also quite prevalent.

- 3. Approximately 10 percent of appointments for abortion are not kept, a figure which probably overestimates the proportion of women who have decided to deliver.
- 4. In large volume free-standing clinics aborting women in the first trimester in the present socio-legal climate, less than 1 percent of abortion applicants are likely to decide not to abort after visiting the clinic. In facilities offering second trimester procedures it is unlikely that more than 2 percent of applicants will change their mind.
- 5. Women more at risk of changing their decision to abort are more likely to be characterized by psychological than by demographic factors. The style of coping with conflicts during decision making, rather than simply the presence of conflict, is more likely to predict late changes of decision.
- 6. Women aborting in the second, versus first, trimester may be at relatively greater risk of changing their decision to abort.
- 7. Between 5 percent and 20 percent of women examined at clinics performing first trimester procedures are refused abortion because of advanced gestational size. At other hospitals an unrecorded number of women have their abortion postponed because they are between 13 and 15 weeks pregnant. For either group of women there is no indication what proportion eventually go on to abort. In the absence of information to the contrary these women must be considered at elevated risk of changing their decision to abort.

- 8. Abortion counseling is a crucial procedure for selecting out of the clinic population women who are at increased risk of changing their decision to abort. An invitation to participate in a research project should only follow, and should be independent of, routine abortion counseling.
- 9. Women who have reached a firm decision to abort are unlikely to change their decision because of participation in a research project. Women more ambivalent about aborting are only likely to change their decision if the research maneuvers emphasize the viability of, and present no risk to, the fetus.

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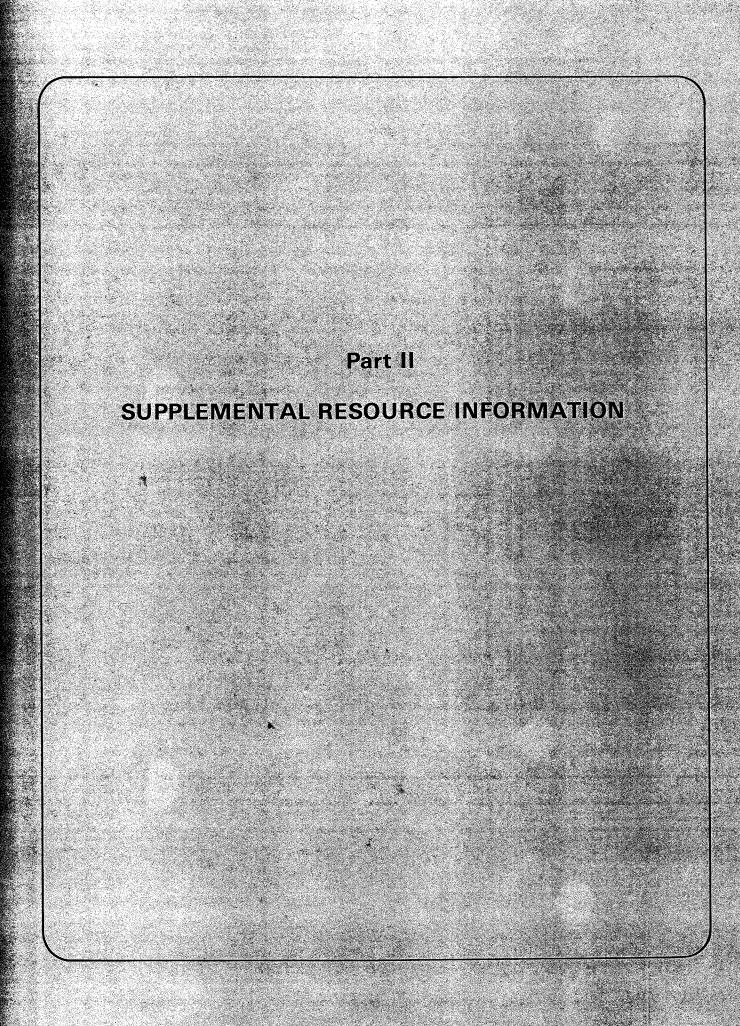
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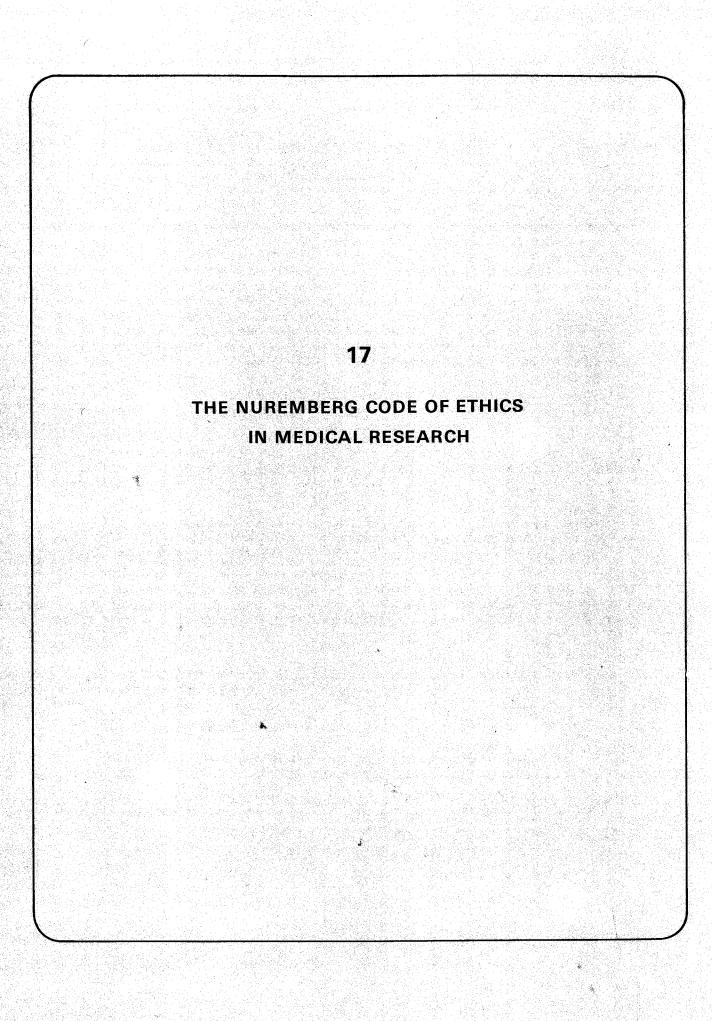
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## The Nuremberg Code of Ethics in Medical Research

(1) The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent: should be so situated as to be able to exercise free power of choice without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

- (2) The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
- (3) The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
- (4) The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
- (5) No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subject.
- (6) The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

- (7) Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
- (8) The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
- (9) During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
- (10) During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill, and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

18 **DECLARATION OF HELSINKI** (Recommendations Guiding Doctors in Clinical Research Adopted by the World Medical Association in 1964)

#### **Declaration of Helsinki**

#### INTRODUCTION

It is the mission of the doctor to safeguard the health of the people. His knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of The World Medical Association binds the doctor with the words: "The health of my patient will be my first consideration" and the International Code of Medical Ethics which declares that "Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest."

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, The World Medical Association has prepared the following recommendations as a guide to each doctor in clinical research. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

In the field of clinical research a fundamental distinction must be recognized between clinical research in which the aim is essentially therapeutic for a patient, and the clinical research, the essential object of which is purely scientific and without therapeutic value to the person subjected to the research.

#### I. BASIC PRINCIPLES

- 1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.
- 2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.
- 3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
- 4. Every clinical research project should be preceded by careful assessment of inherent risks in comparision to forseeable benefits to the subject or to others.
- 5. Special caution should be exercised by the doctor in performing clinical research in which the personality of the subject is liable to be altered by drugs or experimental procedure.

#### II. CLINICAL RESEARCH COMBINED WITH PROFESSIONAL CARE

1. In the treatment of the sick person, the doctor must be free to use a new therapeutic measure, if in his judgment it offers hope of saving life, reestablishing health, or alleviating suffering.

If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity the permission of the legal guardian replaces that of the patient.

2. The doctor can combine clinical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that clinical research is justified by its therapeutic value for the patient.

#### III. NON-THERAPEUTIC CLINICAL RESEARCH

- 1. In the purely scientific application of clinical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom clinical research is being carried out.
- 2. The nature, the purpose and the risk of clinical research must be explained to the subject by the doctor.
- 3a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally incompetent, the consent of the legal guardian should be procured.
- 3b. The subject of clinical research should be in such a mental, physical and legal state as to be able to exercise fully his power of choice.
- 3c. Consent should, as a rule, be obtained in writing. However, the responsibility for clinical research always remains with the research worker; it never falls on the subject even after consent is obtained.
- 4a. The investigator must respect the right of each individual to safeguard his personal integrity, especially if the subject is in a dependent relationship to the investigator.
- 4b. At any time during the course of clinical research the subject or his guardian should be free to withdraw permission for research to be continued.

The investigator or the investigating team should discontinue the research if in his or their judgment, it may, if continued, be harmful to the individual.

We, the undersigned medical organizations, endorse the ethical principles set forth in the Declaration of Helsinki by the World Medical Association concerning human experimentation. These principles supplement the principles of medical ethics to which American physicians already subscribe.

American Federation for Clinical Research
American Society for Clinical Investigation
Central Society for Clinical Research
American College of Physicians
American College of Surgeons
Society for Pediatric Research
American Academy of Pediatrics
American Medical Association

19

# THE USE OF FETUSES AND FETAL MATERIAL FOR RESEARCH

Report of the Advisory Group, Chaired by Sir John Peel, London, 1972

#### MEMBERS OF THE ADVISORY GROUP INCLUDE:

Sir John Peel, KCVO FRCOG FRCS FRCP (Chairman)
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Miss A. Catford, AIMSW
Dr. Christopher Clayson, OBE MD PRCP(E) FRCP (London) DPH
Mr. G. Prys Davies, OStJ LLM
Dr. G. S. Dawes, FRS DM FRCOG
Mr. G. S. Gimson, QC
Mrs. J. J. Godwin-Austen, SRN
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Dr. Pauline M. Jackson, MB BS DCH
His Honour Judge E. B. McLellan

## The Use of Fetuses and Fetal Material for Research

#### INTRODUCTION

1. We were appointed by the Secretary of State for Social Services and the Secretaries of State for Scotland and Wales on 19 May 1970, with the following terms of reference:

"To consider the ethical, medical, social and legal implications of using fetuses and fetal material for research."

#### Number of Meetings

2. We held our first meeting on 30 July 1970 and we have met six times altogether.

#### Evidence

- 3. Factual information on the use of human fetuses and fetal material for research was obtained from the Medical Research Council and the Public Health Laboratory Service. This is summarized in later sections of the report. In addition to this evidence a number of organizations were invited to comment on the matters within the terms of reference and we received some spontaneous representations.
- 4. While there were differences of opinion in the evidence we were impressed by the substantial measure of agreement in the views expressed. Our work has been greatly assisted by the evidence received, which we have studied and taken into account when reaching our conclusions, and we wish to record our thanks to all those who contributed. Their names are listed in Appendix 1.
- 5. The Chairman and members of the Advisory Group would like to put on record their appreciation of the help they have received from the Joint Secretaries, Dr. Laycock and Mrs. S. E. Reeve. Throughout they have facilitated communication with the large number of people involved in the whole investigation, and made an invaluable contribution to the repeated draftings that became necessary. Without their help the enquiry would have been a much more difficult task.

#### MEDICAL BACKGROUND

#### Definitions

6. The ethical problems which have arisen in recent years in relation to organ transplantation have emphasized the difficulties of defining terms as "life" and "death." These difficulties have been encountered in the context of decisions relating to adults and children but in the case of the fetus in midpregnancy an additional difficulty arises in defining viability. In 1950 an Expert Committee of the World Health Organization attempted to meet the problem of definition but since that time advances in medical knowledge have made their definitions unsatisfactory. We have decided to introduce our own definitions of some of the more important terms used in this report, as we consider these to reflect more accurately the current state of medical knowledge. Our definitions are set out below:

The Fetus: the human embryo from conception to delivery (and therefore including what is normally termed the embryonic state).

A Viable Fetus: one which has reached the stage of maintaining the coordinated operation of its component parts so that it is capable of functioning as a self-sustaining whole independently of any connection with the mother.

A Pre-Viable Fetus: one which, although it may show some but not all signs of life, has not yet reached the stage at which it is able, and is incapable of being made able, to function as a self-sustaining whole independently of any connection with the mother.

<u>Fetal Death</u>: the state in which the fetus shows none of the signs of life and is incapable of being made to function as a self-sustaining whole.

Fetal Tissue: a part or organ of the fetus, e.g., the lungs or liver.

Fetal Material: any or all of the contents of the uterus resulting from pregnancy excluding the fetus, i.e., placenta, fluids and membranes.

#### Research Involving the Use of the Dead Fetus and Fetal Material

7. Evidence was sought from a number of organizations known to use dead fetuses, fetal tissues and fetal material in the course of their work. Our enquiries showed that in most instances fetal tissues are used since tissues and cells may continue to live for a period after the fetus itself has died, even if they are separated from it. The use of the fetus as a whole is necessary only in a small number of investigations at present.

- 8. Fetal tissues may be used in various valuable ways, particularly in preventive medicine where there is generally no practical substitute for the fetal tissues used. This is especially the case in the field of virology. The enquiries we made showed that it is often difficult to distinguish between research uses and the diagnostic or therapeutic uses of the work which is being done. Some examples are described below and fuller details are given in Appendix 2.
- 9. Virology: Fetal tissues are used in the routine diagnosis of and research on viruses pathogenic to man, notably those affecting the respiratory tract; the largest present user for this purpose is the Public Health Laboratory Service. Identification of different strains of the rhino viruses (the most common causes of colds) has been made possible on a large scale only by using cultures obtained from fetal tissues since most of these organisms do not grow on cultures of non-human cells.
- 10. The properties of both established and new vaccines against viral infections are investigated in fetal tissue cultures, as these tissues provide excellent purity tests for the vaccines. For example, work is in progress on an influenza vaccine, and the vaccines for poliomyelitis and rubella (German measles) are manufactured from fetal tissue. Thus the use of fetal tissues has gone beyond basic research into the field of established practice in preventive medicine. For the future, it seems probable that the use of fetal tissues will offer the only chance for growing the viruses thought to cause hepatitis and infantile gastroenteritis.
- 11. Cancer Research: Fetal tissues provide the best source of human cells that can be kept growing in tissue culture for the study of induction of disordered growth (analogous to cancerous growth) and of the effect of various agents on that disordered growth. Research in this field opens up future possibilities of diagnosis and treatment of cancer in children and adults.
- 12. Arterial Degenerative Disease: Fetal tissue cultures provide material for research on the development of connective tissues in the arterial wall and so may contribute to the knowledge of the origins of arterial degenerative disease.
- 13. Immunology: Fetal thymus cells and bone marrow grafts are used in research into the treatment of certain diseases of infants where the normal mechanism for resistance against infection is deficient (immuno-deficient conditions). Fetal cells are used to investigate renal and liver transplant rejection phenomena in adults and for tissue typing in transplant surgery.
- 14. Congenital Deformities: Research on the whole dead fetus is essential for the advancement of knowledge of fetal development and to investigate factors that might interfere with this so as to produce congenital deformities. It has already been found that the infection of the fetus with rubella virus can cause congenital heart disease, blindness and deafness, and that certain drugs can cause deformities of the limbs or internal organs; but many other structural deformities remain to be investigated.

#### Research on the Fetus in Utero

15. Observations have been made on the fetus in utero to estimate its growth especially that of the head, to study its responses to sensory stimuli and to investigate the changes in heart rate. Special attention has been given to the variations in blood composition during labour and to the circulatory and respiratory changes which occur during and after birth.

#### Research on the Whole Pre-Viable Fetus

16. Research involving the whole pre-viable fetus has been carried out after delivery in certain countries to increase knowledge of perinatal physiology and pathology especially in regard to steroid metabolism. Stringent precautions have been taken to ensure that the fetuses used for such investigations are not viable.

#### Supply of Fetuses, Fetal Tissue and Fetal Material

17. Since 1958 the Medical Research Council has provided a grant to support the collection, preservation and distribution of fetuses, fetal tissues and fetal material by the Royal Marsden Hospital, London. About 40 different establishments and individuals are supplied by this source. Inevitably costs for storage and transport are incurred and where appropriate these are met by the recipient. Outside the London area those requiring fetal tissues or material make similar arrangements with local hospitals.

#### THE PRESENT LEGAL BACKGROUND

- 18. The law governing the issues under discussion falls naturally into four parts: the criminal, the civil, the administrative (the statutes governing registration of births and deaths etc.) and the disciplinary. In relation to both the criminal and civil law it is pertinent to note that the research under consideration is carried out in three separate legal jurisdictions (England and Wales, Scotland and Northern Ireland) in which the machinery of law enforcement is wholly, and the substantive law in part, different. An attempt to summarize the law in more than broad outline could therefore lead to confusion and no attempt is made to do so.
- 19. It is an important aspect of the law in all three jurisdictions that established practices over the whole range of medical and nursing treatment in the obstetric and paediatric field from the moment of conception until the fetus is firmly established as a live or dead child (in the normal colloquial sense) are subject to the strongest presumptions of legality.

#### Criminal Law

- 20. The purpose behind the criminal law has always been the protection of the fetus at all stages. However, the law was developed and expounded before the great changes brought about by scientific advances and by the passing of the Abortion Act, with the result that the available authoritative statements of the law do not provide clear guidance in the present situation. Development of the law has also been limited by the rarity of cases in which the activities of the medical profession have given rise to prosecution.
- 21. The problem is essentially new and if, as we think, a measure of control is called for by both medical and lay opinion, the limited operation of the criminal law makes it an inadequate guide or instrument for this purpose. Having thus stated the limitations of criminal law, we have summarized what we understand to be its general effect. In all three jurisdictions the following acts may be taken to be criminal:
  - (a) deliberate or reckless injury to the fetus at any time between conception and delivery save under the provisions of the Abortion Act. (In this connection it is worth observing that the protection afforded to the fetus is continuous and is not abrogated by the fact that it may be the intention at the time of the infliction of the injury that the fetus should be prevented by a subsequent abortion from attaining life.)
  - (b) deliberate or reckless injury to the fetus which has become a child born alive or capable of being born alive. (In England and Wales and Northern Ireland there is a statutory presumption that a fetus of 28 weeks development is capable of being born alive.)

#### Civil Law

22. Civil law requires of a medical practitioner who undertakes the treatment of a patient the exercise of reasonable skill and care and treats failure in such care as negligence. Any negligence in diagnosis or treatment (whether experimental or not) which causes injury to a fetus will found a claim for damages notwithstanding that the conduct of the practitioner has been neither criminal nor unethical. Such a claim could also arise from harm caused to a fetus following negligent certification that it was not viable.

#### Administrative Law

23. The administrative law may be briefly summarised. In all three jurisdictions there are broadly similar statutory requirements for the registration of births, deaths and still-births, and for notification of births to the public health authority. These statutes have several purposes, statistical, administrative and protective of life. For present purposes only the last is relevant.

The requirement to register a birth applies only to live-births (irrespective of the duration of pregnancy) and to still-births, i.e., births not being live-births which take place after the 28th week of pregnancy. The delivery of a dead fetus before that stage is not registrable, nor is it notifiable to the public health authority.

#### Disciplinary Law

24. Much more material to the present problem is the disciplinary jurisdiction of the Disciplinary Committee of the General Medical Council and, on appeal, the Judicial Committee of the Privy Council. The Disciplinary Committee are empowered by statute to erase a doctor's name from the register of medical practitioners or to suspend his registration if they are satisfied that his behavior constitutes "serious professional misconduct." They may also admonish a doctor on the same grounds. The limits of serious professional misconduct may extend far beyond those of criminal law. They reflect the high standard of ethical behavior demanded of and accepted by the medical profession. The Disciplinary Committee see their primary duty as protection of the public. Their proceedings are public and their decisions are publicly reported.

## THE IMPLICATIONS OF RESEARCH ON FETUSES AND FETAL MATERIAL

25. During our discussions we have been constantly aware of the public concern and of the ethical problems surrounding the use of fetuses, fetal tissues and fetal material for research. In reaching our conclusions, we have tried to maintain a balance between them and the contribution to medical science made by this form of research. In general, we feel that the contribution to the health and welfare of the entire population is of such importance that the development of research of this kind should continue subject to adequate and clearly defined safeguards. In the following paragraphs we consider the implications of undertaking research using the fetus, fetal tissue or fetal material and indicate the safeguards which we consider essential in the interests of both the public and the medical profession.

#### Research on the Fetus in Utero

26. We have given careful consideration to the question of carrying out research involving the fetus during pregnancy. Investigations and tests may be carried out with the intention of benefiting the mother, her expected child or both, and in each instance ethical or legal objections do not arise. We understand that suggestions have been made if it is the intention to terminate the pregnancy with the idea of preventing a live-birth, then it would be permissible to administer substances to the mother in order to see if these are harmful to the fetus. We cannot accept this. In our view it is unethical for a

medical practitioner to administer drugs or carry out any procedures on the mother with the deliberate intent of ascertaining the harm that these might do to the fetus, notwithstanding that arrangements may have been made to terminate the pregnancy and even if the mother is willing to give her consent to such an experiment.

27. Apart from these ethical considerations such experiments are undertaken at the risk of the investigator since, if the fetus is alive on termination of pregnancy but is handicapped or subsequently dies as a result of experiments conducted during pregnancy, the persons concerned would be liable to prosecution. Also, if the fetus is born alive but is handicapped as a result of such experiments it would be open to the parent to seek compensation through the courts. The existence of arrangements to terminate the pregnancy made before the experiments are conducted would not necessarily constitute a valid defence.

#### Research on the Viable Fetus

- 28. We consider it is important that there should be no ambiguity about the circumstances in which research can be carried out on a viable fetus. In our view when the fetus is viable after delivery the ethical obligation is to sustain its life so far as possible and it is both unethical and illegal to carry out any experiments on it which are inconsistent with treatment necessary to promote its life, although in many instances the techniques used to aid a distressed fetus are so new that they are in some degree experimental.
- 29. In England and Wales evidence of pregnancy for a period of 28 weeks or more is accepted as prima facie proof that the mother is at that time pregnant of a child capable of being born alive (Infant Life [Preservation] Act 1929). However in our view advances in medical knowledge have made it no longer acceptable to take the 28th week of pregnancy as indicating the time at which a fetus becomes capable of survival as fetuses delivered before that date, may, by modern techniques, be enabled to live.
- 30. We noted that in April 1970 the International Federation of Obstetrics and Gynaecology said that advances in neonatology had made parameters for definition of the period of viability based on 28 weeks gestation age unrealistic. It recommended that the term "abortion" which implied that life could not be maintained in the fetus after expulsion from the mother should be restricted to terminations under 20 weeks (140 days). Similar views were expressed by a number of the organizations who submitted written evidence to us including the Royal College of Obstetricians and Gynaecologists and the Royal College of Midwives, although recommendations on the period of gestation which should be taken as prima facie evidence of viability varied from 18 to 24 weeks.
- 31. For ethical, medical and social reasons we recommend that for human fetuses evidence of a period of gestation of 20 weeks (140 days: this corresponds to a weight of approximately 400-500 grammes) should be regarded as prima facie proof of viability at the present time. This date should be reviewed regularly to

take account of the rapid changes taking place in medical knowledge. Accordingly consideration should be given to amendment of the Acts providing for registration and notification of births and deaths, the Infant Life (Preservation) Act 1929 and analogous legislation in Scotland and Northern Ireland.

#### Research on the Pre-Viable Fetus

- 32. We have given long and careful consideration to the position of a fetus which, although it shows signs of life in some of its organs, is pre-viable in that it is incapable of attaining a state in which it could exist as a self-sustaining whole independently of the mother. In our view, if it has been shown that a missing vital function in a fetus cannot be established, for example that the lungs are solid and therefore cannot be inflated, then the fetus has not developed to the stage of being recoverable.
- 33. We have had to weigh the benefits of research involving pre-viable fetuses against the objections which may be generated and the reasoned ethical and social arguments which are involved. In considering whether it is ethically justifiable to undertake such research we noted that society through Parliament, in permitting abortion in certain circumstances has accepted that where an abortion under the Act is carried out the pre-viable fetus is prevented from attaining life. Given this situation we have considered whether through research on such fetuses new knowledge may be gained which would ultimately benefit viable infants.
- The medical evidence we received showed that the whole pre-viable fetus has offered an important opportunity that cannot be obtained in any other way for making observations of great value on the transfer of substances across the human placenta, the reaction of the immature fetus to drugs, and on the endocrinological development of the placenta. There is a particular need to determine the ability or otherwise of the fetus to deal with substances including drugs given therapeutically to benefit the mother, which may cross the placenta. Observations on the pre-viable fetus are necessarily limited to a period of two or three hours. They have, however, already contributed significantly to our understanding of vital physiological and biochemical processes before birth on which the development of a fetus into a normal child essentially depends. As yet our knowledge is not sufficient to enable us either to control or compensate for any deviation from the normal in such processes. Research on the previable fetus promises, however, to be the most hopeful approach to understanding certain failures of the human brain to develop properly and the influence such factors as variants in sexual differentiation in utero may have on inherent behavioural patterns after birth.
- 35. We accept that in the case of single births any fetus of less than 20 weeks gestational age (400-500 grammes) is pre-viable and as such has not yet reached the stage at which it can exist as a living entity. We noted the evidence that in the pre-viable fetus of 300 grammes or less as distinct from the fetus approaching full term those parts of the brain on which consciousness depends

are, as yet, very poorly developed structurally and show no signs of electrical activity. After exhaustive consideration we have reached a unanimous view that it would be wrong to exclude the use of the pre-viable fetus for research, provided the following conditions are observed:

- (1) Only fetuses weighing less than 300 grammes should be used.
- (2) The responsibility for deciding that the fetus is in a category which may be used for this type of research must rest with the medical attendants at its birth and never with the intending research worker.
- (3) Such research should only be carried out in departments directly related to a hospital and with the direct sanction of the ethical committee to which reference is made later in this report (paragraph 47).
- (4) Before permitting such research the ethical committee should satisfy itself: (a) on the validity of the research; (b) that the required information cannot be obtained in any other way; and (c) that the investigators have the necessary facilities and skill.

#### Research on the Dead Fetus

- 36. When considering the implications of research on the whole dead fetus the difference in the Acts governing the use of human tissue for research makes it necessary to distinguish between the fetus which dies after birth and the fetus which is dead because separation from the mother involves the termination of its life.
- 37. Where a fetus dies after birth the provisions of the Anatomy Acts 1832 and 1871 and the Human Tissue Act 1961 apply as they would to any other deceased person. Subject to the proper implementation of these provisions there are no legal restrictions on the use of the whole fetus or parts thereof for research. Where a fetus is born dead the Anatomy Act and the Human Tissue Act do not apply and consequently there are no statutory restrictions on the use of the whole fetus or parts thereof for research.
- 38. After a thorough examination of the evidence, we are satisfied that the benefits to be derived from the use of the whole dead fetus in the prevention and treatment of disease and deformity are such that it would be a retrogressive step to prevent it. In our view it should be allowed to continue, provided it is carried out within the context of the general recommendations which we made later in this report on the control to be exercised whenever fetuses, fetal tissues or fetal material are used for research.

### Research on Fetal Tissues and Fetal Material Other Than the Fetus

- 39. Having regard to the essential contribution that is made by this research to preventive medicine there is, in our view, no reason to object to the use of fetal tissues and fetal material for these purposes subject to our general recommendations for control over research referred to later in the report.
- 40. Since 1968 commercial use of the placenta and retroplacental blood, not otherwise used by the National Health Service, has been accepted practice provided that the products to be derived from them are intended for therapeutic use. We see no ethical or legal objections to this practice.

#### Consent to Research

- 41. Where a fetus is viable the overriding responsibility of the doctor is to promote and preserve its life and the parent's consent can normally be inferred for procedures consistent with this aim. There are also areas of research which whilst not jeopardising the health and welfare of the fetus are not of direct benefit to that particular fetus. In such cases we consider that express consent should be obtained from the parent. As stated in paragraph 37, where the fetus is born alive and later dies the provisions of the Human Tissue Act and the Acts concerned with certification of causes of death and investigation by coroners (in Scotland, Procurators Fiscal and Sheriffs) apply and enquiry must be made as to whether there is no objection on the part of the parent before the body can be used for research.
- 42. Where the separation of the fetus from the mother leads to the termination of its life there is no statutory requirement to obtain the parent's consent for research, but equally there is no statutory power to ignore the parent's wishes. A number of organizations who discussed this question in their evidence expressed the view that to seek consent could be an unnecessary source of distress to parents. We share this view but believe the parent must be offered the opportunity to declare any special directions about the disposal of the fetus. In our view this opportunity could be provided by adding an appropriate clause to the form giving the patient's consent to the operation thus minimising any possible distress.

#### Conscientious Objections

43. The evidence we received strongly suggested that some members of staff may have conscientious objections to the use of fetuses or fetal tissues for research. We recommend that no member of staff should be under any duty to participate in research on the fetus, fetal tissue or fetal material if he or she has a conscientious objection. We also received representations that experiments on the fetus or dissections for fetal tissues should not be carried out within the operating theatre or place of delivery. We have no reason to believe that this has ever occurred, but we agree that it should not happen.

#### Finance

44. The public disquiet voiced about the use of fetuses, fetal tissue and fetal material for research has been influenced in part by the suggestion that financial transactions are involved. In our view any charges made are acceptable only if they do no more than meet the necessary costs incurred in administering these services, such as those provided by the Royal Marsden Hospital. In no other circumstances should there be monetary exchange for fetuses, fetal tissue or fetal material.

### Record of Fetuses, Fetal Tissue and Fetal Material

45. We recommend that wherever fetuses, fetal tissue or fetal material are used for research the relevant institutions should ensure that a record is kept of all such material supplied or received and of its source and destination. In our view this record would be a valuable safeguard and should be available to central advisory body to which we refer later in the report.

#### FUTURE CONTROL OF RESEARCH

46. Because of the concern expressed generally over this form of research we have given particular attention to its future control. We note that a report published in 1967 by the Committee on the Supervision of the Ethics of Clinical Investigations in Institutions set up by the Royal College of Physicians of London recommended that:

"The competent authority (e.g., Board of Governors, Medical Schools Council, Hospital Management Committee, or equivalent body in non-medical institutions) has a responsibility to ensure that all clinical investigations carried out within its hospital or institution are ethical and conducted with the optimum technical skill and precautions for safety. This responsibility would be discharged if, in medical institutions where clinical investigation is carried out, it were ensured that all projects were approved by a group of doctors including these experienced in clinical investigation. This group should satisfy itself of the ethics of all proposed investigations. In non-medical institutions or wherever clinical investigation (i.e., any form of experiment on man) is conducted by investigators with qualifications other than medical the supervisory group should always include at least one medically qualified person with experience in clinical investigation."

This was accepted by the Ministry of Health and Hospital Memorandum (68) 33 asked hospital authorities in England and Wales to arrange with the medical staff of their hospitals for it to be put into effect.

- 47. We recommend that all research using the fetus, fetal tissue or fetal material should be approved by such a committee whatever the institution in which the research is undertaken; research involving the previable fetus should only be carried out in departments directly related to hospitals. The committee should accept responsibility for ensuring that such investigations are ethical. In approving research projects using the fetus, fetal tissue or fetal material the committee should use as a guideline the principles which we set out in the suggested Code of Practice at the end of this report.
- 48. We considered whether this type of research justified any safeguards additional to those mentioned already, in particular whether a lay member should be appointed to the ethical committee. Our conclusion was that clinical decisions are the responsibility of the clinician, and the ethical questions are for the profession to consider. Given a change in the minimum limit of viability (see paragraph 31), and guidance to the profession in a code of practice, together with the overall safeguards of the law, particularly the disciplinary control referred to in paragraph 24, we consider that the interests of all concerned would be sufficiently protected.
- 49. Some of the evidence received suggested that there should be legislation to provide for the licensing of those who wished to undertake research using fetuses, fetal tissue or fetal material similar to the licenses issued to those undertaking research on animals. In our view a system of licensing would be unnecessarily cumbersome and a code of ethical practice would be an adequate safeguard as it is in the case of research involving all patients. A code would have the advantage of flexibility in that it could be modified in the light of future experience without recourse to amending legislation, and it would not entail the establishment of permanent machinery for the issue of licenses and an inspectorate.
- 50. We also considered whether any central body should be set up to advise in cases where the local committee is uncertain of the ethics of particular investigations. We concluded that it would not be necessary to have a permanent body to handle the limited number of enquiries which are likely to rise. Instead we recommend that arrangements should be made for a small informal advisory body with legal representation and including members drawn from the Medical Research Council, the Royal College of Obstetricians and Gynaecologists, the General Medical Council and the British Paediatric Association to be convened when the need for central advice arises. It might be considered appropriate for this advisory body to cover the United Kingdom.

#### RECOMMENDED CODE OF PRACTICE

This code has no binding legal force but is the result of a careful consideration of all relevant factors in the light of the available evidence. It is hoped that it will prove acceptable to the bodies statutorily responsible for disciplinary matters in the medical and nursing professions.

- 1. Where a fetus is viable after separation from the mother it is unethical to carry out any experiments on it which are inconsistent with treatment necessary to promote its life.
- 2. The minimal limit of viability for human fetuses should be regarded as 20 weeks' gestational age. This corresponds to a weight of approximately 400-500 grammes.
- 3. The use of the whole dead fetus or tissues from dead fetuses for medical research is permissible subject to the following conditions:
  - (i) The provisions of the Human Tissue Act are observed where applicable;
  - (ii) Where the provisions of the Human Tissue Act do not apply there is no known objection on the part of the parent who has had an opportunity to declare any wishes about the disposal of the fetus;
  - (iii) Dissection of the dead fetus or experiments on the fetus or fetal material do not occur in the operating theatre or place of delivery;
  - (iv) There is no monetary exchange for fetuses or fetal material;
  - (v) Full records are kept by the relevant institution.
  - 4. The use of the whole previable fetus is permissible provided that:
    - (i) The conditions in paragraph 3 above are observed;
    - (ii) Only fetuses weighing less than 300 grammes are used;
    - (iii) The responsibility for deciding that the fetus is in a category which may be used for this type of research rests with the medical attendants at its birth and never with the intending research worker;
    - (iv) Such research is only carried out in departments directly related to a hospital and with the direct sanction of its ethical committee;
    - (v) Before permitting such research the ethical committee satisfies itself: (a) on the validity of the research; (b) that the required information cannot be obtained in any other way; and (c) that the investigators have the necessary facilities and skill.
- 5. It is unethical to administer drugs or carry out any procedures during pregnancy with the deliberate intent of ascertaining the harm that they might do to the fetus.

#### APPENDIX 1

### Organizations and Individuals Who Submitted Evidence to the Advisory Group

(i) The following organizations submitted evidence to the Group:

Blair Bell Research Society
Board for Social Responsibility of the National Assembly of the
Church of England
British Council of Churches

British Medical Association

British Paediatric Association

Karolinska Institute-Department of Obstetrics and Gynaecology (Stockholm)
Medical Research Council (evidence was also submitted by the Reproduction
and Growth Research Unit of the MRC)

Medical Women's Federation

National Association of Theatre Nurses

National Institute of Health, Bethesda, United States

Office of the Chief Rabbi

Patients Association

Public Health Laboratory Service

Roman Catholic Church

Royal College of Midwives

Royal College of Nursing and National Council of Nurses in the United Kingdom

Royal College of Obstetricians and Gynaecologists

Society for the Protection of Unborn Children

Swedish Committee on International Health Relations

Swedish Medical Research Council-Reproductive Endocrinology Unit

Union of Liberal and Progressive Synagogues

Universities of Aberdeen, Dundee and Edinburgh

(ii) The following individuals submitted evidence to the Group:

Mr. Michael Wilkinson, FRCS

Mr. R. Wilson, MSc

#### APPENDIX 2

#### Projects Utilizing Human Fetuses, Fetal Tissue and Fetal Material

The work reported has been loosely grouped into physiological and anatomical categories. Items mentioned here include some of those already referred to in the text.

#### General Fetal Metabolism

- 1. Fetal head measurements to confirm the accuracy of ultrasonic cephalometry.
- 2. Fetal size in relation to amniotic fluid production.
- 3. Fetal size in relation to maternal smoking habits in and before pregnancy.
- 4. Water exchange between maternal, fetal and amniotic fluid environments.
- The changes in oxygen partial pressures and acid base balance in hypoxia at various stages of pregnancy.
- 6. Carbohydrate metabolism in hypoxic fetuses and the effects of maternal dextrose infusions.
- 7. Glycoprotein synthesis in fetal liver.
- 8. Study of glucoronide metabolism for future treatment of neonatal jaundice or steroid imbalance.

#### Endocrinology

- 1. Detection of hormones that are solely fetal in origin and could possibly be measured in maternal tissues to enable the degree of fetal well-being to be determined.
- 2. Adrenal steroid metabolism in the fetal gland and the excretion of such steroids into the amniotic fluid at various stages.
- 3. Investigation of prolactin using fetal pituitary glands.
- 4. Cholesterol metabolism in relation to plasma protein levels.
- 5. Insulin secretion in the fetal pancreas and the effects on carbohydrate metabolism.
- 6. Gonadotrophin assay in fetal pituitary glands and stimulation of fetal pituitary activity in vitro.
- 7. Fetal intracellular binding site of progesterone with reference to possible blocking of histocompatible antigens.
- 8. Parathyroid metabolism in early pregnancy.

### ${\tt Haematology}$

- 1. Blood volume studies at different maturities.
- 2. Changes in fetal blood composition and development of plasma proteins.
- 3. Bone marrow maturation in relation to peripheral fetal blood.
- 4. Folate metabolism in the fetus and its accumulation in various tissues-notably liver and pancreas.

- 5. Studies of rhesus incompatibility using fresh suspensions of fetal liver cells.
- 6. Structure and properties of fetal haemoglobin and its variants.

#### Cardiology

Fetal electrocardiography performed directly on hysterotomy specimens and correlation with records made whilst the fetus was in utero.

#### Alimentary Tract

- 1. Fetal swallowing mechanisms in mid-trimester and the effects of anencephaly.
- 2. The pharmacology and innervation of small gut of the fetus.
- 3. The activity of some liver enzymes and their alteration with maturity.
- 4. Vitamin A content and activity of liver (and brain).

#### Renal and Urinary Tracts

- 1. Urine excretion and the production of amniotic fluid.
- 2. Changes in constitution of fetal urine in relation to renal maturity.
- 3. Culture of renal tissues to elucidate the development of fetal renal malignancies.

#### Skin

- 1. The origin and shedding of skin cells into the liquor.
- 2. Permeability of fetal skin and its variations with maturity.
- 3. The growth of fetal oral squamous epithelium in tissue culture.
- 4. Steroid metabolism in various skin sites of the body.
- 5. Biochemical assay of glycogen in fetal skin as a means of glycogen storage.

#### Amniotic Fluid Physiology

- 1. The circulation of fluid in relation to fetal and placental weight.
- 2. Composition of fluid in relation to fetal blood.
- 3. The origin and development of cells in the amniotic fluid.
- 4. Electrical conductivity of fluid and its effects in fetal electrocardiographic studies.
- 5. Secretion of steroid hormones from the vessels of the umbilical cord into the liquor.
- 6. Alterations in trace metal metabolism in relation to proteins and electrolytes levels in amniotic fluid.

#### Placental Metabolism

Much work is proceeding in the transfer of various drugs and macromolecules, while other research is investigating glucose, amino-acid and steroid transfers.

#### Immunology

- 1. Fetal antibody production in hosts of other species with subcellular fractions from hemogenates of the fetal tissues.
- 2. Carcinoma embryonic antigens present in adult tumours and fetal tissue only. Developments in their use in diagnosis of cancer in the adult and possibly their use for cancer therapy.
- 3. Fetal thymus cells are used in the investigation of human antilymphocyte globulin and other immunosuppressive agents.
- 4. Research on auto-immune conditions and immunopathological states using fetal tissue.

#### Chromosome Studies

- 1. Abnormalities in therapeutic abortions (providing background figures to those produced after spontaneous abortions).
- 2. Y chromosome detection by fluorescent techniques.
- 3. Effect of X irradiation on chromosomes in ovarian tissue culture and total numbers of ova.

#### Anatomy

- 1. Fetuses are used at all stages of development for teaching of medical and nursing students.
- 2. Studies of neuro-anatomy using fetal brain tissue.

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20 PROTECTION OF HUMAN SUBJECTS: POLICIES AND PROCEDURES Federal Register, November 16, 1973, DHEW

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Volume 38 ■ Number 221

PART II



# DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Protection of Human Subjects

Policies and Procedures

## DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

## National Institutes of Health PROTECTION OF HUMAN SUBJECTS Policies and Procedures

In the Federal Register of October 9, 1973 (38 FR 27882 et seq.), the Secretary of Health, Education, and Welfare issued a notice of proposed rulemaking concerning the protection of human subjects and mentioned that DHEW through the National Institutes of Health, had appointed a special study group to review and recommend policies and special procedures for the protection of children, prisoners, and the institutionalized mentally infirm in research, development, and demonstration activities. The report of this study group has been completed in draft form and reviewed by the Director, NIH.

There may well be elements in the recommendations which will provoke debate and controversy. We recognize that public consideration and comment are vital to the development of our final recommendations to the Secretary and are inviting such comment now even though the materials are still pending final review and completion. The product of our effort after considering public comment will be transmitted to the Assistant Secretary for Health, HEW to recommend to the Secretary, HEW that it appear again in the Federal Register as proposed rulemaking for further public comment. Such a procedure is consistent with long established DHEW policy for permitting extensive public opportunity to affect the promulgation of DHEW regulations.

It must be clearly understood by the reader that the material that follows is not proposed rulemaking in the technical sense, and is not presented as Departmental, Public Health Service, or NIH policy. Rather it is a draft working document on which early public comment and participation is invited.

Please address any comments on these draft policies and procedures to the Director, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014. All comments should be received by January 4, 1974.

Additional copies of this notice are available from the Chief, Institutional Relations Branch, Division of Research Grants, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland

Dated: November 6, 1973.

ROBERT S. STONE,
Director,
National Institutes of Health.

RESEARCH, DEVELOPMENT, AND DEMONSTRA-TION ACTIVITIES: LIMITATIONS OF IN-FORMED CONSENT

SPECIAL POLICY CONSIDERATIONS

Summary

November 5, 1973.

The mission of the Department of Health, Education, and Welfare includes

the improvement of the health of the Nation's people through research, development, and demonstration activities which at times involve human subjects. Thus, policies and procedures are required for the protection of subjects on whose participation these activities depend.

Informed consent is the keystone of the protection of human subjects involved in research, development, and demonstration activities. Certain categories of persons have limited capacity to concent to their involvement in such activities. Therefore, as a supplement to DHEW policies, special protections are proposed for children, prisoners, and the mentally infirm who are to be involved in research, development, and demonstration activities.

Agency "Ethical Review Boards" are to be established to provide rigorous review of the ethical issues in research, development, and demonstration activities involving human subjects, in order to make judgments regarding societal acceptability in relation to scientific value. "Protection Committees" are to be established by the applicant to provide "supplementary judgment" concerning the reasonableness and validity of the consent given by, or on behalf of, subjects. The intent of this policy is that institutions which apply for DHEW funds or submit research in fulfillment of DHEW regulations, must be in compliance with these special protections, whether or not particular research, development, or demonstration activities are Federally activities

- 1. Children. If the health of children is to be improved, research activities involving their participation is often essential. Limitation of their capacity to give informed consent, however, requires that certain protections be provided to assure that scientific importance is weighed against other social values in determining acceptable risk to children. Therefore, research, development, and demonstration activities which involve risk to children who participate must:

  a. Include a mechanism for obtaining
- a. Include a mechanism for obtaining the consent of children who are 7 years of age or older;
- b. Include the applicant's proposal for use of a Protection Committee which is appropriate to the nature of the activity;
- c. Be reviewed and approved, in conformity with present DHEW policy, by an Organizational Review Committee; and
- d. Be reviewed by the appropriate agency Primary Review Committee, the Ethical Review Board, and the appropriate secondary review group.

  2. Special categories.—a. The Abortus.
- 2: Special categories.—a. The Abortus. No research, development, or demonstration activity involving the non-viable abortus shall be conducted which:
- 1. Will prolong heart beat and respiration artificially solely for the purpose of research:
- 2. Will of itself terminate heart beat and respiration;
- Has not been reviewed by the agency Ethical Review Board; and
- 4. Has not been consented to by the pregnant woman with participation of a Protection Committee.

(An abortus having the capacity to sustain heart beat and respiration is in fact a premature infant, and all regulations governing research on children apply.)

governing research on children apply.)
b. The fetus in utero. No research involving pregnant women shall be conducted unless:

- 1. Primary Review Groups assure that the activity is not likely to harm the fetus:
- 2. the agency Ethical Review Board
- has reviewed the activity;
  3. a Protection Committee is operating in a manner approved by the agency;
- 4. the consent of both prospective legal parents has been obtained, when reasonably possible.
- reasonably possible.
  c. Products of in vitro fertilization. No research involving implantation of human ova which have been fertilized in vitro shall be approved until the safety of the technique has been demonstrated as far as possible in sub-human primates, and the responsibilities of the donor and recipient "parents" and of research institutions and personnel have been established. Therefore, no such research may be conducted without review of the Ethical Review Board and of a Protection Committee.
- 3. Prisoners. Research, development, and demonstration activities involving human subjects often require the participation of normal volunteers. Prisoners may be especially suitable subjects for such studies, although there are problems concerning the voluntariness of the consent of normal volunteers who are confined in institutions. Certain protections are required to compensate for the diminished autonomy of prisoners in giving voluntary consent. Research, development, and demonstration activities involving prisoners must:
- a. Include the applicant's proposal for use of a Protection Committee which is appropriate to the nature of the activity:
- b. Be reviewed and approved by an Organizational Review Committee which may already exist in compliance with present DHEW policy or which must be appointed in a manner approved by the appropriate DHEW agency;
- c. Be reviewed by the agency Primary Review Committee; and
- d. Be conducted in an institution which is accredited by the Secretary of Health, Education, and Welfare.
- 4. The mentally infirm. Insofar as the institutionalized mentally infirm might lack either the competency or the autonomy (or both) to give informed consent, their participation in research requires additional protection:
- a. Research, development and demonstration activities involving the mentally infirm will be limited to investigations concerning (1) diagnosis, etiology, prevention, or treatment of the disability from which they suffer, or (2) aspects of institutional life, per se, or (3) information which can be obtained only from such subjects.

All research, development and demonstration activities involving such persons must:

1. Include the applicant's assurance that the study can be accomplished only

with the participation of the mentally infirm

2. Include the applicant's propo for use of a Protection Committee which is appropriate to the activity; and

3. Be reviewed and approved by an Organizational Review Committee, in conformity with present DHEW policy.

#### TABLE OF CONTENTS

#### Introduction.

- I. Definitions.
  II. General policy considerations.
- III. Children.

  - A. Policy considerations.
    B. Agency Ethical Review Board: Ethical review of projects.

    C. Protection Committee: Protection of
  - individual subjects.
  - D. Special provisions. E. The fetus.
- IV. Special categories.
  - A. The abortus.

    B. The products of in vitro fertilization.
- - A. Policy considerations.
  - B. Organizational Review Committee.
    C. Protection Committee.
    D. Payment to prisoners.

- E. Accreditation.
  F. Special provisions.
  VI. The mentally infirm.
- A. Policy considerations.

  B. Ethical review of projects and pro-
- tection of subjects.
- VII. General provisions.
  A. Referrals to the Ethical Review Board.
  - B. Procedures requiring special consideration.
  - C Research conducted in foreign coun-
  - D. Research submitted pursuant to
  - DHEW regulatory requirements.

    E. Clinical research not funded by
    DHEW.
  - F. Confidentiality of information and

Introduction

### records. VIII. Draft regulations.

involve some risk.

The mission of the Department of Health, Education, and Welfare includes the improvement of the health of the Nation's people through biomedical research. This mission requires the estab-lishment of policy and procedures for the protection of subjects on whose participation that research depends. In DHEW

policy, as well as in ethical codes per-taining to research in human subjects, the keystone of protection is informed consent. An uncoerced person of adult years

and sound mind may consent to the application of standard medical procedures in the case of illness, and when fully and properly informed, may legally and ethically consent to accept the risks of participating in research activities. Parents and legal guardians have authority to consent on behalf of their child or ward to established therapeutic procedures when the child is suffering from an illness, even though the treatment might

There is no firm legal basis, however, for parental or guardian consent to participation in research on behalf of subjects who are incompetent, by virtue of age or mental state, to understand the

information provided and to formulate the judgments on which valid consent must depend. In addition, current policies for clinical research afford such subjects inadequate protection. Nevertheless to proscribe research on all such subjects, simply because existing protections are inadequate, would be to deny them potential benefits, and is, therefore, inequitable. Knowledge of some diseases and therapies can be obtained only from those subjects (such as children) who suffer from the disease or who will be receiving the therapy. Their participa-tion in research is necessary to progress in those fields of medicine. When such subjects participate in research, they need more protection than is provided by present policy.

There are other individuals who might be able to comprehend the nature of the research, but who are involuntarily confined in institutions. Insofar as incar-ceration might diminish their freedom of choice, and thus limit the degree to which informed consent can be freely given, they too need additional protection. Current policies do not recognize the limitations on voluntariness of consent which may emanate from incar-

ceration.

This addition to existing policy is of fered as a means of providing adequate protection to subjects who, for one rea-son or another, have a limited ability to give truly informed and fully autonomous consent to participate in research.
The aim is to set standards which are both comprehensive and equitable, in order to provide protection and, to the extent consistent with such protection, maintain an environment in which clinical research may continue to thrive.

1. Definitions. For purposes of this

policy

A. Subject at risk means any individual who might be exposed to the possibility of harm (physical, psychological, sociological, or other) as a consequence of participation as a subject in any research, development or demonstration activity (hereinafter called "activity") which goes beyond the application of established and accepted methods necessary to meet his needs.

- B. Clinical research means an investigation involving the biological, behavioral, or psychological study of a person, his body or his surroundings. This includes but is not limited to any medical or surgical procedure, any withdrawal or removal of body tissue or fluid, any administration of a chemical substance, any deviation from normal diet or daily regimen, and any manipulation or obseravtion of bodily processes, behavior or environment. Clinical research comprises four categories of activity:
- 1. Studies which conform to estab-lished and accepted medical practice with respect to diagnosis or treatment of
- 2. Studies which represent a deviation from accepted practice, but which are specifically aimed at improved diagnosis, prevention, or treatment of a specific illness in a patient.

3. Studies which are related to a patient's disease but from which he or she will not necessarily receive any direct benefit.

4 Investigative non-therapeutic research in which there is no intent or expectation of treating an illness from which the patient is suffering, or in which the subject is a "normal control" who is not suffering from an illness but who volunteers to participate for the potential benefit of others.

It is important to emphasize that "non-therapeutic" is not to be understood as meaning "harmful." Understanding of normal processes is essential; it is the prerequisite, in many interests to resembling of those devices stances, to recognition of those deviations from normal which define disease. Important knowledge can be gained through such studies of normal processes. Although such research might not in any way benefit the subjects from whom the data are obtained, neither

does it necessarily harm them.

Patients participating in studies identified in paragraph B-1, above, are not considered to be at special risk by virtue of participating in research activities, and this policy statement offers no spe-cial protection to them. When patients or subjects are involved in procedures identified in paragraphs B2, B3, and B4, they are considered to be "at risk," and the special policy and procedures set forth in this document pertain. Excluded from this definition are studies in which the risk is negligible, such as research rethe risk is negligible, such as research requiring only, for example, the recording of height and weight, collecting excreta, or analysing hair, deciduous teeth, or nail clippings. Some studies which appear to involve negligible physical risk might, however, have psychological, sociological or legal implications which are significant. In that event, the subjects are in fact "at risk," and appropriate procedures described in this document shall be applied. be applied.

C. Children are individuals who have not attained the legal age of consent to participate in research as determined under the applicable law of the jurisdiction in which the proposed research is to

be conducted.

D. Pregnancy encompasses the period of time from implantation until delivery. All women during the child bearing years should be considered at risk of preg-nancy; hence, prudence requires definitive exclusion of pregnancy when women in this period of life are subjects for experimentation which might affect the

F. Fetus means the product of conception from the time of implantation to the time of delivery from the uterus.

F. Abortus means a fetus when it is expelled whole, whether spontaneously or as a result of medical or surgical intervention undertaken with the intention of terminating a pregnancy, prior to viability. This definition, for the purpose of this policy, excludes the placenta, fetal material which is macerated at the time of explusion, a dead fetus, and isolated

fetal tissue or organs excised from a dead fetus

G. Viability of the fetus, means the ability of the fetus, after either a spontaneous delivery or an abortion, to survive to the point of independently maintaining vital functions; such a "viable" fetus is a premature infant. Determination of viability entails a subjective and objective judgment by the physician at-tending labor or examining the product of conception, and must be made by a physician other than the investigator wishing to use fetal tissue in research. In general, and all other circumstances not-withstanding, a beating heart is not sufficlent evidence of viability. At least one additional necessary condition is the possibility that the lungs can be inflated. Without this precondition, no currently available mechanisms to initiate or maintain respiration can sustain life; and in this case, though the heart is beating, the

fetus or abortus is in fact non-viable.

H. In vitro fertilization is any fertilization of human ova which occurs outside the body of the female, either through admixture of donor sperm and

ova or by any other means.

I. Prisoner is any individual involuntarily confined in a penal institution.
The term in intended to encompass individuals sentenced to such an institution under a criminal or civil statute, or individuals detained by virtue of statutes which provide alternatives to criminal prosecution.

J. Mentally infirm includes the mentally ill, the mentally retarded, the emo-tionally disturbed, the psychotic, the senile, and others with impairments of a similar nature, residing as patients in an institution, regardless of whether or not the individual has been determined to be legally incompetent.

K. Informed consent has two elements: comprehension of adequate information and autonomy of consent. Consent is a continuing process. The person giving consent must be informed fully of the nature and purpose of the research and of the procedures to be used, including identification of those procedures which are experimental, the possible attendant short or long term risks and discomforts, the anticipated benefits to himself and/or others, any alternative methods of treatment, expected duration of the study, and of his or her freedom to ask any questions and to withdraw at any time, should the person wish to do so. There must also be written evidence of the process used for obtaining informed consent, including grounds for belief that the subject has understood the information given and has sufficient maturity and mental capacity to make such choices and formulate the requisite judgment to consent. In addition, the person must have sufficient autonomy to choose, without duress, whether or not to participate. Both the comprehension of information and the autonomy of consent are necessary elements; to the extent that either of these is in doubt, the adequacy of informed consent may be in

L. Supplementary judgment is the judgment made by others to assent, or to refuse to assent, to procedures for which the subject cannot give adequate consent on his or her own behalf. For the purposes of this document, supplementary judgment will refer to judgments made by local committees in addition to the subject's consent (when possible) and that of the parents or legal guardian (where applicable), as to whether or not a subject may participate in clinical research. This supplementary judgment is to be confirmed by the signature of the Chairman of the Protection Committee on the consent form. In accordance with the procedures approved by the agency for the Protection Committee, the Chairman's signature may be affixed on a standard consent form, or may need to be withheld until the Committee approves the participation of the individual

II. General policy considerations. In general, clinical research, like medical practice, entails some risk to the sub-jects. When the potential subject is un-able fully to comprehend the risks which might be involved, or to make the judgment essential to consent regarding the assumption of those risks, current guidelines suggest obtaining the consent of the parents or legal representative.

Whereas it is clear by law that consent of a parent or legal representative is valid for established and generally accepted therapeutic procedures performed on a child or an incompetent adult, it is far from clear that it is adequate for research procedures. In practice, parental or guardian consent generally has been accepted as adequate for therapeutic research, although the issue has not been definitively resolved in the courts. When research might expose a subject to risk without defined therapeutic benefit or other positive effect on that subject's well-being, parental or guardian consent appears to be insufficient.

In the case of prisoners, confinement imposes limitations on freedom of choice which brings into question their ability to give voluntary consent. A prisoner's ability to give consent may be restricted by overt or potential coercion, or by the loss of personal autonomy generally considered to result from incarceration it-self. Therefore, additional protection must be afforded this group even though an individual's competency to understand what is involved might not be in doubt.

The institutionalized mentally infirm are doubly limited: as with children, they might not be competent to make informed judgments, and, as with prisoners, they are confined under conditions which limit their civil freedom and autonomy. Therefore, their participation in research requires special protections.

The law is not clear on these issues. Even if the law were clear, however, ethical questions would remain; specifically, whether, and under what conditions research involving these subject groups may proceed. Resolution of these ethical questions requires judgments concerning

both the ethics of conducting a particular research project, and the adequacy of procedures for protecting the individual subjects who will be asked to participate. subjects who will be asked to participate. The intention of this policy is to broaden the scope of review, preclude or resolve conflicts of interest, and invoke social as well as scientific judgments to protect potential subjects who might have diminished capacity to consent.

The proposed mechanism for protecting subjects with limited ability to give

ing subjects with limited ability to give informed consent culminates in a form of supplementary judgment, which is to be supportive and protective of the sub-ject's best interests and wishes, to the extent that he or she is capable of formulating and expressing a judgment. In the case of children and the mentally infirm, it will supplement their judgment and that of their parents or guardians. In the case of competent individuals who have restricted autonomy, it will support and protect their wishes. Through this mechanism, these subjects will be protected as fully as possible by community review; however, the nature of some re-search procedures might be such that, in addition, court review ultimately will be required

III. Participation of children in research—A. Policy considerations. Children have generally been considered inappropriate subjects for many research activities because of their inability to give informed consent. There are circumstances, however, which not only justify, but even require their participation. Children do differ from adults in their physiologic responses, both to drugs and to disease; if the health of children is to be improved, it is necessary to know the nature and extent of these differences, and to have a full understanding of normal patterns of growth and development, metabolism, and biochemistry in the perinatal, infant, early childhood, pubertal and adolescent stages of devel-opment. Studies of normal physiology and behavior can also provide significant benefit to children suffering from disease; children are the only subjects from whom these data can be obtained. Furthermore, there are diseases which cannot be induced in laboratory animals, and occur only rarely, if at all, in human adults. In such cases, children are the only subjects in whom the disease process and possible modes of therapy can be studied.

The Kefauver-Harris Act 1 requires that drugs be tested for safety, efficacy and dosage in children and pregnant women before being approved for use to treat illness in such patients. Food and Drug Administration (FDA) approval for the use of a new drug depends upon submission of proposed labeling for a new drug, which must include "adequate directions for use" and "adequate warnings" as to unapproved uses.3 Acceptance of a new drug

<sup>&</sup>lt;sup>1</sup> Federal Food, Drug, and Cosmetic Act, 1962 (FDC Act), 21 U.S.C. Sec. 301 et. seq. <sup>2</sup> FDC Act Sec. 502(f), 21 U.S.C. Sec. 352(f).

rests on the adequacy of the research reports submitted with the application to support the proposed labeling. Thus, in order for a drug to be distributed in in-terstate commerce for use in children or pregnant women, sufficient testing must have taken place in children or pregnant women to substantiate claims on the label regarding safety, efficacy, and dos-age for those groups. If the safe and efficacious dosage for children and pregnant women has not been determined, the label must so state. Thus, particips tion of children in drug research might be the only means of meeting licensing requirements for new drugs for use in children, just as studies in pregnant women might be the only means of meeting licensing requirements for new drugs for use in that class of patients.

When the risk of a proposed study is generally considered not significant, and the potential benefit is explicit, the ethi-cal issues need not preclude the participation of children in biomedical research. However, the progression from innocuous to noxious, in terms of risk, is often subtle. Therefore, additional review procedures are necessary for re-search activities which expose children to risk, in order to provide sharp scrutiny, vigorous review, and stringent procedural safeguards for all subjects of

such research.

Judgments concerning the propriety of research depend partly upon the scientific assessment of the potential risks and benefits. Risk has several important elements: severity, probability, frequency, and the timing of possible adverse effects. While it might not always be easy to distinguish these elements, they must be evaluated in the assessment of risk, and in the determination of the acceptable limits of specific risk for an anticipated benefit. The first judgment to be made is whether it is possible to assess the risk. If studies in animals or adults do not provide sufficient information to assess these elements of risk, then the research should not be con-ducted on children. If the risks can be determined from studies in animal and adult human populations, application to children may be considered.

In addition to results from investigations on animals and adult subjects, there are unknowns which must be considered in the weighing of risk to children. These include: (1) differences in physiologic or psychologic response from adult patterns; (2) delayed expression of injury (for example, until puberty); (3) effects on developing organs (especially the cen-tral nervous system); (4) degree of interference with normal routine required by the study; and (5) possibility of misuse of data by institution or school personnel.

Once the severity and probability of risks in a particular study have been identified, a second judgment must be made: given potential benefits of de-scribed dimensions, what are the ac-ceptable limits of risk to which children

ethical review of projects and maximum protection of individual subjects, two procedures are proposed in addition to those currently required: review by an Ethical Review Board at the sponsoring DHEW agency, and participation by a Protection Committee at the institution in which the research is to be conducted. Both groups will provide community involvement in decisions and attempt to balance scientific value and societal acceptability of proposed research involv-

B. Ethical Review Board: Ethical review of projects. Each DHEW agency shall appoint an Ethical Review Board to provide rigorous review of ethical issues in research involving human subjects by people whose interests are not solely those of the scientific community.

Its functions will include:

1. Advising the agency on ethical issues including review of questions of policy, and development of guidelines and procedures:

- Fostering inter-agency coherence through cognizance of the policies and procedures of other agencies;
- 3. Reviewing specific proposals or classes of proposals submitted to the Board by the agency. These will include proposals stipulated herein as requiring review by the Board, as well as proposals submitted on an ad hoc basis by agency staff. In addition, the Board may recom-mend that certain additional classes of research be reviewed.

The acceptability of a research project rests on questions of scientific merit as well as on questions of ethics. The agency Primary Review Committees are responsible for evaluating scientific merit and experimental design. The Ethical Review Board will be concerned with ethical issues and questions of societal acceptability in relation to scientific value. In reaching its determination of acceptability, the Board will rely upon the Primary Review Committees for judgments on scientific merit and design, existence of prerequisite animal and adult human studies, estimated risks and benefits (taking into account the competence and experience of investigators and the adequacy of their resources), and scientific importance. It will review proposals received from these Primary Review Committees.

An investigator proposing research activities which expose children to risk must document, as part of the applica-tion for support, that the information to

be gained can be obtained in no other way. The investigator must also stipulate either that the risk to the subjects will be insignificant, or that although some risk exists, the potential benefit is significant and far outweighs that risk. In no case will research activities be approved which entail substantial risk. except in the case of clearly therapeutic procedures in which the benefit to the patient significantly outweighs the possible harm. The Ethical Review Board shall review all proposals approved by Primary Review Committees involving children in research activities, except when the Primary Review Committees determine that the subjects are not at

In addition to reviewing ethical issues, the Board will review procedures proposed in the research application to be employed by the institution's Protection Committee (see below), and may suggest modifications of these procedures. The Board's recommendation may vary from a general concurrence with the proposal, as submitted by the investigator, to a recommendation that each parental and subject consent must be obtained with the concurrence of the full Protection Committee. Any specific recommendations for procedures to be followed by Protection Committee will be included in the report of the Ethical Review Board which will be forwarded to the National Advisory Councils or other secondary review groups of the agency.

Appropriate information will be provided the agency to assist the Protection Committee.

Inasmuch as the articulation of deciions might clarify both the objectives and the assumptions on which they are based, records of testimony and deliberations, as well as final decisions, should be maintained pursuant to existing regulations. Such records will serve additionally as the basis for public accountability and will facilitate the review of any decision, should such action be requested.

Members of the Board, which shall number 15, shall be drawn from the general public, and shall include, for example, research scientists (including social scientists), physicians, lawyers, clergy, or ethicists, and other representatives of the public, none of whom shall be em-ployees of the agency establishing the Board. Appointments shall be made by the agency, which will establish the terms of office and other administrative procedures of the Board. No more than  $\frac{1}{3}$  of the members of the Board may be actively engaged in research, development, or demonstration activities involving human subjects.

C. Protection Committee: Protection of individual subjects. The determination that it is justifiable to conduct a particular investigation in children, however, does not mean that all children are equally appropriate subjects for inclusion in that research. Numerous considera-tions might affect the proper choice of subjects. Therefore, the sponsoring institution shall designate a Protection Committee to oversee: (1) the process of

ethically may be subjected? Value judgments which must be weighed here transcend scientific issues and suggest that decision requires interaction among individuals in society with diverse training and perspectives. Further, given the complexity of the issues and the opportunity for conflict among the interests of several parties (the child, the parents or guardian, the attending physician, and the research personnel), decisions regarding participation of individual subjects in research activities involving children should not rest solely with persons directly involved in the research.

In order to provide both impartial

FDC Act Sec. 505 (b), (d), 21 U.S.C. Sec. 355 (b), (d).

selection of subjects who may be included in the project; (2) the monitor-ing of their continued willingness to participate in the research; and (3) the design of procedures to permit intervention sign of proceedings we permit the control on behalf of the subject, should that become necessary. This Committee should consider the reasonableness and validity of the consent of the child participants (see below) as well as that of the parents, and should assure that the issue of risk and discomfort has been fully and fairly disclosed to parents and subjects. The procedure employed by the institution to achieve these goals will vary; the latitude for such procedures will be great since it will be related in part to the issue of risk. Investigators proposing research involving children shall include a description of their planned use of the Protection Committee in their research proposal; the proposed use of this Committee will be considered an integral part of the research proposal under review by the agency. Relevant information arising in the review process, including information about safety, risk, efficacy, and protection procedures, will be provided to the Protection Committee by the agency supporting the research.

One member of the Committee shall be designated a representative for the project to whom any participant (or parent of a participant) may go to discuss questions or reservations concerning the child's continued participation in the project.

The signature on the consent form of the Chairman of the Protection Committee, when all the stipulations and conditions identified above have been met, will constitute, for DHEW, supplementary judgment on behalf of the child subject.

The institution's Protection Committee shall be comprised of at least 5 members so selected that the Committee will be competent to deal with the medical, legal, social, and ethical issues involved in the research, and to represent the community from which the subject population is to be drawn. The Committee should include members of both sexes. No more than two of the members may be employees of the institution sponsoring or conducting the research. The Protection Committee may operate as a subcommittee of the Organizational Review Committee. The composition of the Committee must be approved by the awarding agency.

D. Special provisions—1. Consent of both parents. Even where State law may permit one parent alone to consent to medical care, both parents have an interest in the child, and therefore, consent of both parents should be obtained before any child may participate in research activities. Since the risks of research entail the possibility of additional burdens of care and support, the consent of both parents to the assumption of those risks should be obtained, except when the identity or whereabouts of either cannot be ascertained or either has been judged mentally incompetent. If the

consent of either parent is not obtained, written explanation or justification should be provided to the Protection Committee. Consent of school or institutional authorities is no substitute for parental concern and consent.

2. The child's consent. An important addition to the requirement for parental consent is the consent of the child subject. Clearly infants have neither the comprehension nor the independence of judgment essential to consent; older children might or might not have these capabilities. Although children might not have the capacity to consent on their own to participate in research activities, they must be given the opportunity (so far as they are able) to refuse to participate. The traditional requirement of parental consent for medical procedures is intended to be protective rather than coercive. Thus, while it was held to be un-lawful to proceed merely with the consent of the child, but without consent of the parent or legal guardian,5 the reverse should also hold. Therefore, in addition to consent of both parents, consent of the child subject must also be obtained when the child has attained the common law "age of discretion" of 7 years, unless the agency Ethical Review Board specifically exempts a project from this requirement.

3. Exclusions. Despite all the protections afforded by these procedures, certain children are categorically excluded from participation in research involving risk. These include children with no natural or adoptive parents available to participate in consent deliberations, and children detained by court order in a residential facility, whether or not natural or adoptive parents are available.

E. The fetus. Respect for the dignity of human life must not be compromised whatever the age, circumstance, or expectation of life of the individual. Therefore, all appropriate procedures providing protection for children as subjects in blomedical research must be applied with equal rigor and with additional safeguards to the fetus.

The recent decision of the Supreme Court on abortion of does not nullify the ethical obligation to protect the developing fetus from avoidable harm. This obligation, along with the right of every woman to change her decision regarding abortion, requires that no experimental procedures entailing risk to the fetus be undertaken in anticipation of abortion. Further, since the fetus might be at risk in research involving pregnant women, all research involving pregnant women must be reviewed by the Ethical Review Board, unless the Primary Review Committee determines that the research involves no risk to the fetus. Recruitment of pregnant subjects for research reviewed by the Board must involve the institution's Protection Committee in a manner approved by the Board, to provide supplementary judgment.

<sup>6</sup> Bonner v. Moran, 75 U.S. App. D.C. 156, 126 F. 2d 121, 139 A.L.R. 1366 (1941). <sup>6</sup> Roe v. Wade, 410 U.S. 113 (1973). The consent of both parents must be obtained for any research involving the fetus, any statutes to the contrary on consent for abortion notwithstanding. Both the mother and the father have an interest in the fetus, and legal responsibility for it, if it is born. Therefore, the father's consent must be obtained for experimental procedures involving the fetus; consent of the father may be waived if his identity or whereabouts cannot be ascertained, or if he has been judged mentally incompetent.

IV. Special categories—A. The abortus. Prematurity is the major cause of infant death in this country; thus, research aimed at developing techniques to further viability is of utmost importance. Such research has already contributed significantly to improvement in the care of the pregnant woman and of her fetus. In addition, knowledge of fetal drug metabolism, enzyme activity, and the development of organs is essential to progress in preventing or offsetting certain congenital defects. After thorough research in animal models, it often eventually becomes essential to undertake studies in the non-viable human fetus.

The decision of the Supreme Court on abortion does not eliminate the ethical issues involved in research on the nonviable human fetus. No procedures should be undertaken on the non-viable fetus which clearly affront societal values. Nevertheless, certain research is essential to improve both the chance of survival and the health status of premature infants. Such research must meet ethical standards as well as show a clear relation either to the expectation of saving the life of premature in-fants through the development of rescue techniques, or to the furthering of our knowledge of human development and thereby our capacity to offset the disabilities associated with prematurity. It is imperative, however, that the investi-gator first demonstrate that appropriate studies on animals have in fact been exhausted and that therefore the research in question requires that the work be done on the non-viable human fetus. Specific reasons for this necessity must be identified. A thorough review of the ethical issues in proposed research involving the non-viable fetus is of utmost importance.

It must be recognized that consent for abortion does not necessarily entail disinterest on the part of the pregnant woman in what happens to the product of conception. Some women feel strongly about what may, or may not, be done to the aborted fetus; others do not. In order to give every woman the opportunity to declare her wishes, consent of the pregnant woman for application of any research procedures to the aborted fetus must be secured at the time of admission to the hospital for the abortion.

Because research on the abortus involves ethical as well as scientific issues, all projects involving the abortus must be reviewed by the Ethical Review Board, and recruitment of individual pregnant women for such research must involve

the institution's Protection Committee in a manner approved by the Board to provide supplementary judgment. In addition to the requirement for maternal consent, both the Ethical Review Board and the Protection Committee shall, in their deliberations, consider the ethical and social issues surrounding research on the non-viable fetus. The Protection Committee must be satisfied that maternal consent is freely given and based on full disclosure, each time approved research is conducted on an abortus.

In order to insure that research considerations do not influence decisions as to timing, method, or extent of a procedure to terminate a pregnancy, no investigator engaged in the research on the abortus may take part in these decisions. These are decisions to be made by the years and her physician.

by the woman and her physician.

The attending physician, not the investigator, must determine the viability of the abortus at the termination of pregnancy. If there is a reasonable possibility that the life of the fetus might be saved, experimental and established methods may be used to achieve that goal. Artificial life-support techniques may be employed only if the physician of record determines that the fetus might be viable. If the physician determines that the fetus is not viable, it is not acceptable to maintain heart beat or respiration artificially in the abortus for the purpose of research. Experimental procedures which of themselves will terminate respiration and heart beat may not be undertaken.

This policy and these protections apply with equal force to the products of spon-

taneous abortions.

B. The products of in vitro fertilization. In the interest of improving human health and development, the biology of human fertilization and the early events surrounding this phenomenon, including implantation, should be studied. To the extent that in vitro studies of human fertilization might further this aim, they are permissible at the present time with-

in the limits outlined below.

Current technology limits the in vitro development of the human fertilized ovum to a period of several days. This is a rapidly advancing field of blomedical research, however, and the time might come when it is possible to extend in vitro development beyond the stage of early cell division and possibly even to viability.

It is contrary to the interests of society to set permanent restrictions on research which are based on the successes and limitations of current technology. Still, it is necessary ta impose restraints prospectively in order to provide reasonable protections, while at the same time permitting scientific advancements which might well benefit society. A mechanism is required to weigh, at any given time, the state of the art, a specific proposal, legal issues, community standards, and the availability of guidelines to govern the research situation. This mechanism is provided by the Ethical Review Board. Ultimately, the Board will determine the acceptability of a

project involving in vitro fertilization, and by recognizing the state of the art, as well as societal concerns, propose appropriate research policy.

Care must be taken not to bring human ova fertilized in vitro to viability—whether in the laboratory or implanted in the uterus—until the safety of the technique has been demonstrated as far as possible in sub-human primates. To this end:

- 1. All proposals for research involving human in vitro fertilization must be reviewed by the Ethical Review Board.
- 2. No research involving the implantation of human ova fertilized in the laboratory into recipient women should be supported until the appropriate scientific review boards are satisfied that there has been sufficient work in animals (including sub-human primates) to demonstrate the safety of the technique. It is recommended that this determination of safety include studies of natural born offspring of the products of in vitro fertilization.
- 3. No implantation of human ova fertilized in the laboratory should be attempted until guidelines are developed governing the responsibilities of the donor and recipient "parents" and of research institutions and personnel.

V. Prisoners—A. Policy considerations. Clinical research often requires the participation of normal volunteers; for example, in the early stages of drug or vaccine evaluation. Sometimes, the need for standardization certain variables, or for monitoring responses over an extended period of time, requires that the subjects of research remain in a controlled environment for the duration of the project. Prisoners may be especially suitable subjects for such studies, since, unlike most adults, they can donate their time to research at virtually no cost to themselves. However, the special status of prisoners requires that they have special protection when they participate in research.

While there is no legal or moral objection to the participation of normal vol-unteers in research, there are problems surrounding the participation of volunteers who are confined in an institution. Many aspects of institutional life may influence a decision to participate; the extent of that influence might amount to coercion, whether it is intended or not. Where there are no opportunities for productive activity, research projects might offer relief from boredom. Where there are no opportunities for earning money, research projects offer a source of income. Where living conditions are unsatisfactory, research projects might offer a respite in the form of good food, comfortable bedding, and medical attention. While this is not necessarily wrong, the inducement (compared to the deprivation) might cause prisoners to offer to participate in research which would expose them to risks of pain or incapacity which, under normal circumstances, they would refuse. In addition, there is always the possibility that the prisoner will expect participation in research to be

viewed favorably, and to his advantage, by prison authorities (on whom his other few privileges depend) and by the parole board (on whom his eventual release depends). This is especially true when the research involves behavior modification and may be termed "therapeutic" with respect to the prisoner. In such instances, participation inevitably carries with it the hope that a successful result will increase the subject's chances for parole. Thus, the inducement involved in therapeutic research might be extremely difficult to resist; and for this reason, special protection is necessary for prisoners participating in research, whether or not the research is therapeutic.

The first principle of the Nuremburg Code requires that subjects of biomedical research must be "so situated as to be able to exercise free power of choice" concerning their participation. Whether prisoners can be considered to be "so situated" is ultimately a matter for the courts and the legislatures to resolve. In the meantime, it must be recognized that where liberty is limited, and where free-dom of choice is restricted, there is a corresponding limitation of the capacity to give truly voluntary consent. Although the prisoner might be adequately informed, and competent to make judgments, the voluntariness of the person's consent remains open to question. This policy statement is designed to provide additional protections to prisoners para-

ticipating in research.

The mission of the Department of Health, Education, and Welfare does not include rendering judgments on the administration of justice or the management of the correctional system. At the same time, the Department should not support activities which take unethical advantage of those who are under the jurisdiction of the courts and who, for that reason, lack some of the usual defenses to their personal integrity. Participation of prisoners in the research activities of the DHEW in the pursuit of medical knowledge might be beneficial to all concerned, but the relationship which involves a class of persons with diminished autonomy requires careful super-

Many prisoners are strongly motivated to participate in research, and view as unfair suggestions that they be denied this opportunity. Unless society, through its judicial and legislative bodies, decides that such participation should be halted, it is essential to develop mechanisms to protect those who may participate, or who are now participating, from the coercive aspects of incarceration which diminish their capacity for voluntary consent. Pursuant to the obligation to protect the rights of all subjects participating in research conducted under its auspices, the DHEW is proposing special guidelines for the protection of prisoners as subjects in any biomedical or behavioral research.

Two aspects of research involving prison populations require special review and procedural safeguards in addition to those provided by current DHEW policies.

First, when research is conducted under the auspices of a commercial manufac-turer or an individual investigator, it is not always subject to review by an Organizational Review Committee, as is required for similar research conducted at a hospital or a university. Thus, local review has not heretofore been required for ethical considerations or for specific problems related to the population or in-stitution which is to be directly involved. Second, because of the loss of individual dignity, the limitations of personal freedom, and the possibility of real or potential coercion which may accompany con-finement in an institution, special safeguards must be provided to mitigate the inequalities of bargaining power between the prisoners and those who are in positions of authority. While it is important that prisoners have the opportunity to participate in research, it is equally important that they not feel compelled to

B. Organizational Review Committee. All research involving prisoners must be conducted at an accredited correctional facility (see Section F, below) and be reviewed initially, and on a continuing basis, either by the Organizational Re-view Committee of that correctional facility or by the Organizational Review Committee of the institution sponsoring the research. The Organizational Review Committee shall have the duties and responsibilities identified in current DHEW regulations. In addition, for each project, it shall determine the adequacy of clinic or hospital facilities for the particular activity to be conducted, assess the appropriateness of the subject population for that activity, and weigh the questions of scientific importance, social need, and ethical acceptability. In addition to the foregoing, the Organizational Review Committee shall have the following du-ties, with respect to research involving prisoners as subjects:

1. To review and approve or modify the process proposed by the principal investigator for involvement of the Protection Committee (see below) in over-seeing the selection of subjects who may be included in the research, and the process of obtaining their voluntary and in-

formed consent.

To set rates of remuneration, if any, consistent with the expected duration and discomfort or risk of the proposed study, and consistent with other opportunities for employment, if any, at the facility in question.

3. To monitor the progress of the re-search as required by the sponsoring DHEW agency.

The recommendations of this Committee, along with a report describing any site visits, shall be included with the investigator's application to the agency. For facilities which have filed no general assurance, composition as well as recommendations of the Organizational Review Committee will be considered an integral part of the proposal in the agency review.

C. Protection Committee. The primary function of the Protection Committee is to provide supplementary judgment by

overseeing the selection of subjects who may be included in a research project to assure that their consent is as voluntary as possible under the conditions of confinement

Consent is a continuing process. To assure the voluntariness of consent, subjects must be able to withdraw from the research project without prejudice. Each Protection Committee shall estab-

lish such a withdrawal mechanism.

The duties of the Protection Committee, therefore, shall include:

1. Reviewing the information given the potential subjects, with special atten-tion to: adverse effects, the importance of reporting all deviations from normal function, the continuing option of withdrawing from participation at any time. and the identification of a member of the committee who will be available, at reasonable intervals upon request, for consultation regarding the research project. All of this information shall appear on the consent form, a copy of which will be given to each participant. When oral representations are made procedures described under DHEW regulations shall be followed.

2. Overseeing the process of selection of subjects who may be included in the research, to the extent stipulated in the recommendation of the Organizational Review Committee. This may vary from overall approval of the recruitment process, to reviewing a sample of subject selections, to interviewing as a full Com-mittee each individual subject to be in-

cluded in the project.

3. Visiting the institution on a regular basis to invite questions, to monitor the progress of the research, and to assess the continued willingness of subject par-ticipation. The frequency of these visits will be determined by the nature of the research, and any recommendations of the Organizational Review Committee. Depending upon the circumstances and the number of subjects involved, these visits may be made either on a rotating basis by various members of the Committee, or by the full Committee.

4. Maintaining records of its activities including contacts initiated by subjects in the project between regular site visits. These records shall be made available to

the agency upon request.

The Protection Committee shall be comprised of at least 5 members so selected that the Committee will be competent to deal with the medical, legal, social, and ethical issues involved. No more than  $\frac{1}{2}$  of the members shall be scientists engaged in biomedical research or physicians; at least 1 shall be a prisoner or a representative of an organization concerned with the prisoners' interests; no more than 1 (except prisoners or their representatives) shall have any affiliation with the prison facility or with the unit of government having jurisdiction over the facility, with the exception of persons employed by the department of education of a relevant jurisdiction in a teaching capacity. The composition and the investigator's proposed use of the Committee must be reviewed and approved by the DHEW agency.

D. Payment to prisoners. The amount paid for participation in research will vary according to the risks and discomforts involved, and the other employment opportunities in the facility in which the research is to be conducted. The specific amount for each project will be determined by the Organizational Review Committee, which will forward its recommendation as part of the application to the sponsoring agency. The amount paid shall provide a compensation for services, but shall not be so great as to constitute undue inducement to partici-

Any reduction of sentence as a consequence of participation in research shall e comparable to other opportunities at the facility for earning such a reduction.

Any subject who is required by the inrange and the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the stat consultation with the investigator. This does not apply to subjects who withdraw for other reasons. Any disputes regarding certification of withdrawal for medical reasons shall be heard and resolved by the Protection Committee.

Prisoners who serve on the Protection Committee shall be paid an amount consistent with that received by the research

subjects.

E. Accreditation. The Secretary. DHEW, shall establish standards for ac creditation of correctional facilities offering to act as sites for the performance of clinical research, or offering to act as a source of volunteer subjects for clinical research when the research is supported in whole or in part by Departmental funds or the research is to be performed in compliance with requirements of Federal statutes.

The review for certification shall in-

clude, but not be limited to:

Standard of living in the prison facility.

2. Other opportunities for ment and/or constructive activity, either within the prison, or in a work-release program. 3. Adequacy of (a) medical care for

the general prison population (so that participation in research is not the only means of obtaining medical attention), and (b) the proposed methods for maintaining medical records and for protecting the confidentiality of those records.

4. The nature, structure, function, and e. The nature structure, instable, and composition of the Organizational Review Committee (whether located at the prison or at the institution sponsoring the research) which is to review clinical research in that correctional facility.

The Secretary shall also set general guidelines to assist the Organizational Review Committees in determining rates of remuneration, and shall indicate groups who may be considered to represent the prisoners' interests for the purpose of appointment to membership on the Protection Committee. No institution shall be accredited if research, whether or not supported by funds from the DHEW, is conducted under its auspices, or by members of its staff, which is not in conformity with these guidelines. No DHEW funds will be granted for research in institutions lacking such accreditation.

F. Special provisions. 1. Persons detained in a correctional facility while awaiting sentence, or in a hospital fa-cility for pre-sentence diagnostic observation, are excluded from participation in research

2. A child may not be included as a subject in research involving risk if he is detained in an institutional setting pursuant to a court order, whether or not the parents and the child have consented

to the child's participation.

VI. The mentally infirm.—A. Policy considerations. The institutionalized mentally infirm are doubly limited with respect to participation in research activities. First, as with children, they might lack the clear capacity to compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation of the compensation o prehend relevant information, and to make informed judgments concerning their participation. Second, as with prisoners, they experience a diminished sense of personal integrity as a result of confinement in an institution. Such confinement restricts their freedom of choice and imposes elements of coercion, which limit their capacity to give truly volun-tary consent. In addition, the mentally infirm who are confined in institutions have more pressures to cooperate with custodial authorities than do prisoners, for their release might depend entirely upon their behavior and on the impression they make upon those having the power to make decisions concerning termination of their confinement.

Legal guardians, who have authority to consent for medical treatment, might have interests in the matter which do not necessarily coincide with those of the patient. Long-term management of patients with mental disabilities is expensive and time-consuming. Any pro-posal which might reduce either the ex-pense or the supervision required in caring for such persons might be appealing, whether or not there is correlative benefit to the patient. This is certainly the case in projects offering new therapy; it might also occur, albeit in a more subtle form, where free medical or custodial services are perceived to be contingent upon the patient's participation

as a subject in research.

The courts have begun to recognize that persons confined in institutions might not be able to give truly voluntary consent in such matters. It is important to recognize, as well, that persons encumbered with the economic or custodial responsibility for the mentally infirm responsionicy for the memorary minimization of the sufficiently objective to make judgments which are fully in the best interest of the institutionalized per-

The circumstances are limited under which it is justifiable to include the mentally infirm as subjects in biomedical research. These circumstances include projects in which: the proposed research concerns diagnosis, treatment, prevention, or etiology of the disability from which they suffer; the necessary infor-

mation can be obtained only from those subjects; or the studies concern institutional life per se. With these exceptions, the general rule is that the participation of the mentally infirm as subjects in re-

search is not acceptable.

B. Ethical review of projects and protection of subjects. In instances in which a research protocol requires the partici-pation of mentally infirm subjects, the research must be overseen by a Protec-tion Committee in the manner described in Section III-C, pertaining to children. This Protection Committee must be supervised on a continuing basis, as described in Section V-B, by the Organiza-tional Review Committee of the institution in which the research is to be conducted or of the institution sponsoring

the research.
VII. General provisions. These provisions apply to all research activities covered by this policy.

A. Referrals to the Ethical Review

Board. Whenever a Primary Review Committee, secondary review group, or the agency staff perceives an apparent and significant question of ethics or an unusual element of risk—whatever the subject group involved—the research proposal in question may be forwarded to the Ethical Review Board for an opinion. In addition to offering an opinion of acceptability from an ethical viewpoint, the Board may choose to recommend the establishment of a Protection Committee, and suggest guidelines for its opera-

B. Procedures requiring special consideration. All other recommendations notwithstanding, DHEW may identify certain procedures which: (1) Require Protection Committee review of the selection of each individual subject; (2) are acceptable for stipulated subjects only if approved by affirmative declara-tory judgment of a court of competent jurisdiction; or (3) are unacceptable.

C. Research conducted in Foreign Countries. All regulations governing re-search conducted in the United States apply to research conducted in foreign countries under DHEW auspices, and he ethical review must be of equal rigor.

There are sometimes special constraints encountered in foreign settings. Therefore, in addition to the require-ment that consent procedures for re-search to be conducted abroad conform with the policy and regulations set forth in this document, there must be written assurance that the proposed research enjoys local acceptance, and offends no local ethical standards.

D. Research submitted pursuant to DHEW regulatory requirements. Research or testing which is performed pursuant to or in fulfillment of any regulation issued by any agency of the DHEW will be acceptable to the government only if conducted in compliance with these procedures and regulations.

E. Clinical research not funded by DHEW.

If, in the judgment of the Secretary, an organization has failed to comply with the terms of this policy with respect to a par-

ticular DHEW grant or contract, he may require that said grant or contract be ter-minated or suspended in the manner prescribed in applicable grant or procurement

scribed in applicable grant or procurement regulations.

If, in the judgment of the Secretary, an organization fails to discharge its responsibilities for the protection of the rights and welfare of the subjects in its care, whether or not DHEW funds are involved, he may, upon reasonable notice to the organization of the basis for such action, determine that its eligibility to receive further DHEW grants or contracts involving human subjects shall be terminated. Such disqualification shall continue until it is shown to the satisfaction of the Secretary that the reasons therefor of the Secretary that the reasons therefor no longer exist.

of the Secretary that the reasons therefor no longer exist.

If, in the judgment of the Secretary, an individual serving as principal investigator, program director, or other person having responsibility for the scientific and technical direction of a project or activity, has failed to discharge his responsibilities for the protection of the rights and welfare of human subjects in his care, the Secretary may, upon reasonable notice to the individual of the basis for such action, determine that such individual's eligibility to serve as a principal investigator or program director or in another similar capacity shall be terminated. Such disqualification shall continue until it is shown to the satisfaction of the Secretary that the reasons therefor no longer exist."

In reaching a determination on com-

In reaching a determination on com-pliance, with respect to subjects with phiance, with respect to subjects with limited capacity for consent, the Secretary will consider the extent and the nature of the procedures by which the institution offers protection in all studies conducted in or by that institution respectively. gardless of the source of funds, with the expectation that there shall be an ethical review similar to that required of the agency Ethical Review Board (III-B). The existence of a Protection Committee, overseen by an Organizational Review Committee and acting to afford sup-plementary judgment, will be accepted as evidence of responsibility in this

regard.

F. Confidentiality of information and records. Nothing in this policy shall be construed as permitting the release of confidential research protocols nor the violation of State law applicable to the confidentiality of individual medical

records.
VIII. Draft additions to proposed regulations (See Federal Register, Vol. 38, No. 194, Part 2, Tues., Oct. 9, 1973, pp. 27882-27885)

To amend the proposed Part 46 of Subtitle A of Title 45 of the Code of Federal Regulations by deleting \$\$\frac{1}{2}\$\$46.20 through 46.23, redesignating \$\$\frac{1}{2}\$\$46.10 through 46.19 thereof as Subpart A, and adding the following new Subparts B through F:

UBPART B—ADDITIONAL PROTECTIONS FOR CHILDREN INVOLVED AS SUBJECTS IN DHEW SUBPART B-

46.21 46.22

Applicability.
Purpose.
Need for legally effective consent. 46.23

Ethical Review Board; Composition; Duties.

<sup>&</sup>lt;sup>7</sup> FEDERAL REGISTER, Vol. 38, No. 194, Part 2, Tuesday, October 9, 1973, § 46.22, p. 27885.

46.26 Protection Committees; Composition; Dutles

Certain children excluded from par-ticipation in DHEW supported activities.

Activities to be performed outside the 46.28 United States.

BPART C-Additional Protections for Certain Classes of DHEW Activities SUBPART

46.31 Applicability.

Purpose. Definitions.

Duties of the Ethical Review Board.

Maternal consent to activities involving the abortus.

46.36 Additional conditions for activities

involving the abortus.

Prohibition on certain activities in-

volving pregnant women where the fetus may be adversely affected. Parental consent to activities which may affect the fetus.

Activities to be performed outside the United States.

SUBPART D-ADDITIONAL PROTECTIONS JBPART D—ADDITIONAL PROTECTIONS FOR PRISONERS INVOLVED AS SUBJECTS IN DHEW ACTIVITIES

Applicability.

46.41 46.42

Purpose. Definitions

Additional duties of Organizational

Review Committee where prisoners are involved. Protection Committees; Duties; Com-46.45

position. Prohibition on participation in activities prior to conviction.

Remuneration to subjects. 46.46

46.47

Accreditation.
Activities to be performed outside the 46.49 United States.

-ADDITIONAL PROTECTIONS FOR INSTITUTIONALIZED MENTALLY INFIRM IN-VOLVED AS SUBJECTS IN DHEW ACTIVITIES

Applicability.

Definitions Limitations on activities involving the

institutionalized mentally infirm.
Additional duties of Organizational
Review Committee where the mentally infirm are involved.
Protection Committees; Duties; Com-46.55

46.56 position.
Activities to be performed outside the United States. 46.57

SUBPART F GENERAL PROVISIONS

Applicability.
Organization's records. 46.62

Reports.

46.64 Early termination of awards; sanctions for noncompliance.

Conditions.

AUTHORITY: 5 U.S.C. 301.

SUBPART B-Additional Protections CHILDREN INVOLVED AS SUBJECT IN DHEW ACTIVITIES

Section 46.21 Applicability. (a) The regulations in this subpart are applicable to all Department of Health, Education, and Welfare research, development, or demonstration activities in which children may be at

(b) The requirements of this subpart are in addition to those imposed under subpart A of this part.

Section 46.22 Purpose. It is the purpose of this subpart to provide additional safe-guards in reviewing activities to which this subpart is applicable inasmuch as the potential subjects in activities conducted thereunder might be unable fully to comprehend

the risks which might be involved and are legally incapable of consenting to their par-ticipation in such activities. Section 46.23 Need for legally effective consent. Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will neces the procedures set forth herein will necessarily result in a legally effective consent under applicable State or local law to a subject's participation in any activity: nor in particular does it obviate the need for court approval of such participation where court approval is required under applicable State or local law in order to obtain a legally effective consent

Section 46.24 Definitions. As used in this

subpart:
(a) "'DHEW activity" means: (a) "DHEW activity" means:
(1) The conduct or support (through grants, contracts, or other awards) of biomedical or behavioral research involving human subjects; or
(2) Research, development, or demonstration activities regulated by any DHEW

agency.

(b) "Subject at risk" means any individ-(b) "Subject at risk" means any individ-ual who might be exposed to the possibility of harm—physical, psychological, sociologi-cal, or other—as a consequence of partici-pation as a subject in any DHEW activity which goes beyond the application of those established and accepted methods necessary to meet his needs.

(c) "Child" means an individual who has

(c) "Child" means an individual who has not attained the legal age of consent to participate in research as determined under the applicable law of the jurisdiction in which such research is to be conducted.

(d) "DHEW" means the Department of Health, Education and Welfare.
Section 46.25 Agency Ethical Review Board; composition; duties. (a) The head of each agency shall establish an Ethical Review Board, hereinafter referred to as the "Board," to review proposals for research, development, and demonstration activities to which this subpart is applicable, as well as to advise him or her on matters of policy concerning protection of human subjects. The Board shall be composed of research scientists (biomedical, behavioral, and/or social), physicians, lawyers, clergy, ethicists, social), physicians, lawyers, clergy, ethicists, and representatives of the public. It shall consist of 15 members appointed by the agency head from outside the Federal Government. No more than one-third of the members may be individuals engaged in redevelopment, or demonstration activities involving human subjects

(b) It shall be the function of the Board to review each proposed activity to which this subpart applies, and advise the agency this subpart applies, and advise the agency concerning the acceptability of such activities from the standpoint of societal need and ethical considerations, taking into account the assessment of the appropriate Primary Review Committees as to: (1) The potential benefit of the proposed activity, (2) scientific merit and experimental design, (3) whether the proposed activity entails risk of significant harm to the subject, (4) the sufficiency of animal and adult human studies demonstrating safety and clear potential benefit of the proposed pro-cedures and providing sufficient information on which ta base an assessment of the risks, and (5) whether the information to be gained may be obtained from further animal and adult human studies.

(c) The Board shall review the procedures proposed by the applicant to be followed by proposed by the applicant to be followed by the Protection Committee, provided for in § 46.26 of this subpart, in carrying out its functions as set forth in § 46.26. In addition, the Board may recommend additional func-tions to be performed by the Protection Committee in connection with any particular activity.

decisions regarding covered by this subpart, the agency shall take into account the recommendations of the Board.

Section 46.26 Protection Committees: com-Section 46.28 Protection Committees; composition; duties. (a) No activity covered by this subpart will be approved unless it provides for the establishment by the applicant of a Protection Committee, composed of at least five members so selected that the Committee will be competent to deal with the mittee will be competent to deal with the medical, legal, social and ethical issues involved in the activity. None of the members shall have any association with the proposed activity, and at least one-half shall have no association with any organization or individual conductors are association. individual conducting or supporting the activity. No more than one-third of the members shall be individuals engaged in research, development, or demonstration activities involving human subjects. The composition of the Protection Committee shall be subject to DHEW approval.

(b) The duties of the Protection Committee, proposed by the applicant, and reviewed by the applicant, and reviewed by the applicant, and reviewed.

by the agency including the Ethical Review Board shall be to oversee: (1) The selection of subjects who may be included in the activity; (2) the monitoring of the subject's continued willingness to participate in the activity; (3) the design of procedures to permit intervention on behalf of one or more of the subjects if conditions warrant: (4) the evaluation of the reasonableness of the parents' consent and (where applicable) the ents' consent and (where applicable) the subject's consent; and (5) the procedures for advising the subject and/or the parents concerning the subject's continued participation in the activity. Each subject and his or her parent or guardian will be informed of the name of a member of the Protection Committee who will be available for consultation concerning the activity.

(c) The Protection Committee shall establish rules of procedure for conducting its

lish rules of procedure for conducting its activities, which must be reviewed by DHEW, and shall conduct its activities at convened meetings, minutes of which shall be prepared

Section 46.27 Certain children excluded from participation in DHEW activities. A child may not be included as a subject in DHEW activities to which this subpart is ap-

(a) The child has no known living parent who is available and capable of participating in the consent process: *Provided*, That this exclusion shall be implicable in the child is seriously ill, and the proposed research is designed to substantially alleviate his condition; or

(b) The child has only one known living parent who is available and capable of par-ticipating in the consent process, or only one such parent, and that parent has not given consent to the child's participation in the activity: or

(c) Both the child's parents are available and capable of participating in the consent process, but both have not given such con-

The child is involuntarily confined in an institutional setting pursuant to a court order, whether or not the parents and child have consented to the child's participation in the activity; or

(e) The child has not given consent to his or her participation in the research: Pro-vided, That this exclusion shall be inapplica-ble if the child is 6 years of age or less or if explicitly waived by the DHEW; or

(f) The Protection Committee established under § 46.26 of this subpart has not reviewed and approved the child's participation in the

Section 46.28 Activities to be performed outside the United States. In addition to satisfying all other applicable requirements in this subpart, an activity to which this subpart is applicable, which is to be conducted outside the United States, must include written documentation satisfactory to DHEW that the proposed activity is acceptable under the legal, social, and ethical standards of the locale in which it is to be performed.

SUBPART C-Additional Protection for CERTAIN CLASSES OF DHEW ACTIVITIES

Section 46.31 Applicability. (a) The regulations in this subpart are applicable to all Department of Health, Education, and Welfare research, development, or demonstration activities: (1) Involving pregnant women, unless there is a finding by DHEW that the uniess there is a finding by Driew that the activity will have no adverse effect on the fetus, or is clearly thereapeutic with respect to the fetus involved, (2) involving the abortus or the non-viable fetus, or (3) involving in vitro fertilization of human ova.

(b) Nothing in this subpart shall be constituted with

(b) Nothing in this suppart shall be construed as indicating that compliance with the procedures set forth herein will in any way render inapplicable pertinent State of local laws bearing upon activities covered by this subpart.

(c) To the extent the requirements of subpart A of this part are applicable to activities also covered by this subpart, the require-ments of this subpart are in addition to

ments of this subpart are in addition to those imposed under subpart A.

Section 46.32 Purpose. It is the purpose of this subpart to provide additional safeguards in reviewing activities to which this subpart is applicable to assure that they conform to appropriate ethical standards and relate to important societal needs.

Section 46.33 Definitions. As used in this subpart:

subpart:
(a) "DHEW" means the Department of

- (a) "DHEW" means the Department of Health, Education, and Welfare. (b) "DHEW activity" means: (1) The conduct or support (through grants, contracts, or other awards) of bio-medical or behavioral research involving human subjects; or
- Research, development, or demonstra-activities regulated by any DHEW DHEW agency
- "Board" means the Board established
- under § 46.25.
  (d) "Protection Committee" means a com-
- mittee referred to in § 46.26.

  (e) "Pregnancy" means the period of time from implantation of a fertilized ovum until delivery.

  (f) "Fetus" means the product of conception from implantation until delivery.

(g) "Abortus" means the fetus when it has been expelled whole, whether spontaneously or as a result of medical or surgical interor as a result of medical or surgical intervention to terminate a pregnancy, prior to viability. This definition, for the purpose of this policy, excludes the placenta, fetal material which is macerated at the time of expulsion, a dead fetus, and isolated fetal tissue or organs excised from a dead fetus, (h) "viability of a fetus" means capability given the benefit of available therapy, of independently maintaining heart beat and respiration.

respiration.

(i) "In vitro fertilization" means any fer-tilization of human ova which occurs outside the body of a female, through admixture of

human sperm and such ova.

human sperm and such ova.

Section 46.34 Duties of the Ethical Review Board. (a) It shall be the function of the Board to review each activity to which this subpart applies and advise the agency concerning the acceptability of such activities from the standpoint of societal need and ethical considerations, taking into account the assessment of the appropriate Primary Review Committees as to: (1) The potential benefit of the proposed activity, (2) scientific merit and experimental design, (3) the sufficiency of studies involving animals dem-

onstrating the clear potential benefit of the proposed procedures and (4) whether the information to be gained may be obtained

information to be gained may be obtained from further animal or adult human studies.

(b) The Board may recommend the establishment by the sponsoring institution of a Protection Committee to carry out such functions as the Board deems necessary.

Section 46.35 Maternal consent to activities the objective (a). No activity to

Section 40.35 material consent to activities involving the abortus. (a) No activity to which this subpart is applicable may involve an abortus or a non-viable fetus unless maternal consent has been obtained.

ternal consent has been obtained.

(b) No activity to which this subpart is applicable may involve an abortus or a non-viable fetus unless: (1) Individuals involved in the activity will have no part in the decision as to timing, method, or extent of the procedure used to terminate the pregnancy, or in determining viability of the fetus at the termination of the pregnancy; (2) vital functions of the abortus will not be mainrunctions of the abordes will not be mark-tained artificially for purposes of research; and (3) experimental procedures which would terminate heart beat or respiration in

the abortus will not be employed.

Section 46.37 Prohibition on certain ac-Section 46.37 Prohibition on certain activities involving pregnant women where the fetus may be adversely affected. The Board shall review all research, development, and demonstration activities involving pregnant women. No activity to which this subpart is applicable may involve a pregnant woman if the Primary Review Committee finds that the fetus might be adversely affected, unless the primary purpose of the activity is to benefit that fetus. In addition, no activity to which this subpart is applicable may involve pregnant women unless all the requirements of this subpart are satisfied.

Section 46.38 Parental consent to activities which might affect the fetus. No activity involving a pregnant woman which might affect the fetus but which nevertheless is permissible under \$46.37 shall be conducted.

permissible under § 46.37 shall be conducted unless maternal consent has been obtained. as well as the consent of the father if he is available and capable of participating in the consent process.

Section 46.39 Activities to be performed outside the United States. In addition to satisfying all other applicable requirements in this subpart, activities to which this subpart is applicable, which are to be conducted outside the United States, must include written the United States, must include written the United States. ten documentation satisfactory to DHEW
that the proposed activity is acceptable under the legal, social, and ethical standards of the locale in which it is to be performed.

SUBPART D-Additional Protections for Prisoners Involved as Subjects in DHEW

Section 46.41 Applicability. (a) The regu-Section 46.41 Applicability. (a) The legi-lations in this subpart are applicable to all Department of Health, Education, and Wel-fare research, development, and demonstra-tion activities involving prisoners as subjects. (b) The requirements of this subpart are

in addition to those imposed under subparts

in addition to those imposed under subpacts A and B of this part.

Section 46.42 Purpose. It is the purpose of this subpart to provide additional safeguards for activities to which this subpart is applicable inasmuch as the potential subjects in activities conducted thereunder, because of activities conducted interenties, because their incarceration, might be under constraints which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate in such

activities. Section 46.43 Definitions. As used in this

(a) "DHEW activity" means:

(1) the conduct or support (through grants, contracts, or other awards) of bio-medical or behavioral research involving human subjects; or

(2) research, development, or demonstra-on activities regulated by any DHEW tion

agency.

(b) "Prisoner" means any individual involuntarily confined in a penal institution. voluntarily confined in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute and also individuals detained by virtue of statutes which provide alternatives to criminal prosecution. (c) "DHEW" means the Department of Health, Education, and Welfare.

Health, Education, and Weltare.
Section 46.44 Additional duties of Organizational Review Committee where prisoners are involved. (a) In carrying out its responsibilities under subpart A of this part for activities also covered by this subpart, the Organirational Review Committee provided for under subpart A shall also certify: (1) That there will be no undue inducements to participation by prisoners as subjects in the ac-tivity, taking into account among other fac-tors, the sources of earnings generally available to the prisoners as compared with those offered to participants in the activity, (2) that the clinic and hospital facilities are adequate for the proposed activity, (3) that all aspects of the activity would be appropriate for performance on nonprisoners, and (4) that no prisoner will be offered any reduction in sentence or parole for participation in such activity which is not comparable to that offered for other activities at the facility not of a research, development, demonstration or similar nature

similar nature.

(b) In addition, the Organizational Review Committee shall have the following duties: (1) To review, approve, or modify the procedures proposed for the Protection Committee in carrying out its functions as set forth in § 46.45; (2) To recommend any additional functions to be performed by the Protection Committee in connection with a particular activity; (3) To set rates of remuneration, if any, consistent with the anticipated duration, discomfort, and/or risk of the activity but not in excess of that paid for other employment generally available to inmates employment generally available to inmates of the facility in question; and (4) To carry out such other responsibilities as may be stipulated by DHEW in the contract or grant

Activities to which this subpart is ap-(c) Activities to which this subpart is applicable must provide for the designation of an Organizational Review Committee, where no such Committee has been established

under subpart A.
Section 46.45 Protection Section 46.45 Protection Committees; duties; composition. (a) No activity covered by this subpart will be approved unless it provides for the establishment of a Protection Committee to carry out the following functions, as well as any others recommended by the Organizational Review Committee or by DHEW: (1) Reviewing the procedure for by the Organizational Review Committee or by DHEW: (1) Reviewing the procedure for soliciting participation by prisoners in the research activity to determine that all ele-ments of Informed consent, as outlined in \$46.3, are satisfied; (2) overseeing the selec-tion of prisoners who may participate in the activity; (3) monitoring the progress of the research and the continued willingness of subject participation; and (4) intervening on behalf of one or more subjects if condi-tions warrant. In addition, each subject will be informed of the name of a member of the Protection Committee who will be available Protection Committee who will be available to the subject for consultation concerning the

(b) Each Protection Committee shall be composed of at least five members appointed by the applicant and so selected that the Committee will be competent to deal with the medical, legal, social, and ethical issues involved. At least one member of the Committee shall be either a prisoner or a representative of an organization having as a primary con-cern protection of the interests of prisoners. No more than one-third of the members may be physicians or scientists engaged in bio-medical or behavioral research, and no more than one member, other than a prisoners' representative, may have any affiliation with the prison facility or the legal entity having jurisdiction over the facility, except for per sons employed by a Department of Education in a teaching capacity. Any prisoners serving on the Committee shall be compensated at a rate consistent with that set for prisoners participating as subjects in activities at the facility to which this subpart is applicable.

(c) The Protection Committee shall estab-lish rules of procedure for conducting its activities which must be reviewed by DHEW. and shall conduct its activities at convened meetings, minutes of which shall be prepared and retained. The composition of the Com-

mittee shall be subject to DHEW approval.

Section 46.46 Prohibition on participation in activities prior to conviction. No individual confined pending arraignment, trial, or sentencing for an offense punishable as a crime may be used as a subject in any activity supported in whole or in part by a grant or contract to which this subpart is applicable.

ection 46.47 Remuneration to subjects. Where rates of remuneration are set pursuant to § 46.44 of this subpart, any subject who, for medical reasons, is required by a representative of the prison facility, grantee, contractor, or sponsor of the activity, to withdraw before completion of his or her partici-pation in the activity shall continue to be compensated for a period to be set by the Protection Committee after consultation with Section 46.48 Accreditation. It is the in-

tention of DHEW to accredit prison facilities as sites for the performance of activities to which this subpart applies. Accreditation will be based on certification of the acceptability of the facilities and compliance with the procedures required by this subpart, as determined by the Secretary. No activity covered by this subpart may involve prisoners incarcerated in a facility not accredited

by Secretary of DHEW.

Section 46.49 Activities to be performed outside the United States. In addition to satisfying all other applicable requirements in this subpart, an activity to which this subpart is applicable, which is to be conducted outside the United States, must include written documentation satisfactory to DHEW that the proposed activity is acceptable under the legal, social, and ethical standards of the locale in which it is to be performed.

SUBPART E-ADDITIONAL PROTECTIONS FOR IN-STITUTIONALIZED MENTALLY INFIRM INDIVID-UALS INVOLVED AS SUBJECTS IN DHEW AC-

Section 46.51 Applicability. (a) The regulations in this subpart are applicable to a Department of Health, Education, and Wel fare activities involving the institutionalized mentally infirm as subjects.

- (b) Nothing in this subpart shall be con-(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein in connection with activities permitted under \$46.54 of this subpart will necessarily result in a legally effective consent under applicable States or local law to a subject's participation in such an activity; nor in particular does it obviate the need for court approval of such participation where court approval is required under applicable State or local law in order to obtain a legally effective consent.
- (c) The requirements of this subpart are in addition to those imposed under Subparts A, B, and D of this part.

Section 46.52 Purpose. It is the purpose this subpart to provide additional safeguards for the mentally infirm involved in research, development, and demonstration, activities, inasmuch as the potential subjects in such activities are: (1) Confined in an institutional setting; (2) might be unable fully to comprehend the type risks which may be involved; and (3) might be legally incompetent to consent to their participation in such activities.
Section 46.53 Definitions. As used in this

subpart:

"DHEW activity" means:

(a) "DHEW activity" means:
(1) The conduct or support (through grants, contracts, or other awards) of biomedical or behavioral research involving human subjects; or

(2) Research, development, or demonstra on activities regulated by any DHEV

agency.
(b) "Mentally infirm" includes the mentally ill, the mentally retarded, the emotion-ally disturbed, the psychotic, the senile, and others with impairments of a similar nature, regardless of whether or not the individual has been determined to be legally incompetent.

"Institutionalized" means confined, whether by court order or voluntary com-mitment, in an institution for the care and

or treatment of the mentally infirm.

Section 46.54 Limitations on activities involving the institutionalized mentally infirm. No institutionalized mentally infirm indi-vidual may be included as a subject in a DHEW activity unless:

(a) The proposed activity is concerned with: (1) The diagnosis, treatment, prevention, or etiology of the impairment with which he or she is afflicted; or (2) the proposed activity is concerned with the effect of institutional life on the subject and involves me with the middle to the subject. volves no risk of harm to the subject; or the information can be obtained only from such subjects.

The individual's legal guardian has (b) given consent to the individual's participa-tion in such activity;

(c) Where the individual has sufficient

mental competency to understand what is proposed and to express an opinion as to his or her participation, the individual's consuch participation has also been secured; and

(d) The Protection Committee, provided for in \$46.56 of this subpart, has reviewed and approved subject participation in the activity (by class or by individual).

Section 46.55 Additional duties of Organizational Review Committee where the mentally infirm are involved. (a) In addition to its responsibilities under Subpart A of this part, the Organizational Review Committee shall, with respect to activities to which subpart applies:

- (1) Certify that all aspects of the activity would be ethically appropriate for performance on healthy individuals;
- (2) Conduct at least one on-site visit to the institution and prepare a report of the visit, including discussion of such matters as living conditions, availability of medical care, and quality of food, to be submitted to DHEW along with the application;
- (3) Review and approve or modify the procedures proposed by the applicant to be followed by the Protection Committee vided for in § 46.56, in overseeing the re-cruitment of the mentally infirm subjects who may be included in such activity;
- (4) Recommend any additional functions to be performed by the Protection Commit-tee in connection with any particular activity; and
- (5) Carry out such other responsibilities may be recommended by DHEW.
- (b) Activities to which this subpart is applicable must provide for the designation of

an Organizational Review Committee where no such Committee has been established

under subpart A.
Section 46.56 Protection duties; composition. (a) No activity covered by this subpart will be approved unless it provides for the establishment of a Protection Committee to carry out the following functions, as well as any others prescribed by the Organizational Review Committee or by DHEW: (1) Overseeing the process of selection of subjects who may be included selection of subjects who may be included in the activity, (2) monitoring the progress of the activity with special attention to adverse effects on subjects, (3) intervening on behalf of one or more of the subjects if conditions warrant, (4) evaluating the proc-ess and reasonableness of consent of the legal guardian and (where applicable) of the subject, and (5) advising the legal guardian and/or the subject concerning the

continued participation in the activity if conditions warrant.

(b) The composition of each Protection Committee shall conform to the requirements set forth in § 46.26(a).

(c) The Protection Committee shall es-

tablish rules of procedure for conducting its activities, which must be reviewed by DHEW, and shall conduct its activities at convened meetings, minutes of which shall be prepared

Section 46.57 Activities to be performed Section 46.57 Activities to be performed outside the United States. In addition to satisfying all other applicable requirements in this subpart, an activity to which this subpart is applicable, which is to be conducted outside the United States, must include written documentation satisfactory to DHEW that the proposed activity is acceptable under the legal, social, and ethical standards of the locale in which it is to be performed. performed.

#### SUBPART F-GENERAL PROVISIONS

Section 46.61 Applicability. The following regulations are applicable to all activities covered by this part.
Section 46.62 Records. (a) Copies of all

documents presented or required for initial and continuing review by any Organizational Review Committee or Protection Committee and minutes, transmittals on actions, in-structions, and conditions resulting from committee deliberations are to be made part of the official files of the grantee or con-tractor for the supported activity.

(b) Records of subject's and representa-

(b) Records of subject's and representative's consent shall be retained by the grantee or contractor in accordance with its established practice, or, if no practice has been established, in project files.

(c) Acceptance of any DHEW grant or contract award shall constitute consent of

the grantee or contracting organization to inspection and audit of records pertaining to assisted activity by authorized repre-

the assisted activity by authorized representatives of the Secretary.

(d) All documents and other records required under this part must be retained by the grantee or contracting organization for a minimum of three years following termina-

tion of DHEW support of the activity.
Section 46.63 Reports. Each organization with an approved assurance shall provide the Secretary with such reports and other in-formation as the Secretary may from time to time prescribe.

Section 46.64 Early termination of awards: sanctions for noncompliance. (a) If, in the judgment of the Secretary, an organization has failed to comply with the terms of this part with respect to a particular Federal activity, he may require that said grant or contract be terminated or suspended in the manner prescribed in applicable grant or procurement regulations.

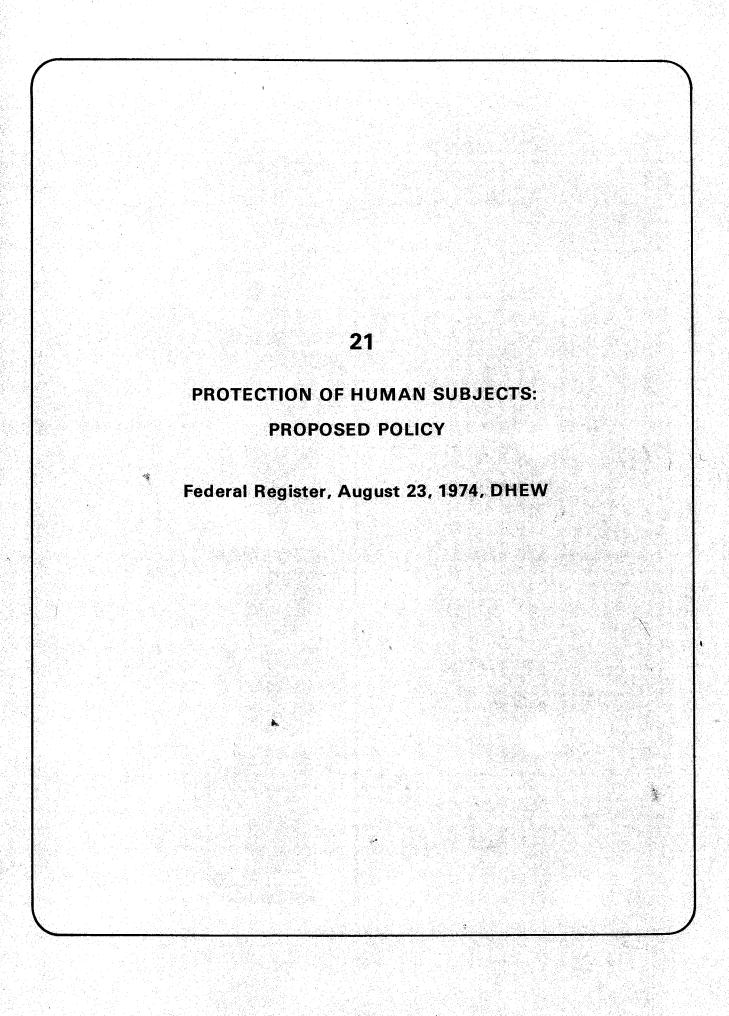
(b) If, in the judgment of the Secretary, an organization fails to discharge its responsibilities for the protection of the rights and welfare of the subjects in its care, whether or not DHEW funds are involved, he may, upon reasonable notice to the organization of the basis for such action, determine that its eligibility to receive further DHEW grants or contracts or participate in DHEW assisted activities, involving human subjects, shall be terminated. Such disqualification shall continue until it is shown to the satisfaction of the Secretary that the reasons therefor no longer exist.

(c) If, in the judgment of the Secretary, an individual serving as principal investigator, program director, or other person having responsibility for the scientific and technical direction of a project or activity, has failed to discharge her or his responsibilities for the protection of the rights and welfare of human subjects in his or her care, the Secretary may, upon reasonable notice to the individual of the basis for such action, determine that such individual's eligibility to serve as a principal investigator or program director or in another similar capacity shall be terminated. Such disqualification shall

continue until it is shown to the satisfaction of the Secretary that the reasons therefor no longer exist.

Section 46.65 Conditions. The Secretary may with respect to any activity or any class of activities impose conditions, including conditions pertaining to informed consent, prior to or at the time of the approval of any activity when in the Secretary's judgment such conditions are necessary for the protection of human subjects.

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PART III



# DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary

PROTECTION OF HUMAN SUBJECTS

Proposed Policy

## DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary
[45 CFR Part 46]
PROTECTION OF HUMAN SUBJECTS

#### Proposed Policy

In the Federal Register of May 30, 1974 (39 FR 18914), regulations were published as Part 46 of Title 45 of the Code of Federal Regulations providing generally for the protection of human subjects involved in research, development, or related activities supported by Department grants or contracts. At that time it was indicated that notices of proposed rulemaking would be developed concerning minors, fetuses, abortuses, prisoners, and the institutionalized mentally disabled.

Coincidentally with the development of the notice of proposed rulemaking set forth below, both Houses of Congress reached agreement on the "National Research Act," and the President signed P.L. 93–348 into law. Among other things, the Act establishes an elevenmember National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research to "\* \* (i) conduct a comprehensive investigation and study to identify the basic ethical principles which should underlie the conduct of biomedical and behavioral research involving human subjects, (ii) develop guidelines which should be followed in such research to assure that it is conducted in accordance with such principles, and (iii) make recommendations to the Secretary (I) for such administrative action as may be appropriate to apply such guidelines to biomedical and behavioral research conducted or supported under programs administered by the Secretary, and (II) concerning any other matter pertaining to the protection of human subjects of

biomedical and behavioral research."
This notice of proposed rulemaking is published today to continue the public dialogue begun in November 1973 when the Director of the National Institutes of Health published draft proposals on these issues in the Federal Register. The comments addressed in this preamble are the result of that issuance.

The comments received as a result of this notice of proposed rulemaking will not only assist the Department to develop final regulations but will also be available to the Commission for their use during the course of their deliberations over the next two years.

In the light of the 450 responses received as a result of the November issuance, largely from grantee and contractor organizations, the Department now proposes that, in addition to the protection afforded generally to all subjects of research, development, and related activities supported by the Department by virtue of Part 46, further protective measures should be provided for those subjects of research whose capability of providing informed consent is or may be absent or limited.

This would be accomplished by amending Part 46 to delete § 46.19 through 46.22, redesignating § 46.1 through 46.18 as Subpart A, and adding new Subparts B through F. If this proposal is accepted, the regulations would be structured as follows:

Subpart A would be the basic regulation, substantially as promulgated on May 30, 1974. This provides that no activity involving any human subject at risk shall be supported by a DHEW grant or contract unless the applicant or offering organization has established an organizational review committee which has reviewed and approved such activity and submitted to DHEW a certification of such review and approval. This subpart also provides that all grant and contract proposals involving human subjects at risk are to be additionally evaluated by the Secretary for compliance with the requirements of said subpart.

Subpart B is reserved for a separate, future proposed rulemaking providing additional protection for children.

Subpart C as described in the present proposed rulemaking would call for the utilization of two special mechanisms for the protection of the pregnant woman and unborn child or fetus, where the pregnant woman participates in a research, development, or related activity. While these mechanisms are designed to allow sufficient flexibility for the pursuit of new information about the perinatal process, they are also designed to provide additional safeguards to assure that the research is acceptable from an ethical standpoint.

Subpart D as described in the present proposed rulemaking would give added responsibilities to an organizational review committee where the contemplated research would involve prisoners as subjects and also would require in such instances that a consent committee be established to supervise the selection and participation of prisoners in the research. Prisoner groups are particularly valuable in properly conducted clinical trials since they provide a stable subject population which can be followed over a period of weeks or months rather than days or hours. From the point of view of the prisoner subject, participation in research offers an opportunity to make a contribution to society and to provide an income, much as other jobs in prison do.

Nevertheless, the dangers of abuse of prisoners' rights are obvious. For this reason, the proposed rulemaking calls for additional safeguards for the rights of prisoners whose capability to provide informed consent may be affected by the very fact of their incarceration.

Subpart E as described in the present proposed rulemaking offers additional protections for the rights of the mentally ill, the mentally retarded, the emotionally disturbed, and the senile who are confined to institutions, whether by voluntary or involuntary commitment. Such persons, by the very nature of their disabilities, may be severely limited in their capacity to provide informed consent to their participation in research. At the

same time, the nature of their disabilities requires extensive research efforts to the study of the etiology, pathogenesis, and therapy of their conditions. The proposed rulemaking limits the research in which such subjects may be allowed to participate to that which is most likely to be of assistance to them or to persons similarly disabled.

In developing the present proposed rulemaking, the Department has taken into consideration the public's comments relevant to certain parts of the Introduction, Definition, and General Policy Sections of the draft regulations published at 39 FR 18914, November 16, 1973, as well as to the draft regulations themselves. The major comments, and the Department's present proposals, are as follows:

#### Introduction, General Policy Considerations

A. Commentators suggested, in several different contexts, that the regulations should (i) apply to all research, regardless of the degree of risk or academic discipline concerned, and (ii) provide for the exclusion of certain types of research, particularly behavioral and social science research as distinguished from biomedical research.

The Department, having considered these comments, notes that the applicability provisions of the basic regulations (45 CFR 46.1) permit the Secretary to determine whether specific programs place subjects at risk. Such determination is to be made only after careful study and publication in the Federal Register, providing an opportunity for comment on the merits of each determination. With respect to research in the social sciences, the Department has already indicated its intention of issuing public rulemaking on this matter (see 39 FR 18914, paragraph A).

B. Comments also included suggestions that regulations should be proposed specifically dealing with activities involving students, laboratory employees, seriously ill or terminal patients, the non-institutionalized mentally disabled, and other special groups.

The Department considers that any abuses relating to these groups are less evident and that they are afforded the protection of the existing regulations published in 39 FR 18914.

C. Several comments suggested the provision of additional guidelines with respect to the distinction between established and accepted methods on the one hand and experimental procedures on the other

While the Department recognizes the theoretical desirability of such guidelines, and that the practical necessity of making such a distinction is arising with increasing frequency, the feasibility of making this distinction on a generalized basis has yet to be demonstrated. At the moment a regulatory approach to this issue does not appear justified.

D. It was suggested that all meetings of organizational review committees and similar groups established pursuant to these regulations should be open to the

The Department notes that since the purpose of these committees is, for the most part, to advise with respect to the conduct of individual projects and proposals by individual investigators, a blanket provision to this effect would appear to be inconsistent with the need to protect the confidentiality of the proceedings and records of institutional review and evaluation committees.

#### DEFINITIONS

A. Comments on the definition of "Subject at Risk" suggested changes in language that would (i) limit the concept of risk to that encountered only in addition to that normally experienced, (ii) eliminate demonstration projects as a possible source of risk, since these are nominally limited to application of established and accepted methods, (iii) specifically identify failure to maintain confidentiality as a source of risk, and (iv) provide a mechanism for identifying activities essentially free of risk.

These comments are similar to those made with respect to the same definition as incorporated in an earlier proposed rulemaking (38 FR 27882). In responding to the criticism, the Department has already (i) redefined "Subject at Risk" in 45 CFR 46.3(b) so as to exclude any activity which does not increase the ordinary risks of daily life or the recognized risks inherent in a chosen occupation or field of service, (ii) substituted in 45 CFR 46.1(a) the term "develop-ment" for "demonstration," (iii) pro-vided in 45 CFR 46.19(b) specific prohibitions against disclosures of infor-mation which refers to or can be identified with a particular subject, and (iv) provided in 45 CFR 46.1(b) authority for determination in advance as to whether a particular Federal program or an investigational method or procedure may place subjects at risk.

B. Comments on the definition of "Clinical Research" suggested inclusion in said definition of the behavioral aspects of research and facets of medical research necessarily concerned with diagnosis and other nonetherapeutic aspects of research.

Since the term "clinical research" does not occur in the present rulemaking, the Department reserves its opinion with respect to these suggestions. However, the proposed regulations are applicable to all departmental research, development, and related activities except with respect to Subpart C, where appli-cability is limited to "biomedical cability is limited to research" (§ 46.303(b)).

C. Comments on "Informed Consent" suggested the addition of language concerning (i) full and complete disclosure, (ii) the likelihood of success or failure of the experiment, (iii) the use of place-bos or other control procedures, (iv) provision of information as to the progress of the research, (v) publication of names of all persons, institutions, and review committees involved in approval of consent procedures, (vi) provision of legal counsel and technical advice, and

(vii) assurance that the subject com-

prehends the disclosure.
The Department, having considered these comments, notes that "Informed Consent" is presently defined in 45 CFR. 46.3(c) and not in the present proposed rulemaking. With respect to the specific suggestions the Department notes that: as far as (i) is concerned, the regulations already call for a "fair explanation" of the procedures and a description of risks and benefits reasonably to be expected; (ii) reflects a basic misunder-standing of the experimental process which begins, essentially, with the comparison of two or more methods, procedures, or modalities on the a priori hypothesis that there will be no differ-ence; (iii) is implicit in the existing regulations and is better emphasized in interpretive materials; (iv) would not be an element of informed consent unless interim findings affected the risk of benefit involved; and (v) touches on the subject of a possible future proposed rulemaking the Department reserves its options for the present. The suggestion in (vi) is met in part by the proposals in the present proposed rulemaking to employ consent committees to advise potential subjects. The last suggestion (vii) goes beyond requirements for informed consent as they have generally been articulated by the courts.

D. Comments also included sugges tions for the inclusion of additional definitions of (i) Institutions, (ii) Legal Guardian, (iii) Organizational Review Committee, (iv) Institutionalized Mentally Infirm, and (v) Children (with regard to age of consent), Parents, and Father.

The Department, having reviewed these comments, notes that (i) "Organization" is defined for the purpose of these regulations to include "institu-tions" at 45 CFR 46.3(a); (ii) "Legally authorized representative" is defined for the purpose of these regulations to include legal guardian at 45 CFR 46.3(h); (iii) the definition of "organizational review committee" is implicit in 45 CFR "Institutionalized mentally disabled" has been defined in the present proposed rulemaking at 46.503(d) to meet the suggestion; and (v) defini-tion of "Children." "Parents." and tion of "Children," "Parents," and "Father" will be reconsidered prior to the issuance of a future rulemaking covering research on children.

E. Several commentators provisions of the draft policy that would have required that activities to be conducted outside the United States satisfy all requirements of the Departments regulations including those based on ethical concepts peculiar to the Judeo-Christian moral heritage or to English common law. It was noted that this would create substantial problems for United States investigators working overseas since these concepts are often inconsistent if not in conflict with normal, ethical, and legal concepts in certain foreign countries. For the same reasons, it was argued that these provisions would create problems for United States citizens assigned, detailed, seconded, or acting as consult-

ants to international organizations or to foreign governmental or private insti-

Having considered these objections, the Department proposes to retain the basic concept that activities supported by Departmental funds should, in general, be subject to a uniform ethical policy wherever they are conducted, but to permit the Secretary to modify consent procedures if it can be demonstrated to his satisfaction that such procedures, as modified, are acceptable under the legal, social, and ethical standards of the locale in which the activities are to be performed.

#### FETUSES, ABORTUSES, AND PREGNANT WOME

Since comments on the draft provisions in 38 CFR 31738 providing additional protections for fetuses, abortuses, in vitro fertilization, and pregnant wom-en were integrated with those on chil-dren, it is difficult to identify the com-munications specifically concerned with these subjects. However, it is estimated that the majority of the more than 400 letters received on research with children, born and unborn, touched on one or more aspects of research with fetuses, abortuses, and pregnant women.

A. A large number of respondents disagreed entirely with the idea of permit-ting research with the fetus, with the abortus (whether living or dead), or with the pregnant woman if the research might conceivably endanger the fetus.

The Department, having carefully considered these comments and similar proposals reflected in general correspondence and in articles in the public media, notes that their adoption would seriously hamper the development of needed improvements in the health care of the pregnant woman, the fetus, and the new-born. The opposition to research involvement of the fetus and abortus appears to be based in part on the assumption that the needed information can be obtained through research with animal species or with adults. Unfortunately, these assumptions are not valid. While much useful research can be conducted in animals, differences in species are nevertheless so great that any research finding in nonhuman species must ultimately be repeated in man before its general application in human medicine. In addition, the fetus and the newborn are not small adults. They suffer from some diseases not encountered in the adult. They may react differently to the diseases commonly affecting both adult and young, and they may have a different response to the same treatment, both with regard to its effectiveness and to its safety. The Department therefore proposes that (i) the ethical probity of any application or proposal for the support of any activity covered by subpart C be reviewed by an Ethical Advisory Board as described in § 46.304, and (ii) the conduct of any such activity supported by the Department be subject to oversight and monitoring by a consent committee as described in § 46.305.

B. Opinion was divided as to the need for an Ethical Advisory Board. Many respondents called it a welcome addi-tion in the review process. Others felt that it would duplicate the function of the local organizational review committee and that its existence would encourage the organizational review committee to be less critical and would impose an additional roadblock that would delay or prohibit important research while needlessly consuming time, energy, and money, and posing potential danger to a patient waiting for treatment. Complaints were voiced that such decisions should be made locally, not in Washington, and that the investigator should be able to present his case in person. Numerous comments suggested that the Board's function should be limited to advising on policy. should be imited to advising on policy, guidelines, or procedures, and not be concerned with the review of individual projects. This would avoid duplicating the function of the organizational review committee. Others suggested that the Ethical Advisory Board should serve as an appeal body from the organizational review committee.

There were also numerous comments to the effect that it is unwise and impossible to totally separate ethical and scientific review. Approval based only on ethics would be unethical if the science were bad. Both should be reviewed

jointly.

The Department, having reviewed these comments, concludes that Ethical Advisory Board remains, in concept, a useful addition to the review process. It does not auplicate the functions of the local organizational review committee, since the latter is primarily concerned with matters of organizational regulations, local standards of professional practice, applicable law within its jurisdiction, and local community attitudes. The Ethical Advisory Board will be primarily concerned with similar issues at the national level. Applications and proposals should be capable of passing scrutiny at both levels. It is therefore proposed that the Ethical Advisory Board be retained as part of the additional protection mechanism.

Specific comments regarding establishment of an Ethical Advisory Board touched principally on (i) the possibility that appointment of members at an agency level might lead to "loaded" Boards, while appointment at a higher level, i.e., by a joint Congressional com-mittee or by independent outside bodies, might produce a more objective group, and (ii) disagreement as to the proper balance between scientist and nonscientist members, with a majority of the commentators suggesting that more than one-third of the members should have the scientific expertise necessary to identify risks and their possible consequences. It was specifically suggested that different sizes, compositions, and administrative locations of the Board be tried before selecting a final mechanism. In addition, it was suggested (iii) that a fifteen member Board was too large, (iv) that all members be human geneticists, (v) that at least one member be a psychologist, if behavioral issues were to be considered. (vi) that there be an absolute ban on departmental agency employees (vii) that all proceedings be confidential, (viii) that all meetings be open to the public, and (ix) that an appeal mechanism be established.

The Department, having considered these views, proposes that while an Ethical Advisory Board to deal with bio-medical research involving fetuses, abortuses, pregnant women, and in vitro fertilization might logically be estab-lished at the National Institutes of Health, (i) the power of appointment should be reserved to the Secretary, (ii) while the membership should include research scientists, physicians, lawyers, clergy or ethicists, and representatives of the general public, the balance between callings should rest with the Secretary as should also (iii) the number of members, so that the membership (iv, v) can be adjusted to the needs of the Board as the workload and the issues before it dictate. The specific suggestion (see vi) that departmental agency employees be excluded is adopted and expanded to include all full-time employees of the Federal Government. The decisions with regard to suggestions (vii) and (viii) wili be governed by the provisions of the Federal Advisory Committee Act which generally require that meetings of similar advisory groups be open to the public for the purposes of policy discussion, but closed and confidential for the purpose of review of specific applications and proposals. Since the Board will be ad-visory to funding agencies, the final action will be that of existing awarding authorities, and appeal mechanisms (ix) ill be provided only to the extent available under other existing departmental regulations and policies. These proposals are incorporated into \$ 46.304.

C. A number of respondents recom-mended that the policy governing in vitro fertilization be strengthened, on the one hand, or liberalized, on the other. The Department has considered these recommendations, and has provisionally chosen not to stipulate at this time protections for the product of in vitro fertilization which is not implanted, but rather to leave that series of issues to the Ethical Advisory Board established under § 46.304(a). The Board will be required to weigh, with respect to specific research proposals, the state of the art, legal issues, community standards, and the availability of guidelines to govern each research situation.

Because biomedical research is not yet near the point of being able to maintain for a substantial period the non-implanted product of in vitro fertilization, no clear and present danger arises from not stipulating in these regulations the protections for it. Given the state of the research, we believe that such stipulation would be premature.

It is the Department's intent that the definition of the term "fetus" (§ 46.303 (d)) be construed to encompass both the product of in vivo conception and the product of in vitro fertilization which is subsequently implanted in the donor of the ovum. Whatever the nature of the conception process, it is intended that upon implantation the protections of subpart C apply to all fetuses. It is only with respect to the protections available to the non-implanted product of in vitro fertilization that the regulations are silent.

With respect to the fertilization of human ova in vitro, it is expected that the Board will consider the extent to which current technology permits the continued development of such ova, as well as the legal and ethical issues surrounding the initiation and disposition of the products of such research.

With respect to implantation of fertilized human ova, it is expected that the Board will consider such factors as the safety of the technique (with respect to offspring) as demonstrated in animal studies, and clarification of the legal responsibilities of the donor and recipi-ent parent(s) as well as the research

Since the Department does reserve the option of later specifying such protections by regulation, we invite com-ment on the question of appropriate regulations in the future.

D. The draft proposals included a suggestion for the establishment of a protection committee which elicited numerous comments that the use of the term "protection committee" implies that the Department recognizes a clear, present need for protection against the investigator, the uncertain relation of this committee to the organizational review committee, and the uniform need for and destrability for such protection.

Having reviewed these comments, the Department proposes an extensive revi-Department proposes an extensive revision in this innovative concept. Initially, it acknowledges that the term "protection committee" is pejorative and proposes the term "consent committee" as more appropriate and consistent with the primary purpose of such bodies. Further, it proposes to eliminate specific requirements for the size and composition of such committees. Instead, applicants and offerors are to propose the establishment of such a committee, specifying its size, composition, and rules of procedure. In addition, where the applicant or offeror believes that the activity involves only negligible risks, it may ask the Secretary to waive or modify the requirement for a consent committee. All proposals for the establishment, modification, or waiver of a consent committee shall be subject to review and approval at the local level by the organizational review committee and at the departmental level by the Ethical Advisory Board. The Ethical Advisory Board may prescribe additional duties for the consent committee. These changes are incorporated in § 46.305. In view of this drastic change in concept of the committee, detailed discussion of the many excellent and often thoughtprovoking comments concerned with details of the original draft seems inappropriate.

E. Many critical comments were addressed to the definitions used in this subpart, specifically:

1. "Pregnancy." It was suggested that pregnancy should be defined (i) conceptually to begin at the time of fertilization of the ovum, and (ii) operationally by actual test unless the woman has been surgically rendered incapable of

While the Department has no argument with the conceptual definition as proposed above, it sees no way of basing regulations on the concept. Rather, in order to provide an administerable policy, the definition must be based on existing medical technology which permits confirmation of pregnancy. This approach is reflected by § 46.303 (c). 2. "Viability of the Fetus" Many rec-

2. "Viability of the Fetus". Many recommendations were received concerning the definition of viability of the fetus after premature delivery or abortion. Some respondents urged that presence of fetal heartbeat be definitive (whether or not there is respiration) while others urged that identifiable cortical activity be specified as an alternative sign of viability. The Department has concluded that the issue of viability is a function of technological advance, and therefore must be decided with reference to the medical realities of the present time. We reserve the option of redefining the parameters as conditions warrant.

Only upon the basis of a definition which is both precise and consistent with current medical capability can a regulation realistically be interpreted and enforced. Current technology is such that a fetus, given the benefit of available medical therapy, cannot survive unless the lungs can be inflated so that respiration can take place. Without this capability, even if the heart is beating, the fetus is nonviable. In the future, if technology has advanced to the point of sustaining a fetus with non-inflatable lungs, the definition can and should be modified.

The Department has therefore chosen to specify, in the definition of viability of the fetus (§ 46.303(e)), that heart beat and respiration are, jointly, to be

the indicator of viability.

3. "Abortus." Various comments noted that this definition is more restrictive than the usual medical definition of the abortus as a "nonviable fetus." and suggested substitution of the broader definition.

The Department proposes to retain the original definition for the purposes of these regulations. There is general agreement that there are distinct ethical problems involved in decisions concerning research use of the intact fetus, or use of organs or tissues obtained from a fetus that has died in utero or from an abortus at autopsy. The definition recurs with minor editorial changes in § 46.303(f).

F. Several comments were critical of the draft regulation's provisions limiting activities involving pregnant women to those not adversely affecting the fetus, except where the primary purpose of the activity was to benefit the fetus. It was suggested that the regulations (i) should contain language permitting exceptions

for research necessary to meet the health needs of the mother, and (ii) should grant the right to participate in research aimed at improvement of methods of abortion, birth control, and genetic intervention.

The Department concurs with the first suggestion, (i), and proposes that the regulations permit research whose primary interest is to benefit the particular fetus or to respond to the health needs of the pregnant woman. It does not fully accept the second suggestion, (ii), and proposes that the regulations permit fetal research concerned with diagnosis and prevention of perinatal disease, and to offset the effects of genetic abnormality or congenital injury, but only when such research is done as part of a procedure properly performed to terminate a pregnancy. These changes are incorporated into § 46.306(a). The Department has tentatively concluded that consideration of risk vs. benefit with respect to the consideration of the consideration of the consideration of the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to the constant to t spect to fetal research does not seem to be appropriate.

G. Draft regulation provisions required maternal consent and the consent of the father if he were available and capable of participating in the consent process. This provision was strongly criticized on the grounds that it could permit the father of the fetus to deny needed health care to the woman or to the fetus even though he had no marital obligations, and that it might result in undue delay in the delivery of health care. It was also pointed out that the regulation did not touch on the question of the validity of consent by a pregnant minor.

The Department agrees. It is now proposed that paternal consent be sought only if the activity is not responding to the health needs of the pregnant woman and the father is reasonably available. These changes are reflected by \$46.306(b).

H. The Department has provisionally chosen, in § 46.306(a), to permit research to be undertaken from which there will be risk of harm to the fetus if such research is conducted as part of the abortion procedure. This decision, upon which we invite comment, has been made in the expectation that such research may produce new technology which will enable countless premature infants to live who now cannot.

It is not intended that this provision

It is not intended that this provision be construed to permit fetal research in anticipation of abortion prior to the commencement of the termination procedure itself

While it is true that the class of fetuses for whom abortion is contemplated will be placed at greater research risk than all fetuses in general, such risk can arise only after implementation of the double safeguard of parental consent to the contemplated abortion, and second parental consent to the research procedure itself.

I. Comments regarding activities involving the abortus were concerned with the issue of maintaining vital functions and signs. It was argued that maintaining vital functions at the level of the organ, tissue, or cell is essential to studies

and involves no prolongation of the dying of the abortus. At the same time, it was argued that termination of the heart beat should not be prohibited since temporary cardiac arrest has proved essential in the development of surgical techniques necessary to correct congenital heart defects.

Neither of these objections appear valid and no significant changes in \$46.307 are proposed. However, in order to emphasize again the distinction between research with the whole fetus or abortus, functioning as an organism with detectable vital signs, and with the dead fetus or abortus, the Department has added § 46.308, concerning activities involving a dead fetus or abortus, and § 46.309, concerning the abortus as an organ or tissue donor. Also § 46.307(d) has been expanded to permit the artificial maintenance of vital functions of an abortus where the purpose is to develop new methods for enabling the abortus to survive to the point of viability.

The Department feels that there is evident distinction between "termination" and "arrest" of the clinical signs as applied to the fetus or premature infant, but that no such distinction is valid or applicable where the abortus is concerned.

#### PRISONERS

Forty-seven responses spoke to the provisions regarding additional protection for prisoners involved as subjects. Of these, two were from individuals identifying themselves as prisoners, seven were from State correctional institutions or State agencies, and four were from representatives of the pharmaceutical industry.

industry.

A. In comments directed at the overall nature of the draft regulations providing additional protection for prisoners, approximately equal numbers of respondents (i) denied that any significant additions were necessary, and (ii) proposed either the exclusion of prisoners from any research or experimentation not intended for the personal benefit of a prisoner, or highly restrictive regulations to accomplish the same purpose.

The Department, having reviewed these comments, has not been persuaded that any change should be made in the initial proposal.

B. A number of comments were concerned with the relationship between the existing organizational review committees and the proposed Protection Committee. It was pointed out by several that, as proposed, the two committees would not only have overlapping functions and authority but could operate independently of each other with conflicting directives and objectives that would not practicably provide additional protection of prisoners used as subjects.

The Department, recognizing the importance of preserving the authority of the organizational review committee as the primary institutional focus for the implementation of the Department of Health, Education, and Welfare regulations, proposes to assign to the organizational review committee the additional duties specified under § 46.404(a).

PROPOSED RULES

A committee auxiliary to the organizational review committee, now designated the consent committee, will have the character and responsibilities specified in § 46.406. In keeping with this modified position it should be noted that when the organizational review committee determines that an activity would involve nrisk or negligible risk to any prisoner while serving as a subject, the organization may request the Secretary to consider a modification or waiver of the requirement for a consent committee.

C. Comments on the proposed prohibition of research involvement of persons awaiting arraignment, trial, or sentencing expressed doubts that these individuals should be denied the benefits of innovative procedures, particularly those concerned with sociological research.

The Department agrees that the uniform exclusion of any such person from research should not be mandatory and proposes to permit his participation in an activity as a subject when the risk is negligible and the intent of the activity is therapeutic for him or relates to the nature of his confinement. This modification is incorporated into § 46.406.

D. The draft requirement for DHEW

D. The draft requirement for DHEW accreditation of prison facilities as sites for the performance of research, development, and related activities involving prisoner subjects was severely criticized, principally because of the jurisdictional problems inherent in any attempt to impose a Federal regulatory requirement on an autonomous State facility.

The Department concludes that this draft proposal was ill-advised. However, in order to attain the objective on an activity basis, certain specific prerequisites for the protection of prisoner subjects within facilities have been added to § 46.404(a) to properly relate conditions in a facility to the issue of undue inducements to participation by prisoners as subjects in an activity.

#### MENTALLY DISABLED

Over 40 of the responses spoke directly to the section of the draft concerned with the "mentally infirm." Many of these objected initially to the use of the word "infirm" as reflecting an antiquated notion of mental illness.

The Department agrees, and proposes to substitute "disabled" for "infirm," though noting that there is no clearly preferable collective term for the groups described.

A. Comments on the purpose of this section expressed satisfaction with the intent to provide additional protection for this group but dissatisfaction with the actual language employed. Specifically, they noted that not institutionalization but rather the limitation of personal rights and freedom imposed by institutionalization is the determining issue. Similarly, it is not only the potential subject's difficulty in comprehending risks that is at issue, but his ability to comprehend generally.

The Department concurs. Proposed changes in language are incorporated in § 46.52.

B. Many of the respondents objected to one or more of the definitions peculiar to this subpart. The criticisms and the Department's proposed changes are as follows:

follows:

1. "Mentally infirm." In addition to requesting substitution of another term for "infirm," respondents raised conflicting objections to the definition's coverage. Some felt that it was overly inclusive; others felt it was too narrow. Some felt that epileptics should be specifically included, as well as those who are temporarily or permanently mentally incapacitated as a result of a physical condition such as stroke, brain damage, trauma, etc.

The Department, having carefully reviewed these comments, proposes no basic change in the definition. It concurs with many reviewers in the opinion that the definition is broad enough to include any category of subjects proposed for specific addition. Minor editorial changes

have been made in § 46.503(b).

2. "Institutionalized." Commentators noted that (i) the regulations should cover all mentally disabled persons regardless of institutionalization, (ii) not all involuntary commitments are by order of a court, (iii) the draft refers to "residence" and "confinement" in similar contexts, though the terms do not carry the same connotation, and (iv) the definition does not specify halfway houses, lodges, day/night hospitals, nursing homes, and psychiatric wards of hospitals as places where subjects might be institutionalized.

The Department notes that (i) the non-institutionalized mentally disabled are covered by the existing regulations published as 39 FR 18914 and need not be included under these additional protections. Such individuals are not necessarily subject to all limitations on their freedom and rights as described in § 46.502 of this proposed rulemaking. Consideration will be given, however, to dealing with the noninstitutionalized legally incompetent who are mentally disabled in a subsequent notice of proposed rulemaking. With regard to (ii), the implication that court orders are the sole basis for involuntary confinement is incorrect and should be removed. Editorial changes have been made in § 46.503 to emphasize that concern there-in is with those "\* \* confined \* \* \* in a residential institution \* \* \*" (see and, in order to designate the type of institutions concerned (see iv), it is proposed to separately define "Institutionalized mentally disabled individuals" in § 46.503 to include examples of such institutions. These changes are incorporated in § 46.503(c) and § 46.503(d).

C. While most respondents endorsed the intent of the draft limitations on activities involving the institutionalized mentally disabled, there were several specific criticisms of the terms used. Several persons suggested that any limitation of research to that related to a particular subject's "impairment" be worded so as to include any illness from which the person suffers so that, for ex-

ample, an institutionalized mentally disabled person with cancer could not be denied the benefits of research in cancer therapy.

Further, this limitation could exclude the use of such subjects as controls in research which might benefit those suffering from a mental disability other than the specific one from which a particular subject suffers. Still further, mentally disabled people should be involved as subjects in research on infirmities other than their own because of lack of knowledge of the causes of mental and emotional disorders.

Many respondents felt that there was inadequate recognition of the need for research with the mentally disabled on basic psychological processes (e.g., learning, perception, and cognitive functions) which are fundamental to the study of the treatment, etiology, pathogenesis, prevention, and treatment of such disabilities.

The Department agrees that the language of the draft limiting research to disease entities affecting individual subjects is probably not in the interests of the institutionalized mentally disabled as a class. The Department does not agree that it would be appropriate to permit this class of subjects to be involved in research unrelated to the causes, nature, or circumstances of their institutionalization. While there possible disadvantages to the institutionalized mentally disabled inherent in this restriction, the possible risks of using the mentally disabled in such research outweigh its advantages. The proposed changes are incorporated in § 46.504(a). Editorial changes are reflected in § 46.504 (b) and \$ 46.504(c).

D. Criticisms of the draft's suggestion of the establishment or a protection committee in connection with each activity conducted in an institution for the mentally retarded were similar to those aimed at the protection committee to be established in connection with research on the pregnant woman and on the fetus. The Department proposes to change the title of the committee to "consent committee" and to change the regulations governing size, composition, and operating rules to conform to those previously described for § 46.305. Such changes are incorporated in § 46.506.

E. With respect to § 46.603(b), the Department reserves the right to amend this section if legislation now being developed by the Executive Branch on the safe guarding of individually linked data used for statistical and research purposes is enacted.

Written comments concerning the proposed regulation are invited from interested persons. Inquiries may be addressed and data, views, and arguments relating to the proposed regulations may be presented in writing, in triplicate, to the Chief, Institutional Relations Branch, Division of Research Grants, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014. All comments received will be available for inspection at the National Institutes of

Health, Room 303, Westwood Building, 5333 Westbard Avenue, Bethesda, Maryland, weekdays (Federal holidays excepted) between the hours of 9:00 a.m. and 4:30 p.m. All relevant material received on or before November 21, 1974 will be considered.

Notice is also given that it is proposed to make any amendments that are adopted effective upon publication in the FEDERAL REGISTER.

Dated: August 15, 1974.

#### CASPAR W. WEINBERGER, Secretary.

It is therefore proposed to amend Part 46 of Subtitle A of Title 45 of the Code of Federal Regulations by:

- 1. Revising §§ 46.19 through 46.22 and renumbering them as §§ 46.603 through 46.606, reading as set forth in Subpart F below.
- 2. Designating §§ 46.1 through 46.18 as Subpart A, renumbering these §§ 46.101 through 46.118, and modifying all references thereto accordingly.
  - 3. Reserving Subpart B.
- 4. Adding the following new Subparts C through F.

Subpart C—Additional Protections Pertaining to Biomedical Research, Development, and Re-lated Activities Involving Fetuses, Abortuses, Pregnant Women, and In Vitro Fertilization

Applicability. 46.301 46.302 46.303 Purpose. Definitions

Ethical Advisory Board. 48 904

Establishment of a consent committee. Activities involving fetuses in utero

46.306 or pregnant women. Activities involving abortuses

Activities involving a dead fetus or 46.308 abortus Activities involving the abortus as an 46.309

organ or tissue donor.

Activities to be performed outside the United States.

## Subpart D-Additional Protections Pertaining to Activities Involving Prisoners as Subjects

46.401 46.402 46.403 Applicability.

Purpose. Definitions.

Additional duties of the organizational review committee where prisoners are involved.

Establishment of a consent commit-46.405 tee. Special restrictions.

46,406 Activities to be performed outside the United States.

## Subpart E—Additional Protections Pertaining to Activities Involving the Institutionalized Men-tally Disabled as Subjects

46.501 Applicability.

Purpose. Definitions. 46.502 46.503

Activities involving the institution-46.504

alized mentally disabled.
Additional duties of the organizational review committee where the
institutionalized mentally disabled 46 505 are involved.

46.506 Establishment of a consent commit-

46.507 Activities to be performed outside the United States.

Subpart F-General Provisions

46.601 Applicability.

Sec. 46.602 Multiple consent committee require-

ments.
Organization's record; confidential-

Reports.
Early termination of awards; evaluation of subsequent applications. 46 606 Conditions.

Activities conducted by Department

employees.
AUTHORITY: 5 U.S.C. 301.

Subpart C-Additional Protections Pertaining to Biomedical Research, Develop-ment, and Related Activities Involving Fetuses, Abortuses, Pregnant Women, and In Vitro Fertilization

#### § 46.301 Applicability.

(a) The regulations in this subpart applicable to all Department of Health, Education, and Welfare grants and contracts supporting biomedical research, development, and related activities involving: (1) the fetus in utero, (2) the abortus, as that term is defined in § 46.303, (3) pregnant women, and (4) in vitro fertilization. In addition, these regulations are applicable to all such activities involving women who could become pregnant, except where the applicant or offeror shows to the satisfaction of the Secretary that adequate steps will be taken in the conduct of the activity to avoid involvement of women who are pregnant.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will in any way render inapplicable pertinent State or local laws bearing upon activities covered by this subpart.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

#### § 46.302 Purpose.

It is the purpose of this subpart to provide additional safeguards in reviewing activities to which this subpart is appli-cable to assure that they conform to appropriate ethical standards and relate to important societal needs.

#### § 46.303 Definitions.

As used in this subpart:

- (a) "Secretary" means the Secretary of Health, Education, and Welfare or any other officer or employee of the De-partment of Health, Education, and Welfare to whom authority has been delegated.
- (b) "Biomedical research, development, and related activities" search, development, or related activi-ties involving biological study (including but not limited to medical or surgical procedures, withdrawal or removal of body tissue or fluid, administration of chemical substances or input of energy, deviation from normal diet or hygiene, manipulation or observation of bodily processes).
- encompasses the (c) "Pregnancy" period of time from confirmation of implantation until delivery.
- (d) "Fetus" means the product of conception from the time of implantation to the time of delivery.

  (e) "Viability of the fetus" means the

ability of the fetus, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration. If the fetus has this ability, it is viable and therefore a premature infant.

(f) "Abortus" means a fetus when it is

expelled whole, prior to viability, whether spontaneously or as a result of medical or surgical intervention. The term does not apply to the placenta: fetal material which is macerated at the time of expulsion; or cells, tissue, or organs excised

from a dead fetus.

(g) "In vitro fertilization" means any fertilization of human ova which occurs outside the body of a female, either through admixture of donor sperm and ova or by any other means.

#### § 46.304 Ethical Advisory Board.

(a) All applications or proposals for the support of activities covered by this subpart shall be reviewed by an Ethical Advisory Board, established by the Secretary within the National Institutes of Health, which shall advise the funding agency concerning the acceptability of such activities from an

ethical standpoint.
(b) Members of the Board shall be so selected that the Board will be competent to deal with medical, legal, social, and ethical issues and shall include, for example, research scientists, physicians, lawyers, and clergy and/or ethicists, as well as representatives of the general public. No Board member may be a reg-ular, full-time employee of the Federal Government.

#### § 46.305 Establishment of a consent committee.

- (a) Except as provided in paragraph (c) of this section, no activity covered by this subpart may be supported unless the applicant or offeror has provided an assurance acceptable to the Secretary that it will establish a consent commit-tee (as provided for in the application or offer and approved by the Secretary) for each such activity, to oversee the actual process by which individual consents required by this subpart are secured, to monitor the progress of the activity and intervene as necessary, and to carry out such other duties as the Secretary (with the advice of the Ethical Advisory Board) may prescribe. The duties of the consent committee may include:
- (1) Participation in the actual selection process and securing of consents to assure that all elements of a legally effective informed consent, as outlined in § 46.3, are satisfied. Depending on what may be prescribed in the application or offer approved by the Secretary. this might require approval by the committee of individual participation in the activity or it might simply call for verification (e.g., through sampling) that procedures prescribed in the approved application or offer are being followed.
- (2) Monitoring the progress of the activity. Depending on what may be prescribed in the application or offer approved by the Secretary, this might

include: visits to the activity site, identification of one or more committee members who would be available for consultation with those involved in the consent procedure (i.e., participants) at the participant's request, continuing evaluation to determine if any unanticipated risks have arisen and that any such risks are communicated to the participants, periodic contact with the participants to ascertain whether they remain willing to continue in the activity, providing for the withdrawal of any participants who wish to do so, and authority to terminate participation of one or more participants with or without their consent where conditions warrant.

(b) The size and composition of the consent committee must be approved by the Secretary, taking into account such factors as: (1) the scope and nature of the activity; (2) the particular subject groups involved; (3) whether the membership has been so selected as to be competent to deal with the medical, legal, social, and ethical issues involved in the activity; (4) whether the committee includes sufficient members who are unaffiliated with the applicant or offeror apart from membership on the committee; and (5) whether the committee includes sufficient members who are not engaged in research, development, or related activities involving human subjects. The committee shall establish rules of procedure for carrying out its functions and shall conduct its business at convened meetings, with one of the members designated as chairperson.

(c) Where a particular activity, involving fetuses in utero or pregnant women, presents negligible risk to the fetus, an applicant or offeror may request the Secretary to modify or waive the requirement in paragraph (a) of this section. If the Secretary finds that the risk is indeed negligible and other adequate controls are provided, he may (with the advice of the Ethical Advisory Board) grant the request in while or in part.

(d) The requirements of this section and § 46.304 do not obviate the need for review and approval of the application or offer by the organizational review committee, to the extent required under Subpart A of this part.

#### § 46.306 Activities involving fetuses in utero or pregnant women.

(a) No activity to which this subpart is applicable, involving fetuses in utero or pregnant women, may be undertaken unless: (1) the purpose of the activity is to benefit the particular fetus or to respond to the health needs of the mother, or (2) the activity conducted as part of (but not prior to the commencment of) a procedure to terminate the pregnancy and is for the purpose of evaluating or improving methods of prenatal diagnosis. methods of prevention of premature birth, or methods of intervention to offset the effects of genetic abnormality or congenital injury.

(b) Activities covered by this subpart which are permissible under paragraph (a) of this section may be conducted

only if the mother and father are legally competent and have given their consent. except that the father's consent need not be secured if: (1) the purpose of the activity is to respond to the health needs of the mother or (2) his identity or whereabouts cannot reasonably be ascertained.

(c) Activities covered by this subpart which are permissible under paragraph (a) (2) of this section may not be unde taken unless individuals engaged in the research will have no part in: (1) any decisions as to the timing, method, or procedures used to terminate the pregnancy, and (2) determining the viability of the fetus at the termination of the pregnancy.

#### § 46.307 Activities involving abortuses.

No activity to which this subpart is applicable, involving an abortus, may be undertaken unless:

Appropriate studies on animals have been completed:

(b) The mother and father are legally competent and have given their consent, except that the father's consent need not be secured if his identity or whereabouts

cannot reasonably be ascertained; (c) Individuals engaged in the research will have no part in: (1) any decisions as to the timing, method, or procedures used to terminate the pregnancy. and (2) determining the viability of the fetus at the termination of the pregnancy

(d) Vital functions of an abortus will not be artificially maintained except where the purpose of the activity is to develop new methods for enabling the abortus to survive to the point of viability; and

(e) Experimental procedures which would terminate the heart beat or res piration of the abortus will not be employed.

#### § 46.308 Activities involving a dead fetus or abortus.

Activities involving a dead fetus or abortus shall be conducted in accordance with any applicable State or local laws governing autopsy.

#### § 46.309 Activities involving the abortus as an organ or tissue donor

Activities involving the abortus as an organ or tissue donor shall be conducted in accordance with any applicable State or local laws governing transplantation or anatomical gifts.

## § 46.310 Activities to be performed outside the United States.

Activities to which this subpart is applicable, to be conducted outside the United States, are subject to the requirements of this subpart, except that the consent procedures specified herein may be modified if it is shown to the satisfaction of the Secretary that such procedures, as modified, are acceptable under the laws and regulations of the country in which the activities are to be performed and that they comply with the requirements of Subpart A of this Subpart D— Additional Protections Pertaining to Activities Involving Prisoners as Subjects

#### § 46.401 Applicability.

(a) The regulations in this subpart are applicable to all Department of Health, Education, and Welfare grants and contracts supporting research, development, and related activities involving prisoners as subjects.

(b) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

#### § 46.402 Purpose.

It is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable, inas-much as, because of their incarceration. they may be under constraints which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate in such activities.

#### § 46.403 Definitions.

As used in this subpart:

(a) "Secretary" means the Secretary of Health, Education, and Welfare or any other officer or employee of the Department of Health, Education, and Welfare to whom authority has been dele-

(b) "Prisoner" means any individual involuntarily confined in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute and also individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution.

#### § 46.404 Additional duties of the organizational review committee where prisoners are involved.

(a) In addition to the responsibilities prescribed for such committees under Subpart A of this part, the applicant's or offeror's organizational review committee shall, with respect to activities covered by this subpart, carry out the following additional duties:

(1) Determine that there will be no undue inducements to participation by prisoners as subjects in the activity, taking into account such factors whether the earnings, living conditions, medical care, quality of food, and amenities offered to participants in the activity would be better than those generally available to the prisoners;

(2) Determine that (i) all aspects of the activity would be appropriate for per-formance on nonprisoners, or (ii) the activity involves negligible risk to the subjects and is for the purpose of studying the effects of incarceration on such subjects:

(3) Determine that the application or proposal contains adequate procedures for selection of subjects, securing consents, monitoring continued subject participation, and assuring withdrawal without prejudice, in ac § 46.405 of this subpart; accordance with

(4) Determine that rates of remunera-tion are consistent with the anticipated duration of the activity, but not in excess of that paid for other employment generally available to inmates of the facility in question, and that withdrawal from the project for medical reasons will not result in loss of anticipated remuneration: and

(5) Carry out such other responsibili-ties as may be assigned by the Secretary.

- (b) Applicants or offerors seeking support for activities covered by this sub-part must provide for the designation of an organizational review committee, subject to approval by the Secretary, where no such committee has been established under Subpart A of this part
- (c) No award may be issued until the applicant or offeror has certified to the Secretary that the organizational review committee has made the determinations required under paragraph (a) of this

#### Establishment of a consent § 46.405 committee.

- (a) Except as provided in paragraph (c) of this section, no activity covered by this subpart may be supported unless the applicant or offeror has provided an assurance acceptable to the Secretary that it will establish a consent committee (as provided for in the application or offer and approved by the organiza-tional review committee and the Secretary) for each such activity, to oversee the actual process by which individual subjects are selected and their consents secured, to monitor the progress of the activity (including visits to the activity site on a regular basis) and the continued willingness of the subjects to participate, to intervene on behalf of one or more subjects if conditions warrant, and to carry out such other duties as the Secretary may prescribe. The duties of the consent committee may include:
- (1) Participation in the actual process by which individual subjects are selected and their consents secured to assure that all elements of a legally effective informed consent, as outlined in section 46.3 of this part, are satisfied. Depending on what may be prescribed in the application or offer approved by the Sec-retary, this might require approval by the committee of each individual's participation as a subject in the activity or it might simply call for verification (e.g., through sampling) that procedures prescribed in the approved application or offer are being followed.
- (2) Monitoring the progress of the activity and the continued willingness of subjects to participate. Depending on what may be prescribed in the application or offer approved by the Secretary, this might include: visits to the activity site, identification of one or more committee members who would be available for consultation with subjects at the subjects' request, continuing evaluation to determine if any unanticipated risks have arisen and that any such risks are communicated to the subjects, periodic contact with the subjects to ascertain are applicable to all Department of

in the study, providing for the with-drawal of any subjects who wish to do so, and authority to terminate participation of one or more subjects with or without their consent where conditions warrant.

- The size and composition of the consent committee must be approved by the Secretary, taking into account such the Secretary, saling into account of the activity; (2) the particular subject groups involved; (3) whether the membership has been so selected as to be competent to deal with the medical, legal, social, and ethical issues involved in the activity; (4) whether the committee includes a prisoner or a representative of an organization having as a primary concern protection of prisoners' interests; (5) whether the committee includes sufficient members who are unaffiliated with the applicant or offeror apart from membership on the committee; and (6) whether the committee includes sufficient members who are not engaged in research, development, or related activities involving human subjects. The commit-tee shall establish rules of procedure for carrying out its functions and shall conduct its business at convened meetings, with one of its members designated as chairperson.
- (c) Where a particular activity involves negligible risk to the subjects, an applicant or offeror may request the Secretary to modify or waive the requirement in paragraph (a) of this section. If the Secretary finds that the risk is indeed negligible and other adequate controls are provided, he may grant the request in whole or in part.

#### § 46.406 Special restrictions

Persons detained in a correctional facility pending arraignment, trial, or sentencing or in a hospital facility for prearraignment, pre-trial, or pre-sentence diagnostic observation are excluded fro participation in activities covered by this subpart, unless (a) the organizational review committee finds that the particular activity involves only negligible risk to the subjects and (b) the activity is therapeutic in intent or relates to the nature of their confinement.

## 407 Activities to be performed outside the United States.

Activities to which this subpart is applicable, to be conducted outside the United States, are subject to the require-ments of this subpart, except that the consent procedures specified herein may be modified if it is shown to the satisfaction of the Secretary that such procedures, as modified, are acceptable under the laws and regulations of the country in which the activities are to be performed and that they comply with the requirements of Subpart A of this part

Subpart E—Additional Protections Pertaining to Activities Involving the Institutionalized Mentally Disabled as Subjects

#### 46.501 Applicability.

whether they remain willing to continue Health, Education, and Welfare grants and contracts supporting research, development, and related activities involving the institutionalized mentally disabled as subjects.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will necessarily result in a legally effective consent under applicable State or local law to a subject's participation in such an activity; nor in particular does it obviate the need for court approval of such participation where court approval is required under applicable State or local law in order to obtain a legally effective consent.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

#### 8 46.502 Purpose.

It is the purpose of this subpart to provide additional safeguards for the protection of the institutionalized mentally disabled involved in activities to which this subpart is applicable, inasmuch as: (a) they are confined in an institutional setting where their freedom and rights are potentially subject to limitation; (b) they may be unable to comprehend sufficient information to give an informed consent, as that term is defined in § 46.103; and (c) they may be legally incompetent to consent to their participation in such activities.

#### § 46.503 Definitions.

As used in this subpart:

"Secretary" means the Secretary of Health, Education, and Welfare or any other officer or employee of the Depart-ment of Health, Education, and Welfare

to whom authority has been delegated.
(b) "Mentally disabled" includes those institutionalized individuals who are mentally ill, mentally retarded, emotionally disturbed, or senile, regardless of their legal status or basis of institutional-

(c) "Institutionalized" means confined, whether by voluntary admission or involuntary commitment, in a residen-

of the mentally disabled.

(d) "Institution for the care or treatment of the mentally disabled.

(d) "Institutionalized mentally disabled individuals" includes but is not limited to patients in public or private mental hospitals, psychiatric patients in general hospitals, inpatients of community mental health centers, and mentally disabled individuals who reside in halfway houses or nursing homes.

## § 46.504 Activities involving the institu-tionalized mentally disabled.

Institutionalized mentally disabled individuals may not be included in an activity covered by this subpart unless:

- (a) The proposed activity is related to the etiology, pathogenesis, prevention, diagnosis, or treatment of mental dis-ability or the management, training, or rehabilitation of the mentally disabled and seeks information which cannot be obtained from subjects who are not institutionalized mentally disabled;
- (b) The individual's legally effective informed consent to participation in the

activity or, where the individual is legally incompetent, the informed consent of a representative with legal authority so to consent on behalf of the individual

has been obtained; and
(c) The individual's assent to such participation has also been secured, when in the judgment of the consent committee he or she has sufficient mental capacity to understand what is proposed and to express an opinion as to his or her participation.

§ 46.505 Additional duties of the orga-nizational review committee where the institutionalized mentally disabled are involved.

(a) In addition to the responsibilities prescribed for such committees under Subpart A of this part, the applicant's or offeror's organizational review commit-tee shall, with respect to activities covered by this subpart, carry out the following additional duties:

(1) Determine that all aspects of the activity meet the requirements of § 46.50

(a) of this subpart;

- (2) Determine that there will be no undue inducements to participation by individuals as subjects in the activity, taking into account such factors as whether the earnings, living conditions, medical care, quality of food, and amenities offered to participants in the activity would be better than those generally available to the mentally disabled at the institutions;
- (3) Determine that the application or proposal contains adequate procedures for selection of subjects, securing consents, protecting confidentiality, and monitoring continued subject participations. tion, in accordance with \$ 46.506 of this subpart; and

(4) Carry out such other responsibilities as may be assigned by the Secretary.
(b) Applicants or offerors seeking support for activities covered by this subpart must provide for the designation of an organizational review committee, of an organizational review committee, subject to approval by the Secretary, where no such committee has been established under Subpart A of this part.

(c) No award may be issued until the

applicant or offeror has certified to the Secretary that the organizational review committee has made the determinations required under paragraph (a) of this section.

§ 46.506 Establishment of a consent committee.

(a) Except as provided in paragraph (c) of this section, no activity covered by this subpart may be supported unless the applicant or offeror has provided a separate assurance acceptable to the Secretary that it will establish a consent committee (as provided for in the application or offer and approved by the orga-nizational review committee and the secretary) for each such activity, to oversee the actual process by which individual subjects are selected and consents required by this subpart are secured, to monitor the progress of the activity (in-cluding visits to the activity site on a regular basis) and the continued willing-

ness of the subjects to participate, to intervene on behalf of one or more subjects if conditions warrant, and to carry out such other duties as the Secretary may prescribe. The duties of the consent committee may include:

(1) Participation in the actual process by which individual subjects are selected and their consents secured to assure that all elements of a legally effective in-formed consent, as outlined in § 46.3, are satisfied. Depending on what may be prescribed in the application or offer ap-proved by the Secretary, this might re-quire approval by the committee of each individual's participation as a subject in the activity or it might simply call for verification (e.g., through sampling) that procedures prescribed in the approved application or offer are being followed.

(2) Monitoring the progress of the activity and the continued willingness of subjects to participate. Depending on what may be prescribed in the application or offer approved by the Secretary, this might include: visits to the activity site, identification of one or more committee members who would be available for consultation with subjects at the subjects' request, continuing evaluation to determine if any unanticipated risks have arisen and that any such risks are communicated to the subjects, periodic contact with the subjects to ascertain whether they remain willing to continue in the study, providing for the withdrawal of any subjects who wish to do so, and authority to terminate participation of one or more subjects with or without their consent where conditions warrant.

(b) The size and composition of the consent committee must be approved by the Secretary, taking into account such factors as: (1) the scope and nature of the activity; (2) the particular subject groups involved; (3) whether the membership has been so selected as to be competent to deal with the medical, legal, social, and ethical issues involved in the activity; (4) whether the committee includes sufficient members who are unaffiliated with the applicant or offeror apart from membership on the committee; and (5) whether the committee includes sufficient members who are not engaged in research, development, or related activities involving human subjects. The committee shall establish rules of procedure for carrying out its functions and shall conduct its business at convened meetings, with one of its members designated as chairperson.

(c) Where a particular activity involves negligible risk to the subjects, an applicant or offeror may request the Secretary to modify or waive the require-ment in paragraph (a) of this section. If the Secretary finds that the risk is in-deed negligible and other adequate con-trols are provided, he may grant the request in whole or in part

§ 46.507 Activities to be performed outside the United States

Activities to which this subpart is applicable, to be conducted outside the

United States, are subject to the requirements of this subpart, except that the consent procedures specified herein may be modified if it is shown to the satisfaction of the Secretary that such procedures, as modified, are acceptable under the laws and regulations of the country in which the activities are to be per-formed and that they comply with the requirements of Subpart A of this part.

#### Subpart F-General Provisions

§ 46.601 Applicability.

Sections 46.602 through 46.606 are applicable to all grant or contract supported activities covered by this part.

§ 46.602 Multiple consent committee requirements.

Where an application or proposal would involve human subjects covered by more than one consent committee requirement imposed under this part, upon approval by the Secretary, these multiple requirements may be satisfied through use of a single consent committee appropriately constituted to take account of the nature of the subject group.

46.603 Organization's records; confidentiality.

- (a) Copies of all documents presented or required for initial and continuing review by the organization's review comor consent committee, such as committee minutes, records or subjects' consent, transmittals on actions, instructions, and conditions resulting from committee deliberations addressed to the activity director, are to be retained by the organization, subject to the terms and conditions of grant and contract
- (b) Except as otherwise provided by law, information in the records or pos session of an organization acquired in connection with an activity covered by this part, which information refers to or can be identified with a particular subject, may not be disclosed except:

(1) With the consent of the subject or his legally authorized representative;

(2) As may be necessary for the Secretary to carry out his responsibilities under this part in the exercise of oversight for the protection of such subject or class of subjects.

#### § 46.604 Reports.

Each organization with an approved assurance shall provide the Secretary with such reports and other information as the Secretary may from time to time prescribe.

- § 46.605 Early termination of awards; evaluation of subsequent applications.
- (a) If, in the judgment of the Secrean organization has failed materially to comply with the terms of this policy with respect to a particular Department of Health, Education, and Welfare grant or contract, he may requre that said grant or contract be terminated or suspended in the manner prescribed in applicable grant or procurement regulations.

(b) In evaluating proposals or applications for support of activities covered by this part, the Secretary may take into account, in addition to all other eligibility requirements and program criteria, such factors as: (1) whether the offeror or applicant has been subject to a termination or suspension under paragraph (a) of this section, (2) whether the offeror or applicant or the person who would direct the scientific and technical aspects of an activity has in the judgment of the Secretary failed materially to discharge his, her, or its responsibility for the protection of the rights and welfare of subjects and (3) whether, where

past deficiencies have existed in discharging such responsibility, adequate steps have in the judgment of the Secretary been taken to eliminate these deficiencies.

### § 46.606 Conditions.

The Secretary may with respect to any grant or contract or any class of grants or contracts impose additional conditions prior to or at the time of any award when in his judgment such conditions are necessary for the protection of human subjects.

§ 46.607 Activities conducted by Department employees.

The regulations of this part (except for this subpart) are applicable as well to all research, development, and related activities conducted by employees of the Department of Health, Education and Welfare, except that: (a) subpart C is applicable only to biomedical research, development, and related activities and (b) each agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint.

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## DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary

[ 45 CFR Part 46 ]

#### PROTECTION OF HUMAN SUBJECTS

**Correction of Preamble to Proposed Policy** 

In the August 23, 1974 issue of the PEDERAL REGISTER (39 FR 30648), the Department of Health, Education, and Welfare published a notice of proposed rulemaking governing research, development, and related activities, supported by the Department, involving the fetus, abortus, presnant women, in vitro fertilization, prisoners, and the institutionalized mentally disabled.

After publication the following errors were noted in the preamble to the proposed rulemaking:

- (1) The initial three paragraphs of Section C on page 30650 fail to indicate that, because of the Department's concern about the ethical issues surrounding in vitro fertilization (whether or not implantation is contemplated), the proposed rulemaking would require that all activities involving in vitro fertilization be reviewed by the Ethical Advisory Board prior to funding. In order to make clear this concern these paragraphs have been revised to read as follows:
- C. A number of respondents recommended that the policy governing in vitro fertilization be strengthened, on the one hand, or liberalized, on the other. The Department has considered these recommendations, and concluded that while it is necessary to impose certain restraints, it is contrary to the interests of society to set permanent restrictions on research which are based on the successes and limitations of current technology. Therefore, the Department would expect the Ethical Advisory Board, which must review all applications involving in vitro fertilization (whether or not implantation is contemplated) to weigh, with respect to specific proposals, the state of the art, legal issues, community standards, and the availability of guidelines to govern each research situation. In sum, if there is a possibility that the conceptus might be sustained in vitro beyond the earliest stages of development, the Ethical Advisory Board is to consider this possibility, and determine what guidelines should govern decisions affecting that fetus, if the research is to be permitted. If, on the other hand, implantation is attempted and achieved, then regulations governing the fetus in utero shall apply.
- (2) Several sentences were inadvertently omitted from the first and second paragraphs of the discussion of "Viability of the Fetus" in the first column on page 30651. These sentences are now inserted and as revised, the paragraphs read as follows:

2. "Viability of the Fetus." Some respondents suggested specific criteria such as birth weight, crown-rump length, or gestational age, similar to those used in England, such criteria to be reviewed and reissued periodically by the Department. It was emphasized that the use of such objective criteria might simplify problems involved in determining what types of research might be permissible. Some respondents urged that presence of fetal heartbeat be definitive (whether or not there is respiration) while others urged that identifiable cortical activity be specified as an alternative sign of viability. Others objected strenuously to any distinction as to the nature of fetal life, holding that the physician's obligation should be the same to any fetus regardless of weight, size, or age of gestation.

The Department, having reviewed these comments, concludes that the distinction between a viable and a non-riable fetus is both valid and meaningful. At the same time, the Department does not believe that the use of weight, size, gestational age and/or cortical activity is a valid substitute for the judgment of a physician, particularly in view of the wide variation in the facilities and arts available to him both in this country and abroad. The Department further concludes that the issue of viability is a function of technological advance Isee § 46.303(e) of the regulations], and therefore must be decided with reference to the medical realities of the present time, while reserving the right to redefine the parameters as conditions warrant."

(3) Section H on page 30651 incorrectly implies that, under the proposed rulemaking, fetuses for which abortion is contemplated may be placed at greater risk than fetuses in general. In fact, however, as is stated already in section F on page 30651, the proposed rulemaking bans the undertaking of research, development, or related activities involving the fetus prior to the commencement of the abortion procedure, at which point the question of risk to the fetus is no longer an issue. Such activities which are permitted under the regulations would be reviewed by the Ethical Advisory Board prior to funding. Section H should therefore be deleted and section I on the same page relettered section H.

Dated: October 21, 1974.

Caspar W. Weinberger, Secretary.

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