REPORT AND
RECOMMENDATIONS

Research Involving Children

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

REPORT AND
RECOMMENDATIONS

Research Involving Children

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

DHEW PUBLICATION NO. (OS) 77-0004

For sale by the Superintendant of Docments, U.S. Government Printing Office
Washington, D.C. 20402

Stock No. 062-003-00481-3

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

Westwood Building, Room 125
5333 Westbard Avenue
Bethesda, Maryland 20016

September 6, 1977

The President
The White House
Washington, D. C. 20500

Dear Mr. President:

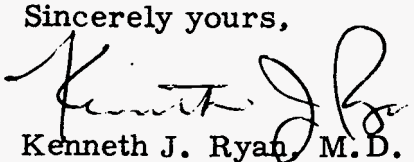
On behalf of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, I am pleased to transmit our Report and Recommendations: Research Involving Children. This is one of several topics of study identified in the mandate to the Commission under Public Law 93-348, which directs the Commission to submit its reports and recommendations to the President, the Congress, and the Secretary of Health, Education, and Welfare.

The involvement of children in research raises particular ethical concerns because of their reduced autonomy and their incompetency to give informed consent. Such concerns would not be answered simply by restricting participation in research to persons who are competent to consent, for the conduct of research involving children is necessary not only to develop new treatment or preventive methods for conditions that jeopardize the health of children, but also to protect children from accepted though unvalidated practices that may be harmful to them. The Commission has therefore sought to answer the following two questions: under what conditions is the participation of children in research ethically acceptable, and under what conditions may such participation be authorized by the subjects and their parents.

The Commission's answers to these questions are reflected in the recommendations set forth at the outset of our report. Substantial background materials, including legal and ethical discussions and statements of members of the Commission regarding the recommendations, are also presented in the report. An appendix volume contains a number of of papers and reports to the Commission that were used in our deliberations.

The Commission continues to find its work most challenging and to be grateful for the opportunity to provide assistance in areas of wide concern.

Sincerely yours,



Kenneth J. Ryan, M.D.
Chairman

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

Westwood Building, Room 125
5333 Westbard Avenue
Bethesda, Maryland 20016

September 6, 1977

The Honorable Walter F. Mondale
President of the United States Senate
Washington, D.C. 20510

Dear Mr. President:

On behalf of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, I am pleased to transmit our Report and Recommendations: Research Involving Children. This is one of several topics of study identified in the mandate to the Commission under Public Law 93-348, which directs the Commission to submit its reports and recommendations to the President, the Congress, and the Secretary of Health, Education, and Welfare.

The involvement of children in research raises particular ethical concerns because of their reduced autonomy and their incompetency to give informed consent. Such concerns would not be answered simply by restricting participation in research to persons who are competent to consent, for the conduct of research involving children is necessary not only to develop new treatment or preventive methods for conditions that jeopardize the health of children, but also to protect children from accepted though unvalidated practices that may be harmful to them. The Commission has therefore sought to answer the following two questions: under what conditions is the participation of children in research ethically acceptable, and under what conditions may such participation be authorized by the subjects and their parents.

The Commission's answers to these questions are reflected in the recommendations set forth at the outset of our report. Substantial background materials, including legal and ethical discussions and statements of members of the Commission regarding the recommendations, are also presented in the report. An appendix volume contains a number of of papers and reports to the Commission that were used in our deliberations.

The Commission continues to find its work most challenging and to be grateful for the opportunity to provide assistance in areas of wide concern.

Sincerely yours,

Kenneth J. Ryan, M.D.
Chairman

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

Westwood Building, Room 125
5333 Westbard Avenue
Bethesda, Maryland 20016

September 6, 1977

The Honorable Thomas P. O Neill, Jr.
Speaker of the House of Representatives
Washington, D.C. 20515

Dear Mr. Speaker:

On behalf of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, I am pleased to transmit our Report and Recommendations: Research Involving Children. This is one of several topics of study identified in the mandate to the Commission under Public Law 93-348, which directs the Commission to submit its reports and recommendations to the President, the Congress, and the Secretary of Health, Education, and Welfare.

The involvement of children in research raises particular ethical concerns because of their reduced autonomy and their incompetency to give informed consent. Such concerns would not be answered simply by restricting participation in research to persons who are competent to consent, for the conduct of research involving children is necessary not only to develop new treatment or preventive methods for conditions that jeopardize the health of children, but also to protect children from accepted though unvalidated practices that may be harmful to them. The Commission has therefore sought to answer the following two questions: under what conditions is the participation of children in research ethically acceptable, and under what conditions may such participation be authorized by the subjects and their parents.

The Commission's answers to these questions are reflected in the recommendations set forth at the outset of our report. Substantial background materials, including legal and ethical discussions and statements of members of the Commission regarding the recommendations, are also presented in the report. An appendix volume contains a number of of papers and reports to the Commission that were used in our deliberations.

The Commission continues to find its work most challenging and to be grateful for the opportunity to provide assistance in areas of wide concern.

Sincerely yours,

Kenneth J. Ryan, M.D.
Chairman

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

Westwood Building, Room 125
5333 Westbard Avenue
Bethesda, Maryland 20016

September 6, 1977

Honorable Joseph A. Califano, Jr.
Secretary of Health, Education, and Welfare
Washington, D.C. 20201

Dear Mr. Secretary:

On behalf of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, I am pleased to transmit our Report and Recommendations: Research Involving Children. This is one of several topics of study identified in the mandate to the Commission under Public Law 93-348, which directs the Commission to submit its reports and recommendations to the President, the Congress, and the Secretary of Health, Education, and Welfare.

The involvement of children in research raises particular ethical concerns because of their reduced autonomy and their incompetency to give informed consent. Such concerns would not be answered simply by restricting participation in research to persons who are competent to consent, for the conduct of research involving children is necessary not only to develop new treatment or preventive methods for conditions that jeopardize the health of children, but also to protect children from accepted though unvalidated practices that may be harmful to them. The Commission has therefore sought to answer the following two questions: under what conditions is the participation of children in research ethically acceptable, and under what conditions may such participation be authorized by the subjects and their parents.

The Commission's answers to these questions are reflected in the recommendations set forth at the outset of our report. Substantial background materials, including legal and ethical discussions and statements of members of the Commission regarding the recommendations, are also presented in the report. An appendix volume contains a number of of papers and reports to the Commission that were used in our deliberations.

The Commission continues to find its work most challenging and to be grateful for the opportunity to provide assistance in areas of wide concern.

Sincerely yours,

Kenneth J. Ryan, M.D.
Chairman

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

MEMBERS OF THE COMMISSION

Kenneth John Ryan, M.D., Chairman
Chief of Staff
Boston Hospital for Women

Joseph V. Brady, Ph.D.
Professor of Behavioral Biology
John Hopkins University

Robert E. Cooks, M.D.
President
Medical College of Pennsylvania

Dorothy I. Height
President
National Council of Negro Women, Inc.

Albert R. Jonsen, Ph.D.
Associate Professor of Bioethics
University of California at San Francisco

Patricia King, J.D.
Associate Professor of Law
Georgetown University Law Center

Karen Lebacqz, Ph.D.
Associate Professor of Christian Ethics
Pacific School of Religion

David W. Louisell, J.D.
Professor of Law
University of California at Berkeley

Donald W. Seldin, M.D.
Professor and Chairman
Department of Internal Medicine
University of Texas at Dallas

Eliot Stellar, Ph.D.
Provost of the University and
Professor of Physiological Psychology
University of Pennsylvania

Robert H. Turtle, LL.B.
Attorney
VomBaur, Coburn, Simmons & Turtle
Washington, D.C.

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

COMMISSION STAFF

PROFESSIONAL STAFF

Michael S. Yesley, J.D.
Staff Director

Barbara Mishkin, M.A.
Assistant Staff Director

Duane Alexander, M.D.
Pediatrics

Tom L. Beauchamp, Ph.D.
Philosophy

Lee A. Calhoun, M.A.
Political Science

Bradford H. Gray, Ph.D.
Sociology

Miriam Kelty, Ph.D.
Psychology

Bonnie M. Lee
Administrative Assistant

James J. McCartney, M.A., M.S.
Research Assistant

Betsy Singer
Public Information Officer

SUPPORT STAFF

Pamela L. Driscoll

Arlene Line

Maria D. Madigan

Coral M. Nydegger

Erma L. Pender

SPECIAL CONSULTANTS

Robert J. Levine, M.D.

Francis Pizzulli, J.D.

Stephen Toulmin, Ph.D.

The members of the Commission and its staff

wish to express their deep sorrow at the

untimely death of their friend and respected colleague

David W. Louisell.

His wise counsel and dedication to the work of

the Commission will be greatly missed.

Table of Contents

INTRODUCTION

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established in 1974 under Public Law 93-348 to develop ethical guidelines for the conduct of research involving human subjects and to make recommendations for the application of such guidelines to research conducted or supported by the Department of Health, Education, and Welfare (DHEW). The legislative mandate also directs the Commission to make recommendations to Congress regarding the protection of human subjects in research not subject to regulation by DHEW. Classes of subjects that must receive the Commission's particular attention include children, prisoners and the institutionalized mentally infirm.

The duties of the Commission with regard to research involving children are as follows:

> The Commission shall identify the requirements for informed consent to participation in biomedical and behavioral research by children... .The Commission shall investigate and study biomedical and behavioral research conducted or supported under programs administered by the Secretary [DHEW] and involving children .... to determine the nature of the consent obtained from such persons or their legal representatives before such persons were involved in such research; the adequacy of the information given them respecting the nature and purpose of the research, procedures to be used, risks and discomforts, anticipated benefits from the research, and other matters necessary for informed consent; and the competence and the freedom of the persons to make a choice for or against involvement in such research. On the basis of such investigation and study the Commission shall make such recommendations to the Secretary as it determines appropriate to assure that biomedical and

> behavioral research conducted or supported under programs administered by him meets the requirements respecting informed consent identified by the Commission.

This responsibility is broadened by the provision that the Commission make recommendations to Congress regarding the protection of subjects (including children) involved in research not subject to regulation by DHEW.

To discharge its duties under this mandate, the Commission studied the nature and extent of research involving children, the purposes for which such research is conducted, and the issues surrounding the participation of children in research. Representatives from professional societies, federal agencies and public interest groups, as well as parents and other members of the public, presented their views to the Commission at a public hearing. The National Minority Conference on Human Experimentation, convoked by the Commission to assure that viewpoints of minorities would be expressed, made recommendations to the Commission on research involving children. The Commission also reviewed papers and reports prepared under contract, including papers on informed consent and a survey of actual practices in research involving children. Finally, the Commission conducted extensive deliberations in public and developed recommendations on the participation of children in research.

The Commission's recommendations are set forth at the outset of this report, followed by chapters presenting background information, summaries of reports and views presented to the Commission, an analysis of the law

with respect to research involving children, critiques of various ethical arguments, and statements of members of the Commission regarding the recommendations. An appendix to this report contains the text of reports and papers prepared under contract, other materials reviewed by the Commission in the course of its study and deliberations, and a selective bibliography.

* * * * *

Definitions. For the purpose of this report:

1. Children are persons who have not attained the legal age of consent to general medical care as determined under the applicable law of the jurisdiction in which the research will be conducted.

Comment: P.L. 93-348 defines children as "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 research is to be conducted." The Commission notes that the legal age of consent to participate in research is not specifically defined in local jurisdictions. For the purposes of this report, therefore, the Commission has used the age of consent to general medical care (as distinguished from age of consent for treatment of specific conditions, such as pregnancy, drug addiction or venereal disease).

2. Research is a formal investigation designed to develop or contribute to generalizable knowledge.

Comment: A research project generally is described in a protocol that sets forth explicit objectives and formal procedures designed to reach those objectives. The protocol may include therapeutic and other activities intended to benefit the subjects, as well as procedures to evaluate such activities. Research objectives range from understanding normal and abnormal physiological or psychological functions or social phenomena, to evaluating diagnostic, therapeutic or preventive interventions and variations in services or practices. The activities or procedures involved in research may be invasive or noninvasive and include surgical interventions; removal of body tissues or fluids; administration of chemical substances or forms of energy; modification of diet, daily routine or service delivery; alteration of environment; observation; administration of questionnaires or tests; randomization; review of records, etc.

3. Minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children.

Comment: In any assessment of the degree of risk to children that is presented by proposed research activities, the age of the prospective research subjects should be taken into account. The possible effects of disruption of normal routine, separation from parents, or unusual discomfort should be considered, as well as more obvious physical or psychological harms. Examples of medical procedures presenting no more than minimal risk would include routine immunization, modest changes in diet or schedule, physical examina-

tion, obtaining blood and urine specimens, and developmental assessments. Similarly, many routine tools of behavioral research, such as most questionnaires, observational techniques, noninvasive physiological monitoring, psychological tests and puzzles, may be considered to present no more than minimal risk. Questions about some topics, however, may generate such anxiety or stress as to involve more than minimal risk. Research in which information is gathered that could be harmful if disclosed should not be considered of minimal risk unless adequate provisions are made to preserve confidentiality. Research in which information will be shared with persons or institutions that may use such information against the subjects should be considered to present more than minimal risk.

4. Institutional Review Board (IRB) is (1) a committee required under P.L. 93-348 and approved by the Department of Health, Education, and Welfare to review research involving human subjects at an institution receiving support for such research under the Public Health Service Act, or (2) any substantially similar committee which reviews research involving human subjects that is conducted, supported or regulated by a federal agency or department.

RECOMMENDATIONS

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research makes the following recommendations for research involving children to:

The Secretary of Health, Education, and Welfare, with respect to research that is subject to his regulation, i.e., research conducted or supported under programs administered by him and research reported to him in fulfillment of regulatory requirements; and

The Congress, with respect to research that is not subject to regulation by the Secretary of Health, Education, and Welfare.

RECOMMENDATION (1) SINCE THE COMMISSION FINDS THAT RESEARCH INVOLVING CHILDREN IS IMPORTANT FOR THE HEALTH AND WELL-BEING OF ALL CHILDREN AND CAN BE CONDUCTED IN AN ETHICAL MANNER, THE COMMISSION RECOMMENDS THAT SUCH RESEARCH BE CONDUCTED AND SUPPORTED, SUBJECT TO THE CONDITIONS SET FORTH IN THE FOLLOWING RECOMMENDATIONS.

Comment: The Commission recognizes the importance of safeguarding and improving the health and well-being of children, because they deserve the best care that society can reasonably provide. It is necessary to learn more about normal development as well as disease states in order to develop methods of diagnosis, treatment and prevention of conditions that jeopardize the health of children, interfere with optimal development, or adversely

affect well-being in later years. Accepted practices must be studied as well, for although infants cannot survive without continual support, the effects of many routine practices are unknown and some have been shown to be harmful.

Much research on childhood disorders or conditions necessarily involves children as subjects. The benefits of this research may accrue to the subjects directly or to children as a class. The Commission considers, therefore, that the participation of children in research related to their conditions should receive the encouragement and support of the federal government.

The Commission recognizes, however, that the vulnerability of children, which arises out of their dependence and immaturity, raises questions about the ethical acceptability of involving them in research. Such ethical problems can be offset, the Commission believes, by establishing conditions that research must satisfy to be appropriate for the involvement of children. Such conditions are set forth in the following recommendations.

RECOMMENDATION (2) RESEARCH INVOLVING CHILDREN MAY BE CONDUCTED OR SUPPORTED PROVIDED AN INSTITUTIONAL REVIEW BOARD HAS DETERMINED THAT: (A) THE RESEARCH IS SCIENTIFICALLY SOUND AND SIGNIFICANT; (B) WHERE APPROPRIATE, STUDIES HAVE BEEN CONDUCTED FIRST ON ANIMALS AND ADULT HUMANS, THEN ON OLDER CHILDREN, PRIOR TO INVOLVING INFANTS; (C) RISKS ARE MINIMIZED BY USING THE SAFEST PROCEDURES CONSISTENT WITH SOUND RESEARCH DESIGN AND BY USING PROCEDURES PERFORMED FOR DIAGNOSTIC OR TREATMENT PURPOSES WHENEVER

FEASIBLE; (D) ADEQUATE PROVISIONS ARE MADE TO PROTECT THE PRIVACY OF CHILDREN AND THEIR PARENTS, AND TO MAINTAIN CONFIDENTIALITY OF DATA; (E) SUBJECTS WILL BE SELECTED IN AN EQUITABLE MANNER; AND (F) THE CONDITIONS OF ALL APPLICABLE SUBSEQUENT RECOMMENDATIONS ARE MET.

Comment: This recommendation sets forth general conditions that should apply to all research involving children. Such research must also satisfy the conditions of one or more of Recommendations (3) through (6), as applicable; Recommendation (7); Recommendation (8), if permission of parents or guardians is not a reasonable requirement; Recommendation (9), if the subjects are wards of the state; and Recommendation (10), if the subjects are institutionalized.

Respect for human subjects requires the use of sound methodology appropriate to the discipline. The time and inconvenience requested of subjects should be justified by the soundness of the research and its design, even if no more than minimal risk is involved. In addition, research involving children should satisfy a standard of scientific significance, since these subjects are less capable than adults of determining for themselves whether to participate. If necessary, the IRB should obtain the advice of consultants to assist in determining scientific soundness and significance. (The Commission will consider problems related to the determination of scientific soundness and significance in a future report on the performance of IRBs.)

Whenever possible, research involving risk should be conducted first on animals and adult humans in order to ascertain the degree of risk and

the likelihood of generating useful knowledge. Sometimes this is not relevant or possible, as when the research is designed to study disorders or functions that have no parallel in animals or adults. In such cases, studies involving risk should be initiated on older children to the extent feasible prior to including infants, because older children are less vulnerable and they are better able to understand and to assent to participation. In addition, they are more able to communicate about any physical or psychological effects of such participation.

In order to minimize risk, investigators should use the safest procedures consistent with good research design and should make use of information or materials obtained for diagnostic or treatment purposes whenever feasible. For example, if a blood sample is needed, it should be obtained from samples drawn for diagnostic purposes whenever it is consistent with research requirements to do so.

Adequate measures should be taken to protect the privacy of children and their families, and to maintain the confidentiality of data. The adequacy of procedures for protecting confidentiality should be considered in light of the sensitivity of the data to be collected (i.e., the extent to which disclosure could reasonably be expected to be harmful or embarrassing).

Subjects should be selected in an equitable manner, avoiding overutilization of any one group of children based solely upon administrative convenience or availability of a population living in conditions of social or economic deprivation. The burdens of participation in research should be

equitably distributed among the segments of our society, no matter how large or small those burdens may be.

In addition to the foregoing requirements, research must satisfy the conditions of the following recommendations, as applicable.

RECOMMENDATION (3) RESEARCH THAT DOES NOT INVOLVE GREATER THAN MINIMAL RISK TO CHILDREN MAY BE CONDUCTED OR SUPPORTED PROVIDED AN INSTITUTIONAL REVIEW BOARD HAS DETERMINED THAT: (A) THE CONDITIONS OF RECOMMENDATION (2) ARE MET; AND (B) ADEQUATE PROVISIONS ARE MADE FOR ASSENT OF THE CHILDREN AND PERMISSION OF THEIR PARENTS OR GUARDIANS, AS SET FORTH IN RECOMMENDATIONS (7) AND (8).

Comment: If the IRB determines that proposed research will present no more than minimal risk to children, the research may be conducted or supported provided the conditions of Recommendation (2) are met and appropriate provisions are made for parental permission and the children's assent, as described in Recommendations (7) and (8) below. If the IRB is unable to determine that the proposed research will present no more than minimal risk to children, the research should be reviewed under Recommendations (4), (5) and (6), as applicable.

RECOMMENDATION (4) RESEARCH IN WHICH MORE THAN MINIMAL RISK TO CHILDREN IS PRESENTED BY AN INTERVENTION THAT HOLDS OUT THE PROSPECT OF DIRECT BENEFIT FOR THE INDIVIDUAL SUBJECTS, OR BY A

MONITORING PROCEDURE REQUIRED FOR THE WELL-BEING OF THE SUBJECTS, MAY BE CONDUCTED OR SUPPORTED PROVIDED AN INSTITUTIONAL REVIEW BOARD HAS DETERMINED THAT:

(A) SUCH RISK IS JUSTIFIED BY THE ANTICIPATED BENEFIT TO THE SUBJECTS;

(B) THE RELATION OF ANTICIPATED BENEFIT TO SUCH RISK IS AT LEAST AS FAVORABLE TO THE SUBJECTS AS THAT PRESENTED BY AVAILABLE ALTERNATIVE APPROACHES;

(C) THE CONDITIONS OF RECOMMENDATION (2) ARE MET; AND

(D) ADEQUATE PROVISIONS ARE MADE FOR ASSENT OF THE CHILDREN AND PERMISSION OF THEIR PARENTS OR GUARDIANS, AS SET FORTH IN RECOMMENDATIONS (7) AND (8).

Comment: The Commission emphasizes that the purely investigative procedures in research encompassed by Recommendation (4) should entail no more than minimal risk to children. Greater risk is permissible under this recommendation only if it is presented by an intervention that holds out the prospect of direct benefit to the individual subjects or by a procedure necessary to monitor the effects of such intervention in order to maintain the well-being of these subjects (e.g., obtaining samples of blood or spinal fluid in order to determine drug levels that are safe and effective for the subjects). Such risk is acceptable, for example, when all available treatments for a serious illness or disability have been tried without success, and the remaining option is a new intervention under investigation. The expectation of success should be scientifically sound to justify undertaking whatever

risk is involved. It is also appropriate to involve children in research when accepted therapeutic, diagnostic or preventive methods involve risk or are not entirely successful, and new biomedical or behavioral procedures under investigation present at least an equally favorable risk-benefit ratio. The IRB should evaluate research protocols of this sort in the same way that comparable decisions are made in clinical practice. It should compare the risk and anticipated benefit of the intervention under investigation (including the monitoring procedures necessary for care of the child) with those of available alternative methods for achieving the same goal, and should also consider the risk and possible benefit of attempting no intervention whatsoever.

To determine the overall acceptability of the research, the risk and anticipated benefit of activities described in a protocol must be evaluated individually as well as collectively, as is done in clinical practice. Research protocols meeting the criteria regarding risk and benefit may be conducted or supported provided the conditions of Recommendation (2) are fulfilled and the requirements for assent of the children and for permission and participation of their parents or guardians, as set forth in Recommendations (7) and (8), will be met. If the research also includes a purely investigative procedure presenting more than minimal risk, the research should be reviewed under Recommendation (5) with respect to such procedure.

RECOMMENDATION (5) RESEARCH IN WHICH MORE THAN MINIMAL RISK TO CHILDREN IS PRESENTED BY AN INTERVENTION THAT DOES NOT HOLD OUT THE PROSPECT OF DIRECT BENEFIT FOR THE INDIVIDUAL SUBJECTS,

OR BY A MONITORING PROCEDURE NOT REQUIRED FOR THE WELL-BEING OF THE SUBJECTS, MAY BE CONDUCTED OR SUPPORTED PROVIDED AN INSTITUTIONAL REVIEW BOARD HAS DETERMINED THAT:

(A) SUCH RISK REPRESENTS A MINOR INCREASE OVER MINIMAL RISK;

(B) SUCH INTERVENTION OR PROCEDURE PRESENTS EXPERIENCES TO SUBJECTS THAT ARE REASONABLY COMMENSURATE WITH THOSE INHERENT IN THEIR ACTUAL OR EXPECTED MEDICAL, PSYCHOLOGICAL OR SOCIAL SITUATIONS, AND IS LIKELY TO YIELD GENERALIZABLE KNOWLEDGE ABOUT THE SUBJECTS' DISORDER OR CONDITION;

(C) THE ANTICIPATED KNOWLEDGE IS OF VITAL IMPORTANCE FOR UNDERSTANDING OR AMELIORATION OF THE SUBJECTS' DISORDER OR CONDITION;

(D) THE CONDITIONS OF RECOMMENDATION (2) ARE MET; AND

(E) ADEQUATE PROVISIONS ARE MADE FOR ASSENT OF THE CHILDREN AND PERMISSION OF THEIR PARENTS OR GUARDIANS, AS SET FORTH IN RECOMMENDATIONS (7) AND (8).

Comment: An IRB must determine that three special criteria are met in order to approve research presenting more than minimal risk but no direct benefit to the individual subjects. First, the increment in risk must be no more than a minor increase over minimal risk. The IRB should consider the degree of risk presented by the research from at least the following four perspectives: a common-sense estimation of the risk; an estimation

based upon investigators' experience with similar interventions or procedures; any statistical information that is available regarding such interventions or procedures; and the situation of the proposed subjects. Second, the research activity must be commensurate with (i.e., reasonably similar to) procedures that the prospective subjects and others with the specific disorder or condition ordinarily experience (by virtue of having or being treated for that disorder or condition). Finally, the research must hold out the promise of significant benefit in the future to children suffering from or at risk for the disorder or condition (including, possibly, the subjects themselves). If necessary, the advice of scientific consultants should be obtained to assist in determining whether the research is likely to provide knowledge of vital importance to understanding the etiology or pathogenesis, or developing methods for the prevention, diagnosis or treatment, of the disorder or condition affecting the subjects.

The requirement of commensurability of experience should assist children who can assent to make a knowledgeable decision about their participation in research, based on some familiarity with the intervention or procedure and its effects. More generally, commensurability is intended to assure that participation in research will be closer to the ordinary experience of the subjects. The use of procedures that are familiar or similar to those used in treatment of the subjects should not, however, be used as a major justification for their participation in research, but rather as one of several criteria regarding the acceptability of such participation.

In addition to these special criteria, the IRB should assure that the conditions of Recommendation (2) are fulfilled and the requirements for assent of the children and permission and participation of their parents or guardians, as set forth in Recommendations (7) and (8), will be met. If the proposed research includes an intervention or procedure from which the subjects may derive direct benefit, it should also be reviewed under Recommendation (4) with respect to that intervention or procedure.

RECOMMENDATION (6) RESEARCH THAT CANNOT BE APPROVED BY AN INSTITUTIONAL REVIEW BOARD UNDER RECOMMENDATIONS (3), (4) AND (5), AS APPLICABLE, MAY BE CONDUCTED OR SUPPORTED PROVIDED AN INSTITUTIONAL REVIEW BOARD HAS DETERMINED THAT THE RESEARCH PRESENTS AN OPPORTUNITY TO UNDERSTAND, PREVENT OR ALLEVIATE A SERIOUS PROBLEM AFFECTING THE HEALTH OR WELLFARE OF CHILDREN AND, IN ADDITION, A NATIONAL ETHICAL ADVISORY BOARD AND, FOLLOWING OPPORTUNITY FOR PUBLIC REVIEW AND COMMENT, THE SECRETARY OF THE RESPONSIBLE FEDERAL DEPARTMENT (OR HIGHEST OFFICIAL OF THE RESPONSIBLE FEDERAL AGENCY) HAVE DETERMINED EITHER (A) THAT THE RESEARCH SATISFIES THE CONDITIONS OF RECOMMENDATIONS (3), (4) AND (5), AS APPLICABLE, OR (B) THE FOLLOWING:

(I) THE RESEARCH PRESENTS AN OPPORTUNITY TO UNDERSTAND) PREVENT OR ALLEVIATE A SERIOUS PROBLEM AFFECTING THE HEALTH OR WELFARE OF CHILDREN;

(II) THE CONDUCT OF THE RESEARCH WOULD NOT VIOLATE THE PRINCIPLES OF RESPECT FOR PERSONS, BENEFICENCE AND JUSTICE;

(III) THE CONDITIONS OF RECOMMENDATION (2) ARE MET; AND

(IV) ADEQUATE PROVISIONS ARE MADE FOR ASSENT OF THE CHILDREN AND PERMISSION OF THEIR PARENTS OR GUARDIANS, AS SET FORTH IN RECOMMENDATIONS (7) AND (8).

Comment: If an IRB is unable for any reason to determine that proposed research satisfies the conditions of Recommendations (3), (4) and (5), as applicable, the IRB may nevertheless certify the research for review and possible approval by a national ethical advisory board and the Secretary of the responsible department. Such review is contingent upon an IRB's determination that the research presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children. Thereafter, the research should be reviewed by the national board and Secretary, with opportunity for public comment, to determine whether the conditions of Recommendations (3), (4) and (5), as applicable, are satisfied, or, alternatively, the research is justified by the importance of the knowledge sought and would not contravene principles of respect for persons, beneficence and justice that underlie these recommendations. In the latter instance, commencement of the research should be delayed pending Congressional notification and a reasonable opportunity for Congress to take action regarding the proposed research.

The provision for national review and approval under Recommendations (3), (4) and (5) is intended to fit the situation where an IRB has difficulty in applying those recommendations but considers the research of suf-

ficient importance to warrant national review. Such difficulty may be resolved by a determination on the national level pursuant to Recommendation (6)(A) that the research does satisfy the conditions of the applicable earlier recommendations. Alternatively, the national review may determine either that the research satisfies the conditions of Recommendation (6)(B) or that it should not be conducted.

The Commission believes that only research of major significance, in the presence of a serious health problem, would justify the approval of research under Recommendation (6)(B). The problem addressed must be a grave one, the expected benefit should be significant, the hypothesis regarding the expected benefit must be scientifically sound, and an equitable method should be used for selecting subjects who will be invited to participate. Finally, appropriate provisions should be made for assent of the subjects and permission and participation of parents or guardians.

RECOMMENDATION (7) IN ADDITION TO THE DETERMINATIONS REQUIRE UNDER THE FOREGOING RECOMMENDATIONS, AS APPLICABLE, THE INSTITUTIONAL REVIEW BOARD SHOULD DETERMINE THAT ADEQUATE PROVISIONS ARE MADE FOR: (A) SOLICITING THE ASSENT OF THE CHILDREN (WHEN CAPABLE) AND THE PERMISSION OF THEIR PARENTS OR GUARDIANS; AND, WHEN APPROPRIATE, (B) MONITORING THE SOLICITATION OF ASSENT AND PERMISSION, AND INVOLVING AT LEAST ONE PARENT OR GUARDIAN IN THE CONDUCT OF THE RESEARCH. A CHILD'S OBJECTION TO PARTICIPATION IN RESEARCH SHOULD BE BINDING UNLESS THE INTERVENTION HOLDS OUT

A PROSPECT OF DIRECT BENEFIT THAT IS IMPORTANT TO THE HEALTH OR WELL-BEING OF THE CHILD AND IS AVAILABLE ONLY IN THE CONTEXT OF THE RESEARCH.

Comment: The Commission uses the term parental or guardian "permission," rather than "consent," in order to distinguish what a person may do autonomously (consent) from what one may do on behalf of another (grant permission). Parental permission normally will be required for the participation of children in research. In addition, assent of the children should be required when they are seven years of age or older. The Commission uses the term "assent" rather than "consent" in this context, to distinguish a child's agreement from a legally valid consent.

Parental or guardian permission, as used in this recommendation, refers to the permission of parents, legally appointed guardians, and others who care for a child in a reasonably normal family setting. The last category might include, for example, step-parents or relatives such as aunts, uncles or grandparents who have established a continuing, close relationship with the child. Recommendation (8) describes circumstances in which the IRB may determine that the permission of parents or guardians is not appropriate because of the nature of the subject under investigation (e.g., contraception, drug abuse) or because of a failure in the relationship with the child (e.g., child abuse, neglect).

Parental or guardian permission should reflect the collective judgment of the family that an infant or child may participate in research. There

are some research projects for which documented permission of one parent or guardian should be sufficient, such as research involving no more than minimal risk (as described in Recommendation (3)), or research in which risks or discomforts are related to a therapeutic, diagnostic or preventive intervention (as described in Recommendation (4)). In such cases, it may be assumed that the person giving formal permission is reflecting a family consensus. For research that is described in Recommendations (5) and (6), the permission of both parents should be documented unless one parent is deceased, unknown, incompetent or not reasonably available, or the child has a guardian or belongs to a single-parent family (i.e., when only one person has legal responsibility for the care, custody and financial support of the child). The IRB should determine for each project whether permission of one or both parents should be required, a substitute mechanism may be used, or the provision may be waived. In making such determination, the IRB should consider the nature of the activities described in the research protocol and the age, status and condition of the subjects.

The IRB should assure that children who will be asked to participate in research described in Recommendation (5) are those with good relationships with their parents or guardians and their physician, and who are receiving care in supportive surroundings. Projects approved under Recommendations (4) and (6) may also require scrutiny of this sort. The IRB may wish to appoint someone to assist in the selection of subjects and to review the quality of interaction between parents or guardian and child. A member of the board or a consultant such as the child's pediatrician, a

psychologist, a social worker, a pediatric nurse, or other experienced and perceptive person would be appropriate. The IRB should be particularly sensitive to the difficulties surrounding permission when the investigator is the treating physician to whom the parents or guardian may feel an obligation.

Because of the dependence of infants, the traditional role of parents as protectors, and the general authority of parents to determine the care and upbringing of their children, the IRB may determine that small children should participate in certain research only if the parents or guardians participate themselves by being present during some or all of the conduct of the research. This role will vary according to the nature of the research, the risk involved, the extent to which the research entails possibly disturbing deviations from normal routine, and the age and condition of the children. As a general rule, when infants participate in research that may cause physical discomfort or emotional stress and involves a significant departure from normal routine, a parent or guardian should be present. However, if discomfort arises only as a result of therapeutic interventions that must continue over a considerable period of time, the continual presence of parents need not be required. Parental presence during the conduct of much behavioral research may not be feasible or warranted, especially with older children. Generally, parents or guardians should be sufficiently involved in the research to understand its effects on their children and be able to intervene, if necessary.

The Commission believes that children who are seven years of age or older are generally capable of understanding the procedures and general purpose of research and of indicating their wishes regarding participation. Their assent should be required in addition to parental permission. However, if any child over six years of age is incapacitated so that he or she cannot reasonably be consulted, then parental permission should be sufficient, as it is for infants. The objection of a child of any age to participation in research should be binding except as noted below.

If the research protocol includes an intervention from which the subjects might derive significant benefit to their health or welfare, and that intervention is available only in a research context, the objection of a small child may be overridden. Such would be the case, for example, with a new drug that is not approved by the Food and Drug Administration for general distribution until safety and efficacy have been demonstrated in controlled clinical trials. Access to a drug under investigation generally requires participation in the research. Similar restrictions may be placed on other innovative therapies as a precaution. As children mature, their ability to perceive and act in their own best interest increases; thus, their wishes with respect to such research should carry increasingly more weight. When school-age children disagree with their parents regarding participation in such research, the IRB may wish to have a third party discuss the matter with all concerned and be present during the consent process. Although parents may legally override the objections of school-age children in such cases, the burden of that decision becomes heavier in relation to the maturity of the particular child.

Disclosure requirements for assent and permission are the same as those for informed consent. Similarly, children and parents or guardians should be free from duress. In order to assure understanding and freedom of choice, the IRB may determine that there is a need for an advocate to be present during the decision-making process. The need for third-party involvement in this process will vary according to the risk presented by the research and the autonomy of the subjects. The advocate should be an individual who has the experience and perceptiveness to fulfill such a role and who is not related in any way (except in the role as advocate or member of the IRB) to the research or the investigators.

Finally, the IRB should pay particular attention to the explanation and consent form, if any, to assure that appropriate language is used.

RECOMMENDATION (8) IF THE INSTITUTIONAL REVIEW BOARD DETERMINES THAT A RESEARCH PROTOCOL IS DESIGNED FOR CONDITIONS OR A SUBJECT POPULATION FOR WHICH PARENTAL OR GUARDIAN PERMISSION IS NOT A REASONABLE REQUIREMENT TO PROTECT THE SUBJECTS, IT MAY WAIVE SUCH REQUIREMENT PROVIDED AN APPROPRIATE MECHANISM FOR PROTECTING THE CHILDREN WHO WILL PARTICIPATE AS SUBJECTS IN THE RESEARCH IS SUBSTITUTED. THE CHOICE OF AN APPROPRIATE MECHANISM SHOULD DEPEND UPON THE NATURE AND PURPOSE OF THE ACTIVITIES DESCRIBED IN THE PROTOCOL, THE RISK AND ANTICIPATED BENEFIT TO THE RESEARCH SUBJECTS, AND THEIR AGE, STATUS AND CONDITION.

Comment: Circumstances that would justify modification or waiver of the requirement for parental or guardian permission includes: (1) research designed

to identify factors related to the incidence or treatment of certain conditions in adolescents for which, in certain jurisdictions, they legally may receive treatment without parental consent; (2) research in which the subjects are "mature minors" and the procedures involved entail essentially no more than minimal risk that such individuals might reasonably assume on their own; (3) research designed to understand and meet the needs of neglected or abused children, or children designated by their parents as "in need of supervision"; and (4) research involving children whose parents are legally or functionally incompetent.

There is no single mechanism that can be substituted for parental permission in every instance. In some cases the consent of mature minors should be sufficient. In other cases court approval may be required. The mechanism invoked will vary with the research and the age, status and condition of the prospective subjects.

A number of states have specific legislation permitting minors to consent to treatment for certain conditions (e.g., pregnancy, drug addiction, venereal diseases) without the permission (or knowledge) of their parents. If parental permission were required for research about such conditions, it would be difficult to develop improved methods of prevention and therapy that meet the special needs of adolescents. Therefore, assent of such mature minors should be considered sufficient with respect to research about conditions for which they have legal authority to consent on their own to treatment. An appropriate mechanism for protecting such subjects might be to require that a clinic nurse or physician, unrelated to the research,

explain the nature and the purpose of the research to prospective subjects, emphasizing that participation is unrelated to provision of care.

Another alternative might be to appoint a social worker, pediatric nurse, or physician to act as surrogate parent when the research is designed, for example, to study neglected or battered children. Such surrogate parents would be expected to participate not only in the process of soliciting the children's cooperation but also in the conduct of the research, in order to provide reassurance for the subjects and to intervene or support their desires to withdraw if participation becomes too stressful.

RECOMMENDATION (9) CHILDREN WHO ARE WARDS OF THE STATE SHOULD NOT BE INCLUDED IN RESEARCH APPROVED UNDER RECOMMENDATIONS (5) OR (6) UNLESS SUCH RESEARCH IS: (A) RELATED TO THEIR STATUS AS ORPHANS, ABANDONED CHILDREN, AND THE LIKE; OR (B) CONDUCTED IN A SCHOOL OR SIMILAR GROUP SETTING IN WHICH THE MAJORITY OF CHILDREN INVOLVED AS SUBJECTS ARE NOT WARDS OF THE STATE. IF SUCH RESEARCH IS APPROVED, THE INSTITUTIONAL REVIEW BOARD SHOULD REQUIRE THAT AN ADVOCATE FOR EACH CHILD BE APPOINTED, WITH AN OPPORTUNITY TO INTERCEDE THAT WOULD NORMALLY BE PROVIDED BY PARENTS.

Comment: It is important to learn more about the effects of various settings in which children who are wards of the state may be placed, as well as about the circumstances surrounding child abuse and neglect, in order to improve the care that is provided for such children by the community. Also, it is important to avoid embarrassment or psychological harm that might re-

sult from excluding wards of the state from research projects in which their peers in a school, camp or other group setting will be participating. Provision must be made to permit the conduct of such studies in ways that will protect the children involved, even though no parents or guardians are available to act in their behalf.

To this end, the IRB reviewing such research should evaluate the reasons for including wards of the state as research subjects and assure that such children are not the sole participants in a research project unless the research is related to their status as orphans, abandoned children, and the like. The IRB should require, as a minimum, that an advocate for each child be appointed to intercede, when appropriate, on the child's behalf. The IRB may also require additional protections, such as prior court approval.

RECOMMENDATION (10) CHILDREN WHO RESIDE IN INSTITUTIONS FOR THE MENTALLY INFIRM OR WHO ARE CONFINED IN CORRECTIONAL FACILITIES SHOULD PARTICIPATE IN RESEARCH ONLY IF THE CONDITIONS REGARDING RESEARCH ON THE INSTITUTIONALIZED MENTALLY INFIRM OR ON PRISONERS (AS APPLICABLE) ARE FULFILLED IN ADDITION TO THE CONDITIONS SET FORTH HEREIN.

NOTE: The foregoing recommendations were adopted unanimously with the exception of Recommendation (5), from which Commissioners Cooke and Turtle dissented.

CHAPTER 1. WHY CHILDREN ARE INVOLVED AS RESEARCH SUBJECTS

The argument in favor of conducting research involving children rests on a combination of two factors: the absence, in numerous instances, of a suitable alternative population of research subjects, and the consequences of not conducting research involving children in those instances. Such consequences might include the perpetuation of harmful practices, the introduction of untested practices, and the failure to develop new treatments for diseases that affect children.

The lack of an alternative population. Possible alternative populations for research involving children are animals and adult humans, but there are limitations to both. No animal model has been found for a number of diseases that affect children or adults, such as cystic fibrosis and Down's syndrome. Furthermore, animal models are inappropriate for studying certain processes that are uniquely human, such as development of speech and cognitive functions. The amount of brain development that occurs in humans after birth has no parallel in the animal world, and studies of such development must be done in humans. Even normal biological measures or functions in animals, such as blood sugar levels or drug metabolism, are not consistent from one animal species to another and cannot be extrapolated to humans; thus, it eventually becomes necessary to examine the function in human subjects.

There are also no adult models for disorders that are unique to childhood, such as hyaline membrane disease, erythroblastosis fetalis, and in-

fantile autism. Studies of normal development and of such phenomena as the "critical period" and child–parent interaction, by their very nature, can be conducted only in children. Research involving children is important, also, because both in sickness and in health, the child is not a small adult, and, consequently, results of studies on adults cannot be directly extrapolated to children. For example, administration of intravenous fluids to infants or children based on adult requirements would be disastrous, providing either too much or too little of various substances. It was only by studying normal constituents of body fluids and their metabolism in normal infants and children that requirements for specific age groups could be identified and intravenous fluid therapy could be utilized. A more obvious difference between children and adults is in their food requirements, not only in type and nutrients but in calories -- an infant provided calories based on adult requirements would soon starve. An assumption that drugs which are useful and safe in adults are effective and safe in children, and that it is necessary only to adjust dosage on the basis of body weight or surface area, is likewise not only fallacious but also dangerous, as exemplified by the examples of chloramphenicol and sulfisoxazole cited below.

Just as children are not small adults, it is also erroneous to consider all children as a homogeneous category. A child is a developing and constantly changing organism: the newborn infant, in its body composition and metabolism as well as its response to drugs and stimuli, differs from the toddler; the early school–age child differs from the pubertal adolescent.

Growth imposes its own special set of constraints and challenges. Consequently there is a need not only for research on children, but across the full spectrum of childhood.

The consequences of not involving children in research. Prohibiting children's participation in research would impede innovative efforts to develop new treatments for diseases that affect children, while research to prevent or treat adult diseases would continue. Even research efforts on adult diseases would be hampered, as many of the most common and serious diseases that affect adults, such as atherosclerosis, probably have their origins in childhood. Many adults with cystic fibrosis or juvenile diabetes mellitus would not be alive today without the benefit of research that involved children.

Prohibiting children's participation in research would also result in the introduction of innovative practices without benefit of research or evaluation. The history of misadventures from such untested and unvalidated innovation argues as strongly for research as does the failure to innovate that would result from impeding research. For example, introduction of the practice of supplying oxygen in high concentrations to premature infants with hyaline membrane disease to enable them to survive was successful in many cases. However, the price paid for this course of action was the blinding of thousands of children due to retrolental fibroplasia before it was found that high oxygen levels had a toxic effect on the blood vessels supplying the retina in premature infants.

Another iatrogenic disease whose cause went undetected for years was the "gray-baby syndrome," which resulted in the death of many newborn infants until a research project (terminated early because the results were so clear) demonstrated that the drug chloramphenicol was responsible. This drug was an effective and generally safe antibiotic in adults, and it had been extended to use in children and infants without special study. The use of chloramphenicol for newborn infants was quickly abandoned when research demonstrated that poisoning occurred from the toxic levels of the drug that accumulated, because the enzyme system that metabolizes the drug is inadequately developed in the newborn. Another antibacterial agent, sulfisoxazole, was also abandoned for use in newborn infants after it was shown to cause severe neural injury (kernicterus) and cerebral palsy by binding to serum albumin so that bilirubin could not be bound and was free to damage nerve cells. Use of Vitamin K to prevent hemorrhagic disease of the newborn was a major advance, but its use in excessive doses also produced many cases of kernicterus due to its destruction of red blood cells with resultant increase in bilirubin levels, until research demonstrated this danger and established a safe and effective dose.

Even such a seemingly simple matter as feeding and hydrating a newborn infant has, without proper research, been subject to faddism and untested innovation. Because premature infants tend to look edematous, for years it was routine practice to give them no food or water for 48 to 72 hours after birth, with a high incidence of brain damage ensuing from an excessive amount of sodium in the blood of the few who survived the drying out procedure. Despite abandonment of such practices and conduct of much

research, there still exists no general agreement on when to begin feedings for premature infants and how much of what to give.

Another standard treatment, whose adverse effects continue to be manifested 20 to 30 years later in the form of radiation-induced thyroid cancer, was prophylactic radiation to the neck and chest, used in the 1940's to shrink an infant's thymus. This treatment was administered on the hypothesis that it would prevent the sudden infant death syndrome, with no basis in fact other than the observation that many victims of the syndrome had an enlarged thymus at autopsy.

Nonmedical practices also may have harmful effects, and be equally ill-founded but firmly entrenched, and modifiable only by research. For example, only when research was conducted were the ill effects of the routine practices of institutionalization on child development demonstrated, and changes in practices initiated.

There are other standard practices whose effects remain matters of speculation. For example, concern is currently being expressed over the practice of isolating premature infants from their parents in intensive care nurseries, based on evidence from research that shows the importance of very early physical contact between the mother and infant for the establishment of parental bonding, and the significantly higher incidence of child abuse of premature infants.

In sum, there is historical evidence of undesirable consequences resulting from the introduction of innovations in pediatric practice without

adequate research, and there are many areas of inquiry that are important for improving the health and well-being of children (and adults), and for which there is no research population other than children.

CHAPTER 2. THE NATURE AND EXTENT OF RESEARCH INVOLVING CHILDREN

Children participate as subjects in a wide variety of research undertakings. A survey of government agencies' research activities involving children during fiscal year 1975 provides an indication of the diversity of these projects, and may be considered a reflection of nongovernment-supported research with children as well. This survey is based on reports provided to the Commission by components of DHEW and on information compiled by the Social Research Group of George Washington University. It should be noted that the definitions of "child" vary among agencies (sometimes including individuals through age 25); similarly, some agencies include conferences, literature searches and training projects as research involving children, while others use a narrower definition, referring only to projects involving children directly as subjects. Thus, the data are not compatible.

Of the numerous departments and agencies conducting or supporting research with children, DHEW supports the largest amount (see pages 38 and 39). Within DHEW, the largest dollar amount for biomedical research involving children is provided by the National Institutes of Health; the largest amount of nonbiomedical research supported by DHEW is funded by the Education Division. Although the National Institute of Child Health and Human Development (NICHD) is identified most closely with research on children, virtually all the institutes have research programs that directly involve them.

Much of the research conducted and supported by NICHD, in contrast to the categorical disease institutes, involves the study of normal and abnormal

physical, cognitive, behavioral and social development. Examples of such research include studies of normal and abnormal development of cellular immunity, developmental pharmacology research to identify age-related changes in metabolism of endogenous substances and drugs by infants and children, evaluations of mental development of malnourished children, attempts to develop or improve methods for predicting mature stature from assessment of skeletal maturity at various ages, analyses of learning patterns of children and the impact of preschool educational experiences, intense studies of acquisition and development of language skills, and studies of the relation of parental authority style to development of responsibility and independence in children. Other research focuses on determining the causes and prevention of such conditions as mental retardation, the sudden infant death syndrome, low birth weight, and accidents. Research of this type supported by NICHD has included evaluation of the effects of differing types of intervention on mental retardation associated with malnutrition, attempts to prevent mental retardation in children of retarded mothers by infant stimulation and developmental programs, development of continuous positive airway pressure ventilation as treatment for newborns with respiratory distress syndrome, studies of the incidence of congenital infections in newborn infants and their role as a cause of low birth weight and mental retardation or death, and assessments of the relation of sleep disturbance or cardio-respiratory dysfunction as well as viral infection to the sudden infant death syndrome.

Research supported by the National Institute of Dental Research and involving children consists primarily of clinical trials, usually in schools,

of techniques to reduce tooth decay. Such techniques include fluoride mouthrinses, mechanical plaque removal from teeth, and sealants. Other studies range from those involving children only as sources of biologic materials for study (saliva, plaque), or comparing behavioral responses to an initial visit to the dentist after various means of orientation and preparation, to developing new surgical and orthodontic rehabilitative procedures for cleft palate and other craniofacial birth defects.

Examples of child research supported by the National Institute of General Medical Sciences include follow-up studies of children given various drugs as newborns or whose mothers received certain drugs during pregnancy, developing new methods of instrumentation for procedures such as cardiac catheterization, devising noninvasive techniques of sampling or monitoring (salivary drug levels, skin oxygen electrode), and conducting eye exams and constructing pedigrees to ascertain the genetics of refractive errors.

The focus of research involving children that is conducted and supported by the National Institute of Neurological and Communicative Disorders and Stroke is on perinatal factors associated with cerebral palsy and mental retardation, discovering the enzymatic basis of hereditary disorders of the nervous system and in certain instances attempting enzyme replacement therapy, and determining the causes and evaluating treatments of such conditions as learning disability, dyslexia, stuttering and aphasia. Children are also involved with adults in NINCDS studies of the etiology and treatment of the various epilepsies, investigations of slow virus infections of the central

nervous system, management of spinal cord injuries, and development of improved sensory aids for the handicapped.

The National Cancer Institute does not target its programs toward children as a group, but many children are included in the research protocols for particular cancers. The research involves testing of various therapies to develop improved treatment, and evaluating new diagnostic methods.

The National Eye Institute conducts and supports a number of studies of eye disorders involving children. These include evaluation of medical and surgical treatments for congenital and juvenile glaucoma, development of improved diagnostic procedures for juvenile macular degeneration and retinitis pigmentosa, use of new techniques to evaluate eye movements, use of color TV for color vision screening, and research on the perceptual components of reading.

A large number of studies of the National Heart, Lung and Blood Institute involve children. Some involve minor intervention, such as studies of blood pressure and blood lipids in large populations of school children to obtain information on prevalence of hypertension and of certain risk factors (hyperlipidemia). Other noninterventional studies include evaluating risk factors in children whose parents have heart disease, obtaining longitudinal information on blood pressure determinations of children, and studying the long term natural history of congenital heart defects by following the status of children with the defects over many years. The Institute also supports studies of effective therapy for pediatric lung disorders, including respiratory distress syndrome, cystic fibrosis, and bronchiolitis. Blood disorder

research involving children includes study of Factor VIII inhibitors in hemophilia (using a sample of the child's blood obtained at routine clinic visits), recording the incidence and source of infection in children with sickle cell disease, assessing the mental and emotional development of children with sickle cell disease, recording sexual maturation of sickle cell patients compared to their unaffected siblings, identifying the effects of a tutoring program on school attendance and performance of sickle cell patients, and evaluation of prophylactic penicillin to reduce the incidence of infection in patients with sickle cell disease.

Children's research programs supported by the National Institute of Allergy and Infectious Diseases focus on asthma and allergic conditions, immunodeficiency states, and infectious diseases. Included in the broad range of activities are studies designed to develop or improve tests to specifically diagnose allergy to various agents at different ages; a double-blind clinical trial of use of transfer factor as therapy for certain immuno-deficiency states; development and clinical testing in infants and children of vaccines against Hemophilus influenza type B, meningococcus, pneumococcus, streptococcus, and several viruses; identification from stool samples of the virus responsible for a large portion of the cases of infant diarrhea; and epidemiologic studies of a wide variety of infections.

Children are usually involved with adults in studies of the National Institute of Arthritis, Metabolism, and Digestive Diseases, although some of the disorders studied (such as juvenile rheumatoid arthritis or juvenile diabetes) strike first during childhood. Examples of the studies which

include children are comparisons of new drugs or various schedules of administration in treating lupus nephritis, evaluation of dietary modification as therapy for certain genetic defects (such as galactosemia) or for uremia or deficiency diseases, comparison of growth and sexual development as well as psychosocial function with peritoneal dialysis as opposed to hemodialysis in chronic renal failure, and evaluation of the physical and behavioral effects of hypertransfusion to maintain hemoglobin level at 12 grams rather than 9 grams in patients with Cooley's anemia.

The National Institute of Environmental Health Sciences supports a variety of research on methods of diagnosing, treating and preventing lead poisoning in children, as well as the extent and consequences of the condition. Similar types of studies are supported for other environmental hazards, such as mercury, cadmium, sulfur dioxide, and various pollutants. These studies involve such procedures as developing assays to measure lead in one drop of blood or one hair and applying them in large screening programs, developing and studying the effects of various treatments to remove lead from the body, correlating lead levels in shed teeth with neuropsychologic test performance of children, or longitudinal testing of pulmonary function of school children in cities with different levels of pollutants. A number of epidemiologic studies have examined the relation of such factors as prenatal x-ray exposure to the development of childhood cancer, pesticide exposure to chromosome damage, or exposure to various known toxins to mental retardation.

The Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), through its three component institutes (NIMH, NIDA, NIAAA), serves as the focus of DHEW behavioral research, although many of its activities are biomedical as well. The National Institute of Mental Health conducts or supports studies of developmental processes of the child and the family, child abuse, early diagnosis of dysfunction, and intervention programs to promote healthy emotional and cognitive growth. Examples include longitudinal studies of mother-infant interactions, studies of the effect of obstetric medication on infant perceptual functioning, effects of maternal behavior on infant learning, behavioral identification of the hyperkinetic syndrome, effects of methylphenidate and amphetamine on hyperactive children and their influence on urinary dopamine metabolites, genetic studies of the offspring of schizophrenics, studies of the delivery of psychiatric screening and services to children, and investigation of factors contributing to juvenile delinquency.

The National Institute on Drug Abuse targets a significant portion of its research program toward children. Much of this research involves development and evaluation of education programs for children regarding drug abuse, with special attention to appealing to elementary school children and minorities. Other research involves study of attitudes among children toward drug use, investigation of the extent of drug use by children, and assessment of the effects of maternal narcotic addiction on the fetus and newborn infant. Studies comparing various treatment methods and the efficacy of treatment for the young drug abuser are also supported.

The National Institute on Alcohol Abuse and Alcoholism supports some research involving children. These projects generally involve experimental education programs for children on alcohol use and abuse, study of the social and cultural antecedents of alcoholism, evaluation of treatment programs for the very young alcoholic, studies of the effects of maternal alcohol use during pregnancy on the newborn and on family health, and surveys of the nature and extent of alcohol use among children of various ages and socioeconomic groups.

Other agencies within the Public Health Service also conduct or support research involving children. Although its primary mission is providing health services, the Maternal and Child Health Service of the Bureau of Community Health Services, Health Services Administration, devotes considerable effort to research related to its programs. In addition to studies of pregnancy and childbirth, the MCHS supports studies of means of improving patient compliance with physicians' directions, the impact of improved health insurance coverage of maternity care on infant mortality, disability outcomes for childhood amputees, using a trained mother as therapist in cerebral palsy therapy, and numerous evaluations of MCHS programs and projects. The largest portion of research involving children that is conducted or supported by the Center for Disease Control is the development, testing, and evaluation of vaccines. Epidemiologic studies of the CDC often involve children, such as in studies of the incidence of childhood cancer in relation to arsenic levels near a smelter, or analysis of interpersonal contacts among patients with Hodgkin's disease as a possible factor in its epidemiology. Surveillance activities

may involve children, as in the study indicating that an outbreak of Reye's syndrome closely followed an epidemic of influenza B virus infections, and in the birth defects monitoring program (which involves children only by utilizing newborn infants' hospital discharge summaries). Within the Food and Drug Administration, the Bureau of Biologics supports some research involving testing of vaccines in children; pharmaceutical testing in children is regulated but not conducted or supported by the FDA.

Some DHEW components outside the Public Health Service also conduct or support research involving children. Three divisions of the Office of Human Development (Office of Child Development, Office of Youth Development, and Rehabilitation Services Administration) have child research programs. Research in the OCD Head Start program includes studies of the effects of different ratios of caregivers to children in child care centers, evaluation of progress made by children in different types of Head Start programs, and analysis of a family oriented "Home Start" program in rural areas. OCD also supports studies related to determining causes of child abuse and neglect and developing intervention programs to assist parents of such children, studies of attempts to improve the interface of parents with schools and social institutions to assist the developing child, and research on the impact of residential institutional experiences on child development. The research supported by OYD focuses on analysis of causes and various support services for runaway youths. The RSA supports research on rehabilitative techniques for children with cerebral palsy, mental retardation, or other disabling conditions.

Another DHEW component, the Social and Rehabilitation Service, supports research with children related to child welfare services, child support, and health services. Studies involve developing methods to identify early warning signals of child abuse and neglect, assessing the cost-effectiveness of different types of day care, developing alternative approaches to foster care and adoptions, evaluation of income maintenance programs and their effect on children, assessing the impact of family planning services on reducing the number of unwanted births (especially to teenagers), and evaluating the cost-effectiveness of various methods of providing Early and Periodic Screening, Diagnosis and Treatment services. (In 1977 a departmental reorganization abolished the Social and Rehabilitation Service, and most of its programs have been transferred to the Office of Human Development or the Health Care Financing Administration.)

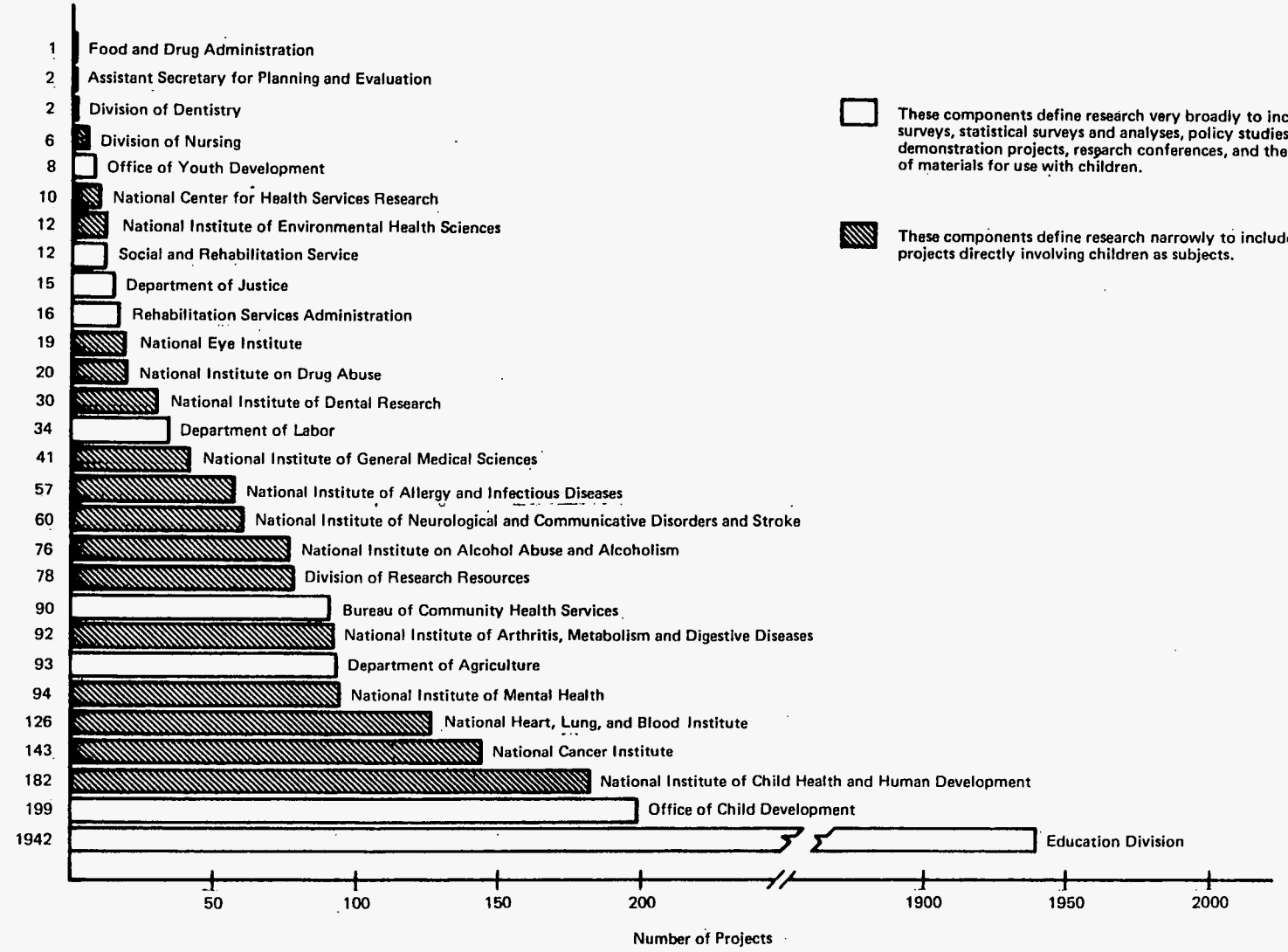
The largest amount of research involving children in DHEW, both in terms of funds and number of projects, is conducted and supported by the Office of Education and the National Institute of Education. This research is intended to improve the quality of education by developing and demonstrating the effectiveness of new approaches to education. To the extent that changes in education techniques or practices are considered behavior research, these activities fall within the mandate of the Commission. Examples of the types of research supported include studies of the multiunit school system as a means to reorganize elementary schools to provide more individual attention, evaluation of a program combining

on-the-jobexperience with academic learning, developing improved methods for acquisition of basic skills as well as better means to assess achievement, evaluation of various primary education programs (Project Follow Through) for their ability to maintain gains achieved by children in Project Head Start, developing improved techniques for early childhood education and teaching handicapped children, and research in the Right-To-Read program designed to develop effective remediation procedures for children who are functionally illiterate.

Departments of the federal government other than DHEW also conduct or support research involving children. The Department of Agriculture supports research through land grant institutions and the Agriculture Extension Service on childhood nutrition and growth, education, and child development. The Department of Justice, through the Law Enforcement Assistance Administration and its Office of Juvenile Justice and Delinquency Prevention, conducts and supports research relating to juvenile delinquency and rehabilitation of young offenders. The Department of Labor supports experimental programs to improve vocational education and job opportunities for adolescents, with emphasis on minorities, the disadvantaged and the handicapped. Finally, physicians and other personnel in the military hospitals of the Department of Defense conduct a wide variety of biomedical and behavioral research involving children.

Figures 1 and 2 show the number and proportion of federally sponsored research projects supported by the various departments and agencies.

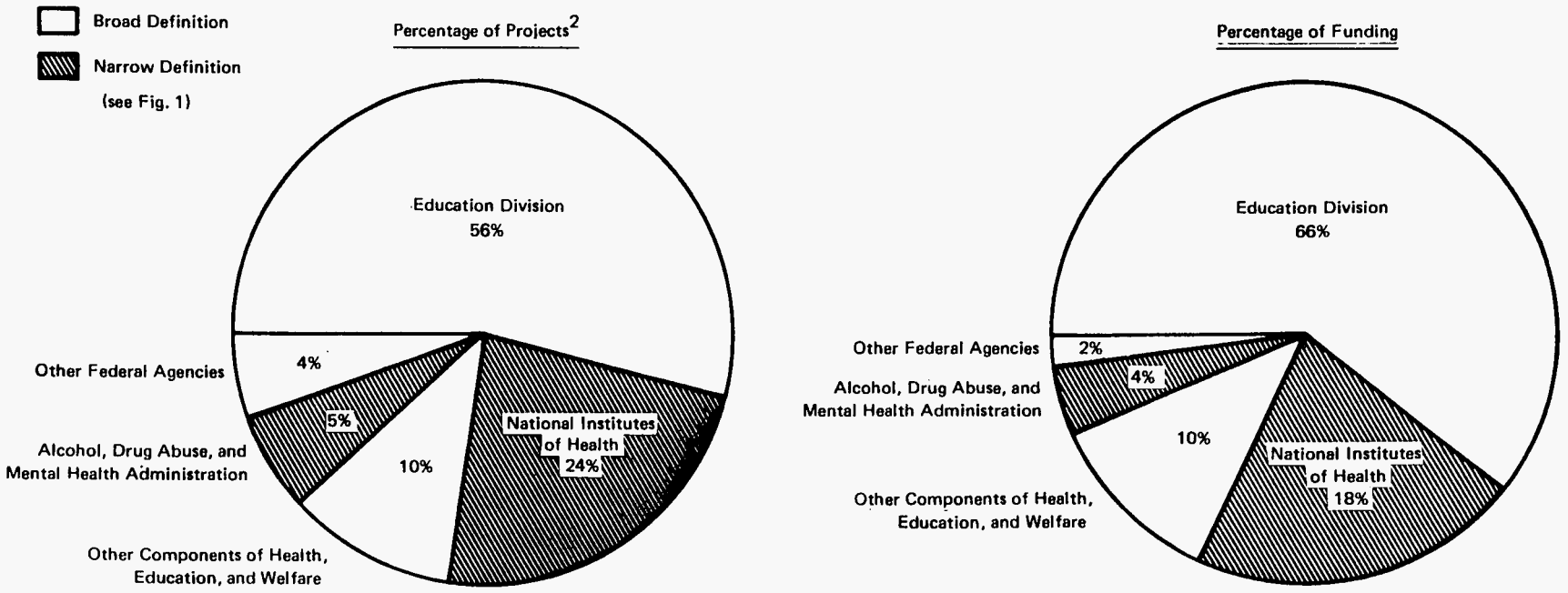
FISCAL 1975
FEDERALLY SUPPORTED RESEARCH PROJECTS INVOLVING CHILDREN AS SUBJECTS AS REPORTED BY FEDERAL AGENCIES[1]



[1]Compiled from information supplied by the Chief, Research Documentation Branch, Division of Research Grants, NIH and by the Social Research Group, The George Washington University

FIG. 1

Fig. 2
FISCAL 1975
FEDERALLY SUPPORTED RESEARCH PROJECTS INVOLVING CHILDREN AS REPORTED BY FEDERAL AGENCIES[1]



Number of Projects

Education Division	1942
National Institutes of Health	840
Other Components of Health, Education, and Welfare	346
Alcohol, Drug Abuse, and Mental Health Administration	190
Other Federal Agencies	142
TOTAL	3460

Amount of Funding

Education Division	$256,667,573
National Institutes of Health	72,113,441
Other Components of Health, Education, and Welfare	38,019,816
Alcohol, Drug Abuse, and Mental Health Administration	17,129,033
Other Federal Agencies	7,179,620
TOTAL	$391,109,483

[1] Compiled from information supplied by the Chief, Research Documentation Branch, Division of Research Grants, NIH and by the Social Research Group, The George Washington University.

[2] Percentages do not add up to 100% due to rounding.

CHAPTER 5. SURVEY OF REVIEW AND CONSENT PROCEDURES

Information about informed consent, risks and benefits, and review procedures in research involving children was obtained in the Commission's larger survey of review and consent procedures for research involving human subjects. The survey, which was conducted under the direction of Robert A. Cooke, Ph.D., and Arnold S. Tannenbaum, Ph.D., of the Survey Research Center at the University of Michigan, focused on review procedures and research at a probability sample of 61 institutions drawn from the more than 420 institutions with Institutional Review Boards (IRBs) approved by DHEW.* Research projects in which more than 25 percent of the subjects were children constituted more than one-fourth of all projects approved by sample IRBs during the period under study, July 1974 to June 1975. The Survey Research Center's report on research involving children was based primarily on interviews with 471 investigators whose research involved children, analyses of consent forms used in this research, and interviews with 144 subjects or third parties who consented on their behalf.

Research involving children was reviewed in many types of institutions, most frequently in medical schools (almost half of the research) and to a lesser extent in universities, hospitals, and institutions for the mentally retarded and mentally ill. Overall, slightly more biomedical than behavioral research involving children was conducted. In most of the biomedical research

---

* The study was confined to institutions from which DHEW had accepted a "general assurance" of compliance with DHEW regulations for protection of human subjects.

projects involving children, the subjects were identified by investigators as patients with diseases to which the research was related. The most common biomedical studies involved drug administration or examination of tissue or bodily fluids. Subjects in behavioral research were selected most frequently because of a behavioral or educational problem they were experiencing. Most of the behavioral research involved observation, testing, interviews or questionnaires; about one-fourth of the behavioral research involved the study of a behavioral intervention.

Risks and benefits of research involving children. Investigators provided assessments of the probability and magnitude of the risks and benefits of their research. Most risks to subjects were described as pertaining to minor psychological stress, embarrassment, or minor medical complications, and most risks were indicated to be of a "very low" probability. Higher probabilities of medical or psychological harm were reported in only about five percent of the studies involving children.

In analyzing investigators' responses to questions regarding risk, studies expected to benefit subjects were compared to studies not expected to benefit subjects. Projects expected to benefit subjects were defined as those which were reported (a) to be conducted for the primary purpose of benefiting subjects or (b) to have a medium or high probability of benefiting subjects. So defined, these "beneficial projects" made up 57 percent of the total.

Investigators' assessments of the probability of psychological stress or medical complications were substantially lower for research not expected

to benefit subjects. For example, in studies expected to benefit subjects, investigators reported a very low probability of "serious medical complications" in 18 percent of the studies, and a higher probability in an additional five percent of the studies. In studies not expected to benefit subjects, comparable figures for the risk of serious medical complications were six percent and zero percent. The only risks for which there was no difference between these types of studies were those in which a breach in confidentiality might result in embarrassment (a factor in about one-fourth of all studies involving children, usually at a "very low" probability) or in legal jeopardy (a factor in about 10 percent of all studies, usually at a "very low" probability).

Informed consent.* IRBs showed considerable concern with informed consent in their review of proposed research involving children. About one-fourth of the investigators doing research with children reported that their IRB had requested changes in the way consent would be obtained in their studies. Almost all of these changes pertained to the content of consent forms rather than to the setting or circumstances under which consent would be obtained. Consent modifications were requested most frequently in projects that involved the secondary use of materials gathered for other purposes; the most common consent change in such research was the requirement that consent be

---

* Because the terms "consent of children" and "third-party consent" were used in the survey, they appear in this section. As is explained in the Commission's recommendations, the Commission has generally referred to the "assent" of children in order to distinguish this from the legally effective informed consent that an adult can give, and to third-party "permission," which it believes to be a more accurate term than third-party "consent."

documented in writing rather than obtained orally. Among other biomedical and behavioral projects, the most common consent change was the addition of materials to consent forms.

Oral or written consent was sought in almost all projects in which children participated, the exceptions being projects involving questionnaires (where the return of the questionnaire was seen as implying consent), routine treatment, or research presenting no risk. In almost all projects from children's hospitals and about two-thirds of the projects from other settings, investigators requested consent from third parties, usually from parents, relatives or legal guardians. Most investigators felt that such involvement of third parties protected subjects "very well" or "fairly well," but a small number indicated otherwise. The median age of subjects above which no consent was obtained from a third party was 18 years of age, while the median age below which consent was not obtained from subjects, in addition to third-party consent, was seven years of age.

Written consent forms were used in almost all research in children's hospitals and in about three-fourths of the projects in other institutions. Oral consent, without consent forms, occurred most frequently in behavioral research (18 percent), but also occurred in seven percent of biomedical studies. About 10 percent of the behavioral researchers and two percent of the biomedical researchers reported that consent forms were used in their studies, but that no oral explanation was provided.

The consent forms themselves were frequently incomplete in terms of six consent elements mentioned in DHEW regulations (45 CFR 46.103(c)) --

the purpose of the research, the procedures involved, the risks, the benefits, a statement that subjects are free to withdraw from the research, and an invitation to ask questions. Only 20 percent of the consent forms from children's hospitals and other biomedical institutions, and only five percent of the consent forms from other institutions, contained as many as five of these six elements. Descriptions by investigators of the topics covered in oral explanations added only negligibly to the report of information transmitted to subjects.

Some elements appeared much less frequently than others in consent forms. There was no description of the purpose of the research in 30 percent of the consent forms, and no description of the research procedures in 18 percent. Risks were not discussed in 54 percent of consent forms. Two-thirds of these cases were in studies described by investigators as entailing at least a very low probability of minor harm to subjects. The benefits of the research (or absence of benefits to the subjects) were not described in 64 percent of the consent forms; benefits to subjects were mentioned in only one-fourth of the forms in studies which investigators described as being expected to benefit subjects. A statement regarding withdrawal from the study was not present in 14 percent of the consent forms; however, many of these may have been from studies in which the active participation of subjects ended quickly. An offer to answer questions appeared in half of the consent forms. A description of alternative treatments might have been expected in projects designed primarily to benefit subjects. However, alternatives to participation in the research were not mentioned on more than 80 percent of the consent forms in these studies.

The survey also showed that consent forms tend to be written in language that may be difficult for the lay person to understand. A "reading ease score" was computed for each consent form, using a standard measure, the Flesch Readability Yardstick.* In spite of the review and approval of these forms by IRBs, consent forms tended to be written in scientific language. Descriptions of the procedures to be used in the research tended to be somewhat more readable than descriptions of the purpose of the research. But, overall, fewer than 15 percent of the consent forms were written in language as simple as is found, e.g., in Time magazine. This raises doubt about whether many subjects would find these consent forms of substantial use to them in making decisions regarding participation in research. No information is available on the degree to which the difficult language of consent forms is mitigated by oral explanations in language more readily understood by the average lay person.

Subjects' and third parties' perceptions of research. A representative sample of subjects and third parties was not obtained, and data from these sources must therefore be interpreted with caution. Almost three-quarters of the respondents reported that they were given as much information as they wanted; 19 percent said that they were given less than they wanted. Almost all said the information was clear and understandable and that the researchers were willing to answer any questions, but 17 percent reported that they did not understand, prior to the subject's participation,

---

* Rudolf Flesch, A New Readability Yardstick, Journal of Applied Psychology, Vol. 18, No. 3, June 1948, pp. 221-233.

that the subject "was to be involved in research." The most frequent reason given for participation in a research project was some anticipated medical or psychological benefit. Ninety-six percent of the respondents reported no unexpected difficulties, and the four percent who did report difficulties felt that they were not very serious. Sixty percent felt that the subject benefited from the research.

IRB impact on proposals involving children. IRBs requested modification in about 60 percent of the research proposals involving children, usually during the formal review process but occasionally through informal contacts prior to review. The most frequent modifications, occurring in about one-third of the proposals, were for clarification or additional information. As discussed above, modifications related to informed consent were required in one-fourth of the proposals. Changes pertaining to reduction of risk or discomfort were required in about five percent of the proposals.

Investigators' attitudes toward the IRBs were, for the most part, more favorable than unfavorable. Nonetheless, half of the investigators offered suggestions for improvement or expressed concern about such problems as the time-consuming nature of the review process and the failure of IRBs to discriminate between research involving high risk and research involving minimal or no risk. Their suggestions included elimination of parts of the review process (e.g., regarding research with minimal or no risk or research using previously gathered materials), elimination of written consent procedures for studies with minimal or no risk, changes in IRB

composition (some want more lay representation, while others want less), and better information about the expectations of the IRB.

Summary. This survey indicated that IRBs give considerable attention to their review of research involving children and that significant risks, to the limited extent to which they are present in such research, are found in studies that are expected to be of benefit to the subjects. However, the survey also provided evidence of shortcomings in the obtaining of informed consent. Although oral or written consent was generally reported to have been obtained whenever appropriate, a small percentage of investigators indicated that no oral explanation had been provided, and consent forms were frequently incomplete and tended to be written in language that the lay person might find difficult to understand. Despite this, the survey provided no indication that there is widespread dissatisfaction among children or parents regarding their experience in research, although a significant minority of respondents indicated that they had not understood, prior to the subject's participation, that research was to be involved.

CHAPTER 4. VIEWS PRESENTED BY THE NATIONAL MINORITY CONFERENCE ON HUMAN EXPERIMENTATION

In order to assure that minority viewpoints would be heard, the Commission contracted with the National Urban Coalition to organize a conference on human experimentation. The conference was held on January 6–8, 1976, at the Sheraton Conference Center, Reston, Virginia. Attended by over 200 representatives, it provided a format for presentations of papers and workshop discussions from which a set of recommendations emerged. Two sections of the Minority Conference focused on children as research subjects.

Henry W. Foster, Jr., M.D., in a background paper, suggested that children not be excluded from participation in "nontherapeutic" research, since "there clearly exists the need to continue the search for better therapies and cures for the many childhood diseases that are so prevalent and devastating." However, he urged that a proper balance between risks and benefits be maintained, and that definitions of childhood take into account social and ethnic differences in age of maturation. He recommended that parental consent for the participation of children in research be accepted as legally and ethically valid, and that no socio-economic groups participate disproportionately as research subjects.

Crystal A. Kuykendall, Ph.D., spoke about institutionalized children, emphasizing the disproportionate numbers of minority children who are labeled mentally retarded or mentally disabled and placed in institutions. She indicated that these children are most vulnerable to the effects of institutionalization. Citing a 1975 study on the Futures of Children, by

Vanderbilt University, she noted that there are currently 200,000 individuals in public institutions who are diagnosed as mentally retarded, and thirty percent of these are children. She urged the development of alternatives to institutionalization for all but the most severely disabled individuals, better criteria for diagnosis, and better educational methods to develop the capacities of each person as fully as possible.

The Conference Workshops on Children submitted recommendations which included: (1) a prohibition of the exploitation of any one segment of the child population; (2) an exclusion of institutionalized children from research, except that which is designed to improve their conditions; (3) a prohibition of the use of psychosurgery on children; (4) the consent of a children's advocate in addition to that of parents; and (5) the consent of children over age seven when their participation in "nontherapeutic" research is solicited.

CHAPTER 5. VIEWS PRESENTED AT PUBLIC HEARINGS

On April 9, 1976, the Commission conducted a public hearing on the issue of research involving children. Summaries of the testimony follow.

William Charlesworth, Ph.D. and Julius Richmond, M.D. (Society for Research in Child Development) presented the results of a survey in which a sample of the Society's members were polled regarding their research practices. The sample included investigators involved in a wide variety of pediatric research, although it is almost entirely behavioral rather than biomedical. A majority of the investigators were funded by DHEW or other federal agencies. All of the investigators reported that they followed a specific code of ethics, and 80% reported that their research is reviewed by an ethics committee. Ninety-six percent reported that they had worked at one time with normal subjects, 31% had worked with handicapped or retarded subjects, and 25% had worked with institutionalized persons.

A third of those studying preschoolers obtained consent from the children as well as from parents (or, in a very few cases, from school officials). From that age group on, there was a greater tendency to obtain consent from the subjects. Eighty-three percent mentioned that they informed the subjects that they may refuse to participate or withdraw from the study at any point without prejudice. Deception was employed by 23% of the investigators if they felt it necessary for research purposes, and approximately 40% reported that they used various kinds of inducements or compensation to persuade or reward subjects or parents to participate in the research. (The offer of compensation for participating is often viewed as an inducement to persuade.)

Respondents were asked to answer questions about risks involved in their own studies and to identify any occurrences of injury. Physical risks were a possibility in only four of the 3,400 studies represented in the sample, and psychological/social risks were reported in less than 2% of the sample (60 studies). None of the physical risks led to any known undesirable consequences, but in about 13 cases, subjects reportedly experienced some consequences of the psychological/social risks, most of which appeared to be short-term. Thus, in only 1/4 of 1% of the 3,400 studies were children placed at any risk, and no serious or long-term injury was reported. The questionnaire also inquired about the risks posed by studies not conducted by the respondents but about which they had first-hand knowledge. The survey revealed that 9 respondents were familiar with a total of 16 studies involving some sort of physical risk and with 173 studies involving psychological/social risk. Dr. Charlesworth believes that this survey indicates that the overwhelming majority of investigators maintain a high level of research ethics. The Society recommends that the potential dangers involved in the use of deception (e.g., the child's losing trust in adults) be studied further, that there be increased education about the importance of research ethics, that review procedures be improved and that, if necessary, professional sanctions be invoked in cases of proven violations.

Edward F. Zigler, Ph.D. (Division of Developmental Psychology, American Psychological Association) suggested that investigators should educate the public about the nature and benefits of behavioral studies involving children

in order to dispel suspicion and distrust. In addition, they should develop enlightened informed consent procedures which respect the child's wishes as much as possible, although Dr. Zigler acknowledged that it is difficult to determine when a child is possessed of sufficient understanding that he or she should be consulted. He urged that investigators turn their attention more frequently to applied science to enrich both the theoretical structure of their field and the quality of life in our society. He further suggested that the Commission develop guidelines which protect both the rights of subjects and the rights of behavioral scientists, so that the latter may continue their exploration of human behavior. Should the task of the behavioral scientist ever become impossible, the ultimate loser will be society. Dr. Zigler believes that increased parent involvement in the research process, especially in institutional settings, is a crucial step in resolving the problems of distrust which, he believes, threaten research activities.

Frank Oski, M.D. (Society for Pediatric Research) presenting the testimony of Frederick C. Battaglia, M.D., described a variety of major contributions arising from pediatric research. He urged the Commission not to try to distinguish, in all cases, between "therapeutic" and "nontherapeutic" research, but rather, to focus on evaluation of risks. He suggested that the proper protection of children involved in long-term studies of development, maturation and aging could be accomplished without a cumbersome review mechanism. In cases where child abuse is present or likely, however, as well as in adoption and juvenile delinquency programs, he suggested there may be a need for an advocacy system. Dr. Battaglia expressed concern that the

government's continued diversion of training funds from research to primary care will further reduce the pool of investigators who may be best qualified to judge the merits of research involving children. He suggested two review mechanisms: (1) for "therapeutic" research protocols where "parenting" is adequate and parental consent appropriate, the review should be conducted by the IRB which should include experts in pediatrics and child psychiatry; (2) for all "nontherapeutic" research protocols and any "therapeutic" research where the question of adequate "parenting" is raised, an "Ethical Review Group" at NIH would be responsible for review and no local review would be required. In no case should the investigator also serve as the child's physician. Long-term studies requiring normal controls and involving procedures of minimal risk should be permitted without burdensome review.

Alvin M. Mauer, M.D. (St. Jude's Children's Research Hospital) testified primarily about research involving children with cancer. He emphasized the importance of random assignment of children to different treatment programs in order to evaluate the efficacy of the new therapies. Further, he views the random assignment of subjects as preferable to asking parents to choose which treatment their child should have. Dr. Mauer warned that if local protection committees are required to review each patient's consent form, committee review might become a rubber stamp operation. In addition, he prefers local review to national review since IRB members are closer to the issues and bureaucratic problems are avoided. The consent of both parents should not always be required for "therapeutic" research, nor should a child's formal consent be a prerequisite for all "therapeutic" research

procedures. Dr. Mauer proposed that about five percent of the children and parents involved in a particular research protocol be questioned to determine whether they understood the consent forms.

Sheridan Neimark, Esq. (National Society for Autistic Children) indicated that the Society is deeply concerned that federal legislation may inhibit research of potential benefit to children and severely impaired adults. They believe that existing regulations are sufficient and suggest that certain provisions be reconsidered (e.g., requiring incompetent children and both parents to consent to a research protocol). The consent of both parents should not be required if one parent has legal custody or if the other parent cannot be located after a reasonable effort has been made. While the Society does not approve of the use of patients as research subjects before appropriate or adequate animal studies have been conducted, it believes that careful and discriminating investigators should be supported. Studies involving high-risk drugs should be permitted as long as there is strong evidence that they may benefit the patient. Parents should have the option of vetoing their child's participation in any research they feel would be detrimental. Information on the risks, benefits, and any known side effects of experimental programs should be provided whether or not the parents request such information; and parents should be free to refuse their child's participation in any experiments which are not an integral part of their overall treatment program without prejudice.

Bertrand G. Winsberg, M.D. (State of New York Department of Mental Hygiene) expressed his concern about two major issues: minority group participation in

research and the appropriateness of obtaining informed consent from children. He stated that the assertion that the poor and ethnic minorities are being exploited by researchers has only partial validity. Much of the research data collected from these populations contributed significantly to their health care and, in many instances, only to theirs (e.g., nutrition studies). To inhibit research involving minorities will reduce the quality of resources and services available to them, and to restrict "nontherapeutic" research will handicap efforts to understand the nature of many disease processes. Dr. Winsberg sees no way in which to present research protocols to children so that meaningful consent can be obtained; in addition, he believes that subjecting children with physical or behavioral disabilities to such consent procedures may be harmful since it would expose them to requests which characterize them as abnormal. He further believes that the biomedical research establishment could be regulated effectively, like any other business, through federal and state agencies, although he would like to avoid a complex and unworkable bureaucracy. In the last analysis, he said, various responsible and knowledgeable agents of society must determine whether the risks and discomforts of any procedure are justified in the case of given children, taking into consideration the needs of both the research subject and the social system. Finally, Dr. Winsberg urged that a mechanism be incorporated in any new regulation to assess its effectiveness. In response to a question, Dr. Winsberg indicated that he viewed the problem of distinguishing between "therapeutic" and "nontherapeutic" research as insoluble.

Norman Kretchmer, M.D., Ph.D. (National Institute of Child Health and Human Development) stated that since any biological or behavioral event which

occurs in children is intertwined with their growth and development, two conclusions follow: (1) children must be studied in order to advance pediatric medicine, and (2) the long-term effects of any procedures which are performed on a child must be considered. Dr. Kretchmer offered the following recommendations: (1) children with no natural or adoptive parents, children detained by court order in a residential facility, and institutionalized handicapped children should be excluded from participation in "nontherapeutic" research involving risk; (2) a list of clinical procedures deemed to be without risk (e.g., collecting blood, urine and stool samples) should be exempted from the review process, but not from the informed consent requirement; (3) minors should be given the opportunity to refuse to participate in "nontherapeutic" research, and such a refusal should be honored (children might be more inclined to express their fears or objections to research if placed in a discussion group of three or four peers); and (4) panels reviewing protocols involving the use of children should include among their members a child advocate from outside the research community. It is extremely important, he added, that parents participate in the research process on a continuing basis.

Jean A. Cortner, M.D. (Association of Medical School Pediatric Chairmen) described many advances in pediatric care which have reduced infant mortality and profoundly affected child health. Dr. Cortner believes that basic and applied research are both necessary and should not compete with each other. A middle ground must be cultivated between children's right to a better tomorrow (through the acquisition of new knowledge) and their right to a safe today.

Dr. Cortner believes that safety can be assured through proper peer review. Since young children cannot give informed consent, their parents or guardians, who bear responsibility for their welfare, must give consent. Research which will place children at unnecessary risk must not be allowed, but research which promises to improve the health of everyone should be encouraged.

Elizabeth J. Levinson, Ph.D. (Psychologist, Orono, Maine) expressed concern about three issues: (1) the "Buckley law" which places restrictions on the release of data from school records to outsiders, (2) the entry into these records of certain types of data, and (3) restrictions on the administration of tests to children without "fully informed" parental consent. These restrictions conflict with state laws requiring that children be evaluated to determine the presence or absence of certain handicaps and they interfere with the research aims of the Office of Child Development and the National Center on Child Abuse and Neglect. Dr. Levinson has found that parents who abuse their children, who are emotionally unstable or are mentally retarded, are least likely to consent to studies of family interactions, I.Q., or psychological status. By informing the parents, the children, or both, of the purpose of such studies, there is a real danger of introducing anxieties and other harmful effects. Hence, there is an urgent need to modify the disclosure requirements for such research projects. Dr. Levinson suggested obtaining informed consent from the parents but not necessarily providing them with a full description of the study. She suggested further that giving parents complete control over their children and an almost absolute right to privacy appears to be based on an assumption either

that all parents are good and wise or that children have no rights. Dr. Levinson has discovered, however, that some parents are unwise and may invoke privacy to veil child abuse and neglect. She urged the Commission to resolve this conflict between the rights of parents and the rights of children.

Mr. Robert A. Bogorff (Candlelighters, South Florida Chapter) explained that the Candlelighters are especially interested in pediatric cancer research. They advocate careful monitoring of institutional review committees and suggest the IRB composition include more nonbiomedical members. Both the chairman and co-chairman of these committees should be required to demonstrate their knowledge of policies and laws regulating research. Further, since patients' advocates are essential and must be free to devote as much time as necessary to their duties, the Candlelighters recommend that funding agencies provide salaries for them. They should be well read in medicine, law and ethics and be able to work on a professional, full-time basis. They believe further that it is unrealistic to assume that parents of young cancer patients will comprehend a full statement of research procedures after one reading, while surrounded by hospital personnel and by other family members under similar stress. Rather, they say "parents will sign anything when confronted with cancer." They question the prevailing practice of random assignment to treatment groups and urge the Commission to give careful consideration to this problem. Finally, they are concerned about the inherent conflict in the doctor's dual role of physician/investigator, and about the lack of provisions for compensation for injury.

Joseph A. Bellanti, M.D. (American Pediatric Society) stressed the importance of research involving children for improving pediatric medicine, the distinction between "therapeutic" and "nontherapeutic" research in children, the varying levels of potential risk in "nontherapeutic" research in children, the role of the child and the parent in the consent process, and the equitable allocation of the risks and benefits of research. Dr. Bellanti suggested that children should be involved as much as possible with the consent process depending upon their level of understanding. A child's refusal to participate in a "therapeutic" procedure need not be respected if the parents or the courts are in disagreement, but for "nontherapeutic" research, the child's wishes should govern. He recommended that a detailed description of the research protocol be given to the parents and that the results of investigations be made available to them unless they specifically request not to be told. To avoid conflicts of interest when the attending physician is part of the research team, someone else should be prepared to serve as the child's and parent's advocate.

George G. Graham, M.D. (American Institute of Nutrition) noted that our knowledge of pediatric nutrition is limited, and we lack even a definition of desirable growth rates for infants and children. Most of our knowledge about nutrition derives from research with animals; at some point, it must be confirmed in humans. Well over 50% of all nutritional research is conducted outside of the United States, primarily because in poor countries the question is one of survival. In this country, however, evidence is increasing that infant and child feeding practices may influence degenerative

vascular disorders and other diseases which occur in adults. Longitudinal nutritional studies involving normal infants and children must be conducted if progress is to be made in determining proper levels of nutrients and ideal growth rates, or in developing alternative ways of meeting nutritional requirements which can be proven safe for children of varying ages, health status and heredity. Subjects of nutrition research should be followed for as long as one's resources permit; and nutritional supplements should not be withdrawn abruptly at the end of a research project. (This is a major source of concern when conducting research on food supplements in impoverished areas.) Dr. Graham was not aware of any experimental feeding programs for the institutionalized mentally retarded, though there have been studies correlating nutrient intakes with the development of institutionalized children. Generally, institutions are not desirable sites for these studies. Negotiations for conducting research overseas generally involve community representatives.

Richard B. Stuart, D.S.W. (Association for Advancement of Behavior Therapy) spoke about behavior therapy and the development of innovative services for youth. Generally, these programs utilize the least intrusive technology available to enhance social functioning. According to Dr. Stuart, if research means monitoring the effect of an intervention, then behavioral research and therapy are indistinguishable. He identified three stages of research: (1) the evaluation of existing services; (2) the development of innovative methods; and (3) the large scale testing of methods which have withstood developmental evaluation. The omission of any stage, he said,

would seriously hinder proper delivery of services. Dr. Stuart recommended that research be founded upon an explicit contract between the investigator and the participant, and he took the view that parents have the right to offer informed consent on behalf of their children. The point at which children are able to act as their own agents is difficult to define. Requiring participants to give written answers to questions about the research is one method suggested for determining the adequacy of informed consent. Dr. Stuart urged the Commission to endorse the following principles: (1) that all children have the right to carefully evaluated programs; (2) that children must have the opportunity to participate in the development and evaluation of programs of which they are the beneficiaries; and (3) that the rights of children as research participants can be protected through the development of precise standards which are strengthened by the addition of behavioral tests of compliance.

Marvin Cornblath, M.D. (The Endocrine Society) stated that advances in pediatric endocrinology and metabolism depend upon knowledge of normal values; this requires the study of normal infants and children. The goal of research must include discovering the etiology of diseases in order to prevent them. Dr. Cornblath urged that a subcommittee of the IRB should monitor all research involving children and that it should include child advocates among its members. Further, he recommended that consent of one parent be deemed adequate, and suggested that review boards develop a sliding scale for consent based on the age of subjects and the procedures involved. He noted that the parents have the final say about their child's participation in research, but that

the protocol should be fully explained to the child. Any effort to establish a specific age of discretion would be unnecessarily restrictive. He questioned the morality of depriving infants and children of the potential benefits of well supervised and controlled clinical research.

Sanford Cohen, M.D. (American Academy of Pediatrics) stated that reliance upon pharmacological data obtained in animal models and adults has been proven inadequate; further, infants and children must participate in the testing of drugs because adult counterparts to pediatric conditions do not always exist. The Academy believes that clinical investigations in pediatric pharmacology must continue, but under stringent requirements for review and monitoring. Studies should not be conducted, even if they entail minimal risk, if no benefits are anticipated. If "nontherapeutic" investigations are to be conducted in children, only agents that are generally regarded as safe in the dose to be administered should be used; further, if such studies involve pain or discomfort in excess of that associated with usual hospital procedures or clinic visits, they should be done only in children mature enough to offer their own consent (in addition to that obtained from their parents or guardians). In general, when children are conscious and neurologically competent, consent should be obtained from those who have reached the age of thirteen; and assent should be obtained from children aged seven or older after their legal guardian has consented but before the child is enrolled in the study. Dr. Cohen supported the inclusion of patient advocates on the review committee.

James J. Gallagher, Ph.D. (Frank Porter Graham Child Development Center) highlighted three major research issues: confidentiality, informed consent

and the protection from harm and exploitation. He urged the inclusion of child advocates along with members of the public on institutional review committees. IRBs should have unrestricted access to records and the power to approve or disapprove research on institutionalized children. In addition, parents should be continuously involved in the consent process, particularly if their child is institutionalized. Dr. Gallagher believes that observing normal procedures (e.g., observing interactions in a classroom) is not an intervention requiring informed consent. Dr. Gallagher emphasized the great risks in severely restricting research, urging that future generations have the right to a better chance for full growth and normal development.

Annina M. Mitchell, Esq. (Michigan Legal Services) charged that institutionalized children are exploited for research purposes (especially by drug companies) because they are cheap, accessible and out of the public's eye. Her position is that institutionalized minors cannot constitutionally be used as subjects in biomedical or behavioral experimentation because the politics of institutionalization preclude valid third party consent, and the children are in no position to give adequate consent because of the coerciveness of the institutional setting. Recently, she said, the Michigan State Department of Mental Health adopted administrative rules which prohibit the use of recipients of department services as subjects in medical research if they are under 18 years old. She urged the Commission to adopt a similar position. Ms. Mitchell is concerned that some experimentation in the name of mentalhealth raises the spectre of increasing classification of children

as deviant, and that such labeling will take its toll in later years. She asked the Commission to impose a moratorium on research involving children until it can determine whether, and under what conditions, such experimentation should be sanctioned.

Judson Van Wyk, M.D. and Maria New, M.D. (The Lawson Wilkins Pediatric Endocrine Society) stated that studies in adults or in experimental animals are not adequate to understand, diagnose and treat abnormalities which occur during childhood. Further, Dr. Van Wyk said, the subjects of research benefit from their participation by receiving more attention and consideration than those treated solely in a therapeutic context. He recommended that local committees have the primary responsibility for continuing review of research, and that they be empowered to approve no-risk projects. In addition, a National Clinical Research Advisory Board should establish policy and review all questionable research. Restraint should be exercised before inflexible standards are imposed, for we should not exclude children, as a class, from the benefits of new knowledge. In some instances, he added, it is difficult to distinguish between "therapeutic" and "nontherapeutic" research; and often, there can be no "therapeutic" research without "nontherapeutic" research.

Donald F. Klein, M.D. (Long Island Jewish-Hillside Medical Center) suggested that the biomedical investigator cannot claim the privileges of the medical practitioner when research is aimed at generating new knowledge rather than providing service. Experimentation involving nonpatients (1) should entail low risk to the subject and society, (2) should be likely to benefit

society, and (3) should be founded upon well established procedures for experimental intervention. In addition, the experimental effect should be easily reversed and temporary, and there should be no other alternative procedure which can yield the information. The subject or the subject's guardian should be able to comprehend the nature of the experiment. Dr. Klein believes that the protection necessary for "therapeutic" research has been exaggerated, especially since research often occurs under the rubric of professional services. He suggested that the social trust in researchers could be bolstered by certification of investigators. Institutional Review Boards should be composed of certified investigators, along with lay members and ethicists, with an opportunity for appeal to a board of biomedical research. Dr. Klein argued that to prohibit the use of sick children and the mentally ill as experimental subjects, when no feasible alternatives are available, is to condemn them to continued suffering. He suggested that instead of a contract model of consent, the IRB assist in determining the appropriate participation of children and the incompetent.

Robert Reichler, M.D. (American Academy of Child Psychiatry) believes that when the needs of suffering individuals conflict with community priorities, the individual should come first. However, this is not always the case. He described the diversity of pediatric mental health problems in this country to emphasize the enormity of the challenge to science, adding that the clinician is often characterized as warm and compassionate, while the investigator is viewed as cold and unfeeling. As a result, poor clinical treatment is more readily tolerated than good research because it is assumed

that children in behavioral research projects are at a greater risk than those receiving no treatment, or poorly evaluated drugs. Dr. Reichler believes that obtaining fully informed consent from children is unrealistic and legally impossible, whether they participate in research or in treatment. Whenever parental protection is inadequate or unavailable, additional review mechanisms should be invoked. When normal controls are required for a study, and samples of substances have been obtained for some other appropriate purpose, the samples might be utilized in such studies if no additional burden or risk is placed on the child. The rights of children include the right to better, safer, and more adequate treatment as well as protection from unnecessary risks and exploitation. While additional guidelines for review committees may be useful, Dr. Reichler urged that rigid barriers to research involving children not be imposed.

Robert L. Sprague, Ph.D. (Institute for Child Behavior and Development) urged the Commission to view research on children from the standpoint of social costs and benefits. The parents of handicapped children often expect the development of new information and new techniques to help them with their problems, and Dr. Sprague considers that expectation to be reasonable. He challenged the assumption that accepted clinical practice always involves less risk than an experimental procedure, citing several experimental programs for retarded and handicapped children which proved more beneficial than standard practice. He urged the Commission to weigh the cost, in humanitarian terms, of whatever regulations for human experimentation they may recommend.

Mrs. Gladys Kazyak (National Coalition for Children) is particularly concerned about behavior modification programs which are offered in schools under the guise of compulsory education. She views the school system as a form of involuntary institutionalization, and challenged both the methodology and objectives of behavior modification programs in such settings. In addition, she feels that any behavioral research involving deception is dishonest and should be eliminated. The consent of both parents should be required, and there should be no substitutions. All research protocols should include an evaluation of the potential effect they will have on the subjects, and investigators should accept responsibility for the outcome of their investigations. Unethical research should be eliminated by withdrawing public funding; ethically acceptable research should continue.

Marian R. Yarrow, Ph.D. (National Institute of Mental Health) emphasized the need for "nontherapeutic" behavioral research involving children. She made four comments about informed consent: (1) it has many levels of meaning for different kinds of children; (2) it is a continuing process and not a one time affair; (3) it is improper and meaningless to propose an age at which a child may give informed consent, since there can be no single criterion; (4) we must question the purpose of informed consent. Dr. Yarrow suggested that the issues of informed consent are different for medical studies involving risk than for behavioral studies without risk. Occasionally, fully informed consent may pose an additional hazard to the subject, or full disclosure may result in biased findings. Complete parental control of the consent process assumes that parents always act with both good will and good

sense. Since this may not always be true, the child's wishes should be respected. In long-term studies, one should reinstate and reevaluate consent from time to time. When an investigator uncovers some potentially serious problems during the course of research, the investigator's responsibility is unclear, particularly with regard to confidentiality. The investigator should allay the fears and anxieties of the subjects after the study is completed, and provide additional information when necessary. To assure that scientific objectives do not overshadow an evaluation of the effects of a study on children, the investigator should be knowledgeable about their vulnerabilities and capacities, always attending to the social and psychological child as well as the biological child.

CHAPTER 6. PSYCHOLOGICAL PERSPECTIVE

Lucy Rau Ferguson, Ph.D., a developmental psychologist, wrote a paper for the Commission on "The Competence and Freedom of Children to Make Choices Regarding Participation in Biomedical and Behavioral Research." She emphasizes, first and foremost, that the child is a person and parental consent should therefore be a necessary, but not sufficient, condition for children's participation in research: "Investigators should conduct research so as not only to respect but to enhance the child's developing capacity for informed choice." An important aspect of research involving children, she suggests, is that they can learn from the experience that the generation of knowledge is, in itself, a good; in addition, the most legitimate motive for involving children in research is an appeal to their intrinsic curiosity and their developing sense of altruism.

Investigators should never offer incentives which are so great as to overcome a child's reluctance to participate, nor should pressure be brought to bear on peers, parents or others in authority. The child should be given as much information as he or she is capable of understanding; and this will vary with the nature of the research, and the maturity of the individual child. In general, according to Ferguson, informed consent of the parents should be sufficient for infants and toddlers; but pre-school and primary-age children should be given explicit information about what participation in research will mean and about the purpose of the research, since children of this age can understand considerably more than they can articulate. (It is important to keep in mind that the investigators should have experience

and competence in working with children.) For the pre-adolescent (school-age) child, participation should be based upon the same principles of informed consent as apply to adult subjects (including, if appropriate, signing a consent form), although parental consent should be obtained as well. At this age, children are quite capable of understanding what is involved in most studies, if the problem is stated in nontechnical language. Investigators, according to Ferguson, should never underestimate the curiosity or the capacity of school-age children for making informed choices; and participation in research which is an informative and positive experience can have the function of strengthening a child's scientific curiosity. The adolescent should be treated as an adult so far as "nontherapeutic research is concerned (although parental consent should be obtained as well for those who are still legal minors), for it is particularly important to adolescents that their autonomy and competence be respected.

Ferguson believes that children of all ages should be treated with honesty; therefore, research that involves deception should not be undertaken, for children will only learn from such experiences that scientists are not to be trusted. Incomplete disclosure is acceptable, in some instances, so long as the children are given a fair explanation of what their participation will involve. Privacy should be protected; and parents of young children should be informed of any conditions which warrant attention. Parents, and children who are old enough to understand, should be given reports of the findings of the research.

Chapter 7. Legal Issues

There is currently a legal trend toward enunciation and expansion of children's rights. Considerable tension remains, however, between emerging rights of children to exercise self-determination, on the one hand, and the traditionally-held rights of parents and the state, on the other hand, to protect children from their own judgment and to insist that their behavior conform to what is determined to be in their own best interests, in the best interest of the family unit, or in the best interest of the state.

According to the common law, as in the philosophy of Hobbes, Locke and Mill, children are chattels of their parents and wards of the state, owing obedience in return for necessary care. Parents have the authority to control their children, to educate them, and generally to provide for them, with the state reserving the right, as *parens patriae*, to intervene when parents fail in their duty to provide and protect, or when discipline oversteps into the realm of cruelty. Children have no right to liberty, but only to custody; and the underlying presumption is that parents and society act in the best interests of the child.[1]

Children's rights as against their parents or the state have been enunciated recently in several broad areas: education, divorce and custody proceedings, juvenile delinquency and civil commitment. The notion that parents' interests always coincide with those of their children, or that the state will always act in the best interest of its ward, has been challenged and at times has yielded to a determination that the rights of children may not always be

properly represented by their parents or the state.[2] In the area of consent to biomedical and behavioral research, however, there has been little development of a judicial or statutory body of law. Before examining these few articulated rules, it would be appropriate to review the capacity of children and the authority of parents to consent to related and other interventions.

The primary issue with respect to the applicability of the doctrine of informed consent is the capacity of the child to comprehend and weigh the benefits and risks of proposed research. Although a child may be conclusively presumed to lack the capacity to consent in certain contexts (e.g., to contract for non-necessary items or to make a will), there are other situations in which capacity is an issue of fact to be decided on a case-by-case basis.

For example, in certain circumstances a child may be precluded from recovering damages for negligent acts toward the child if the defendant can prove that the child "assumed the risk." The assumption of risk defense is a question of fact which depends on finding that the child was aware of, and appreciated, the known risks in his or her conduct and nevertheless engaged in it. Thus, in a suit by a 15-year-old high school student against his school system for severe injury (broken neck) sustained in a football game, the court stated that an athlete may be taken to consent to physical contact consistent with the understood rules of the game.[3] On the other hand, children at a very young age may be conclusively presumed to be unable to assume all types of risks.[4]

The area of law most pertinent to the issue of consent to research for the direct benefit of the minor is that involving consent to medical treatment. The issue of consent usually arises in one of three situations. First, in a suit by a minor against a physician for assault and battery, the physician will attempt to argue that the minor's consent is a sufficient defense. Second, a state legislature may create exceptions to the general rule of incapacity of minors to consent to medical treatment by permitting consent to specific treatment without reference to parental consent. Third, a constitutional right of the minor may be violated where the state reinforces parental authority to consent to certain treatments of a minor without the latter's consent.

The area of law having relevance to issues of research not involving direct benefit to the minor concerns consent by a minor-donor to be involved in skin, kidney or bone marrow transplantation. Finally, there is one reported case specifically dealing with participation of minors in research.

Direct Benefit to the Minor: Law of Treatment. The law in most states is that parental consent is necessary and sufficient for treatment of persons under 18 years of age (see Table 1).[5] Three exceptions to this general rule have been incorporated to various degrees. First, courts have implied legally valid consent on behalf of the minor when there was an emergency condition threatening the child's life or serious bodily harm and the parents could not be reached quickly.[6] Legislatures in a number of states have expanded the definition of emergency to include immediate danger to the "health" or "mutual well-being" of a child.[7]

Second, courts and legislatures have found "emancipated minors" to be capable of giving legally valid consent to medical treatment. The definitions of emancipation have varied somewhat among the states, but usually refer to minors who are married or maintain their own residence and manage their financial affairs.[8]

Third, a minority of courts and legislatures have adopted the so-called "mature minor" rule. The rule originated in several decisions holding a doctor not liable for assault and battery where the consenting minor patient (between 17 and 19 years of age) was sufficiently intelligent to comprehend the nature and consequences of a proposed treatment.[9] A few legislatures have enacted such a rule, thereby making capacity to consent primarily an issue of fact.[10]

Another method for carving out exceptions to the general rule of exclusive parental authority to consent has been legislation of age limitations on an ad hoc basis. The conditions meriting the attention of the legislature have involved public health problems with high social costs (e.g., venereal disease and drug abuse) and other sex-related health care (e.g., contraception and pregnancy, excluding abortion). Some states have set a minimum age floor with respect to certain treatments while other statutes permit VD treatment to any consenting minor. (See Table 1.)

While many recent pronouncements of children's rights are articulated in an affirmative manner, several court decisions have expanded such rights by striking down statutory restrictions on the autonomy of children. In so

doing the courts have limited the authority of parents to act as primary protector and judge of their children's best interest.

A leading case is Planned Parenthood of Central Missouri v. Danforth,[11] where the United States Supreme Court invalidated a state statute requiring parental consent to an abortion on a minor. Building upon Supreme Court cases which had found minors to possess protectible constitutional rights,[12] the court held, in a sharply divided decision, that the statute, which reflected an interest in the safeguarding of the family unit and of parental authority, impermissibly infringed upon the "competent" minor's constitutional rights of privacy.[13] Vigorous dissents from this opinion supported the right of parents to guide their children and right of the state to protect the immature from imprudent decisions.

The Planned Parenthood decision, however, does not provide clear-cut answers for determining the scope of a minor's right of privacy with respect to other medical treatments. While the Court emphasized that not every minor, regardless of age or maturity, could legally consent to an abortion, it did not set out a test for "competency." Moreover, only an absolute parental veto over the abortion decision was invalidated. In a companion case the court left open the possibility that requiring parental consultation or a court order authorizing an abortion if in the minor's best interests may not "unduly burden" the minor's constitutional right.[14] Furthermore, the Court expressly reserved the issue of whether different consent requirements may be maintained for different medical procedures.[15]

In Carey v. Population Services International[16] the Supreme Court recently struck down a statute banning the sale of nonprescription contraceptives to minors under the age of 16 years, but only four justices relied on the Planned Parenthood holding on abortion as the *a fortiori* rationale for extending minors' rights to the area of contraceptives.[17] Two justices joined the result, on the grounds *inter alia* that the statute prohibited parents from distributing contraceptives to their children, thereby infringing their constitutional interests in the rearing of their children.[18] Thus the issue of the unit of autonomy at stake (and also the standard of judicial review to be utilized in evaluating restrictions on a minor's access to treatments) remains to be decisively settled. Moreover, even the four-man plurality failed to elaborate upon the statement in Planned Parenthood that not all minors, "regardless of age or maturity, may give effective consent."[19]

With respect to treatment of mental illness, a three-judge federal district court has limited parental authority by striking down a statute permiting civil commitment of children to state mental institutions by virtue of parental consent. The court enunciated various due process rights to which a minor is entitled, including a hearing, right to counsel and to confront witnesses, and requiring the state to prove the need for institutionalization by clear and convincing evidence. (The case was appealed to the Supreme Court, which vacated the result and remanded the case for reconsideration by the three-judge court, on the grounds that the facts of the case had changed and required a new review.[20]) The California Supreme Court has also invalidated procedures for admitting minors, if 14 years or older, to state mental hospi-

tals upon parental consent where the minor has not voluntarily acquiesced in the decision and thereby waived his or her due process rights to a commitment hearing.[21]

The state may also limit parental authority in another sphere of medical treatment decision-making: the decision to refuse medical treatment. The state may override the parent's refusal to seek treatment by resort to its *parens patriae* authority, as complemented by "neglect" statutes. When the child's life is in immediate danger, a court can clearly authorize treatment. The more difficult cases involve a state claimed need of a minor for elective surgery that is at odds with the parents' own system of values. Some decisions superimpose the state's interest in providing a more "normal" psychological environment over the parents' judgment.[22] Other courts, however, have upheld parental authority to refuse elective surgery,[23] especially where the child's desires have been taken into account.[24]

In conclusion, a reasonable inference from the law of consent to medical treatment is that consent to research holding out the prospect of direct benefit is probably similar enough to bring the same doctrines into play. Nevertheless, consent to research has been virtually unanalyzed by courts and legislatures. It is possible that age floors for consent to various types of research might be as uneven as age floors for various types of treatment. For example, state statutes authorizing minors to consent to venereal disease or drug abuse treatment are silent with respect to consent to behavioral research, e.g., survey questionnaires regarding minors' need for such treatment. It is reasonable for a court to construe such legislation as providing for an identical

age limit with respect to research on such treatment; answers to such a survey questionnaire would enable state authorities to design better methods for effectuating the public health purposes embodied in the statutes. Thus, a national research policy must be flexible enough to allow for the varying consent standards among the states for biomedical and behavioral interventions that hold out the prospect of direct benefit to the child.

No Direct Benefit to the Minor: Law of "Donation." The only area of authority in a related context bearing upon the issue of consent to research interventions that are not for the direct benefit of minor subjects is that involving donation by minors of kidneys, skin grafts and bone marrow. In these cases, the donors are undergoing medical procedures that are not for their direct benefit but rather for the purpose of saving the lives of relatives, Bonner v. Moran[25] is the leading case on the necessity (but not necessarily the sufficiency) of parental consent for an intervention that involves risk and no direct benefit to the minor. Bonner was a 15-year-oldwho was persuaded by his aunt to donate skin for a graft to his seriously burned cousin. Bonner's mother did not know of the first operation beforehand. She was later advised that her son was returning to the hospital to be "fixed up," and she did not protest. Subsequently, an action for damages for assault and battery was brought. Evidence was presented that the mother had publicly expressed pride in her son's courage. At issue was whether parental consent was necessary and whether the mother had given consent by implication or ratification. The trial court instructed the jurors that if they believed the boy was capable of understanding the nature and consequences of the operation and had actually consented, parental permission was not necessary. The jury so

found. On appeal, the court held that the jury should have been instructed that parental consent was necessary, because the operation was not for the benefit of the child in question and involved "sacrifice on the part of the infant of fully two months of schooling, in addition to serious physical pain and possible results affecting his future life."[26] Thus, the trial court's reliance on a mature minor exception to the requirement for parental consent was rejected on the ground that such exceptions apply only when the procedures in question will provide direct benefit to the minor. The issue of whether concurrent consent on the part of the child was necessary was not decided.

A series of three Massachusetts cases that approved kidney donations by teen-age donors to their identical twins focused on the "grave emotional impact" that the healthy twins would suffer if they did not donate to save their brothers' lives.[27] In all three cases, consent was given by the parents as well as the minors (one was nineteen years old, two were fourteen years old), and the court found psychological benefit for the donors. A subsequent Connecticut case involving seven-year-old twins differed in that there was no possibility of consent by a mature minor, although the court found that the young donor had been informed of the operation and "insofar as she may be capable of understanding" desired to donate her kidney.[28] Noting that the proposed operation would be life-saving to the donee, "of some benefit to the donor," and of "negligible risk" to both, the court found that it would be inequitable to prohibit parental consent when such consent was favorably reviewed by a guardian *ad litem* and by community representatives including a court of equity.[29]

By contrast, a Louisiana court denied authority to a parent to permit a 17-year-oldmentally retarded boy to donate a kidney to his 33-year-old sister.[30] There, the court reasoned that the closest analogy in Louisiana law was that of donation of a minor's property, and that:

> Since our law affords this unqualified protection against intrusion into a comparatively mere property right, it is inconceivable that it affords less protection to a minor's right to be free in his person from bodily intrusion to the extent of loss of an organ unless such loss be in the best interest of the minor.

The court found benefit to the donor to be "not only highly speculative but . . . highly unlikely," and concluded that the operation would be against his best interest.[31]

In a case more relevant to the research context, where the proposed procedure involved donation of bone marrow rather than permanent loss of an organ, a Massachusetts court observed that the evidence did not permit a finding that the procedure would be of any benefit to the six-year-olddonor.[32] The court permitted the operation nonetheless, saying it did "not believe that a finding of benefit to the donor is essential, or that the absence of such a finding is fatal, to the allowance of such a transplant," and noting that risks to the donor were "minimal." The court found that the parents had authority to consent for the operation, but that their consent should be subject to court review because of the possibility of conflict between their responsibility for the care and custody of the donor, and their similar responsibility for the donee.

Merriken v. Cressman[33] is virtually the only relevant case involving consent for the participation of children in research (other than the bone marrow cases).[34] In Merriken, a suit brought by a junior high school student and his mother, a federal district court enjoined implementation of an experimental drug abuse prevention program. The program required students' responses to questionnaires that asked highly sensitive questions concerning their home life, an area protected by Supreme Court decisions,[35] and also asked students to identify classmates whose behavior was unusual or inappropriate. On the basis of such information, compulsory remediation was to be instituted by teachers who lacked proper training in psychological therapy. Further, the results of the questionnaires were to be made available to individuals not involved in the program, such as athletic coaches, administrators, and members of the PTA and school board. When the suit was filed, the defendants had planned what the court called a "book-of-the-month-club approach to obtaining parental consent, in which silence would be construed as acquiescence. (They later offered to change that approach and require written parental consent, and also to give students notice that they were free to return a blank questionnaire.)

The court found that the program infringed on the child's constitutional right of privacy, and further that "there probably is no more private a relationship, excepting marriage, which the Constitution safeguards than that between parent and child."[36] Finding defects in the procedures for parental consent, which precluded knowledgeable waiver of their children's rights, the court raised but did not resolve the issue of a requirement for consent of the

children. It did conclude, however, that the program would be administered "without the knowing, intelligent, voluntary and aware consent of parents or students."[37]

This case, then, supports the necessity (but not necessarily the sufficiency) of parental consent for participation of children in research, just as Bonner did with respect to medical interventions for the benefit of others. Whether courts would require the assent of children, in addition, remains unclear.

TABLE I

CONDITIONS DEFINING ABILITY TO CONSENT TO MEDICAL CARE (BY STATE STATUTE)

Chart prepared by Commission staff in June 1976 (revised June 1977)

(Source: Hospital Law Manual)

	General Conditions Defining Ability to Consent				Specific Treatments Which May be Obtained by Minors without Parental Consent				
		Overriding Circumstances							
STATE	Age	Married or emancipated	Pregnant or parent	Other	V.D.	Addiction	Pregnancy	Contraception	Other
Ala.	14	X	X	high school graduate	X	X	X		emergency or any reportable disease
Alaska	19	X	X		X		X		
Ariz.	18	X			X	12			rape victim (over 12 yrs.)
Ark.	18	X*		"of sufficient intelligence"	X		X[a]		
Cal.	18	X		in armed services	12		X	X	reportable communicable disease (over 12 yrs.)
Colo.	18	X*			X	X		p or parent	
Conn.	18				X	X			
Dela.	18	X			12		12[a]		communicable disease (over 12 yrs.)
D.C.	18				X	X	X	X	psychological disturbance
Fla.	18	X			X		X[a]	p or parent	blood donation (over 17 yrs.) or emergency
Ga.	18	X			X	X	X	X	
Hawaii	18				14		14		
Idaho	18				14	16			infectious or communicable disease (over 14 yrs.)
Ill.	18	X	X		12		X	m, p or parent	emergency or referred for treatment by physician, clergy, or planned parenthood agency
Ind.	18	X			X	X			
Iowa	18	X			16				

X may consent at any age under such circumstances or for such treatment

a except abortion
m married
p pregnant
* unmarried, emancipated minors must be over 15 yrs.

CONDITIONS DEFINING ABILITY TO CONSENT TO MEDICAL CARE (BY STATE STATUTE)

	General Conditions Defining Ability to Consent			Specific Treatments Which May Be Obtained by Minors without Parental Consent				
		Overriding Circumstances						
STATE	Age	Married or emancipated	Pregnant or parent	Other	V.D.	Addiction	Pregnancy	Contraception	Other
Kan.	18			no parent or guardian available (over 16 yrs.)	X	X	X**		
Ky.	18	X	X		X	X	X		
La.	18				X	X			actual or believed illness including but not limited to V.D. and drug addiction
Me.	18				X	X			
Md.	18	X	X		X	X	X	X	emotional disorders (over 16 yrs.)
Mass.	18	X	X		X	12	X		emergency or disease "dangerous to the public health"
Mich.	18	X		in armed services	X	X			kidney donation to parent, sibling, or child w/court approval (over 14 yrs.)
Minn.	18	X	X		X	X	X		blood donation (over 17 yrs.)
Miss.	21	X		"of sufficient intelligence"	X		X		
Mo.	21				X	X	X[a]		
Mont.	18	X	X	high school graduate	X	X	X	X	acute psychological disturbance and no parent or guardian available
Neb.	19	X			X				
Nev.	18	X			X	X			
N.H.	18				14	12			
N.J.	18	X			X		X		
N.M.	18	X			X		X		

X may consent at any age under such circumstances or for such treatment

a. except abortion
m married
p pregnant
** no parent or guardian available

CONDITIONS DEFINING ABILITY TO CONSENT TO MEDICAL CARE (BY STATE STATUTE)

	General Conditions Defining Ability to Consent				*Specific Treatments* Which May Be Obtained by Minors without Parental Consent				
		Overriding Circumstances							
STATE	Age	Married or emancipated	Pregnant or parent	Other	V.D.	Addiction	Pregnancy	Contraception	Other
N.Y.	18	X	X		X		X		
N.C.	18	X			X				
N.D.	18				14	14			
Ohio	18				X	X			
Okla.	18	X[a]	X[a]	in armed services[a]	X		X[a]		
Ore.	15	X			12	X		X	
Pa.	18	X	X	high school graduate or professing competency	X		X		any reportable disease or emergency
R.I.	18				X				emergency (over 16 or m)
S.C.	16[o]	X			X				"necessary services"
S.D.	18				X				
Tenn.	18				X			m, p, parent, or referred	
Texas	18	X		in armed services	X	13	X[a]		any reportable communicable disease
Utah	18	X			X				
Vt.	18				12	12			
Va.	18				X	X	X	X	
Wash.	18	X[s]			14				
W.Va.	18				X	X			
Wisc.	18	X							
Wyo.	19				X				

X may consent at any age under such circumstances or for such treatment

a except abortion
m married
p pregnant
o except operations
s spouse must be of legal age

FOOTNOTES

1. Kleinfeld, The Balance of Power Among Infants, Their Parents and the State, Parts II and III, 4 Fam. L.Q. 409 (1970), and 5 Fam. L.Q. 63 (1971); see also Rodham, Children Under the Law, 43 Harvard Educational Review 487 (1973).

2. See generally id.

3. See Vendrell v. School District, 233 Ore. 1, 376 P.2d 406 (1962).

4. E.g., Greene v. Watts, 210 Cal. App. 2d 103, 26 Cal. Rptr. 334 (1962) (3 1/2 year old).

5. Some states set a lower standard, e.g., Alabama (14 years); South Carolina (16 years).

6. W. Prosser, Torts 103 (4th ed. 1971).

7. Ga. Code Ann. § 88—2905(1971).

8. See, e.g., Colo. Rev. Statute § 13—22—103(1973).

9. Younts v. St. Francis Hospital, 205 Kan. 292, 469 P.2d 330 (1970) (17 year old consent to skin transplant for damaged finger); Lace v. Laird, 166 Ohio 12, 139 N.E.2d 25 (1956) (18 year old consent to plastic surgery on nose); Bakker v. Welsh, 144 Mich. 632, 108 N.W. 94 (1906) (17 year old consent to surgery to remove tumor).

10. E.g., Miss. Code Ann. § 41—41—3(h)(1972); see N.H. Rev. Stat. Ann. § 318—B, 12—a (Supp. 1975).

11. 428 U.S. 52 (1976).

12. Goss v. Lopez, 419 U.S. 565 (1975) (procedural due process in context of school discipline); Tinker v. Des Moines School District, 393 U.S. 503 (1969) (freedom of expression in school); In re Gault, 387 U.S. 1 (1967) (right to counsel at delinquency proceeding).

13. 428 U.S. at 72—75.

14. Bellotti v. Baird, 428 U.S. 132, 147—50 (1976).

15. Id. at 857; see Cal. Welf. & Inst'ns. Code § 5325 et seq. (prohibition of psychosurgery on persons under 18 years of age); Aden v. Younger, 57 Cal. App. 3d 662, 129 Cal. Rptr. 535 (1976) (constitutional issues raised in regulation of experimental psychosurgery; prohibition on minors not directly considered).

16. 52 L. Ed. 2d 675 (1977).

17. Id. at 689–94 (Brennan, J.) (plurality opinion).

18. Id. at 699 (Powell, J., concurring); id. at 702–03 (Stevens, J., concurring).

19. Id. at 690 n. 16 (Brennan, J.) (plurality opinion).

20. Bartley v. Kremens, 402 F. Supp. 1039 (E.D. Pa. 1975), vacated and remanded, 45 U.S.L.W. 4451 (1977).

21. 19 Cal. 3d 655 (Crim. No. 19558, July 18, 1977).

22. E.g., Matter of 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 (1971), aff'd per curiam, 29 N.Y.2d 900, 328 N.Y.S.2d 686 (1972) (state imposed cosmetic surgery on face of 15–year-old boy).

23. In re Hudson, 13 Wash. 2d 673, 126 P.2d 765 (1942) (parental refusal to permit amputation of deformed arm of 11–year-old daughter upheld).

24. Matter of Seiferth, 309. N.Y. 80, 127 N.E.2d 820 (1955) (parental refusal to permit corrective surgery of 14–year–old boy's harelip and cleft palate upheld where minor in accord with parents' desires).

25. 126 F.2d 212 (D.C. Cir. 1941).

26. Id. at 123.

27. Masden v. Harrison, No. 68651 Eq. (Mass. Super. Ct., June 12, 1957); Huskey v. Harrison, No. 68666 Eq. (Mass. Super. Ct., August 20, 1957); Foster v. Harrison, No. 68674 Eq. (Mass. Super. Ct., November 20, 1957); discussed in Louisell and Williams, Medical Malpractice ¶ 19.14 (1976).

28. Hart v. Brown, 29 Conn. Supp. 368, 289 A.2d 386 (1972).

29. Id. at 391.

30. In re Richardson, 284 So. 2d 185 (La. App. 1973).

31. Id. at 187.

32. Nathan v. Farinelli, Civ. No. 74–87 (Mass. Super. Ct., July 13, 1974).

33. 364 F. Supp. 913 (E.D. Pa. 1973).

34. Nielsen v. The Regents of the University of California, No. 665–049 (Cal. Super. Ct., County of San Francisco, filed Sept. 11, 1973).

35. See Pierce v. Society of Sisters, 268 U.S. 510 (1925); Meyer v. Nebraska, 262 U.S. 390 (1923).

36. 364 F. Supp. at 918.

37. Id. at 922.

CHAPTER 8. ETHICAL ISSUES

The general purpose of research involving children is to obtain scientific information about them. Often the research provides some direct benefit to the subjects involved in the research. However, some research may produce benefits only for other children, and frequently it is quite uncertain whether the subjects themselves will ultimately benefit from the research. In some cases benefits are long-range or unpredictable, and the major objective is to develop a body of knowledge. Ethical issues about the involvement of children arise because of competing answers to the following question: Under what conditions (if any) are these various types of research justified? When the objective of procedures is that of directly benefiting the subjects, the research is generally agreed to be justifiable, under certain limiting conditions, if there is a reasonable prospect that the subjects will benefit. However, research in which procedures present no prospect of direct benefit to the subjects raises a variety of ethical problems about the protection and the rights of children and about the authority of parents. Although only alluded to in classical ethical codes and regulations, these problems have received extensive attention in recent ethical literature.

Codes and Regulations. The Nuremberg Code (1949) has seemed to some to preclude the participation of children in research. The first principle of that code states explicitly:

> The voluntary consent of the human subject is absolutely essential. This means that the person involved should have the legal capacity to give consent, . . .[1]

The apparent clarity of this statement, however, is clouded by the written statements of two individuals who participated in the drafting of the Code. Leo Alexander, whose first draft of principles formed the basis of the Code, has written that the original draft contained provisions for consent by next of kin on behalf of incompetent patients, but that the judges omitted those provisions in the final version "probably because they did not apply in the specific cases under trial."[2] Similarly, Andrew Ivy, chief medical consultant to the War Crimes Trials, wrote (in the same year the Code was published) that:

> The ethical principles involved in the use of the mentally incompetent are the same as for mentally competent persons. The only difference involves the matter of consent. Since mental cases are likened to children in an ethical and legal sense, the consent of the guardian is required.[3]

The record does not show whether the judges at Nuremberg disagreed with their medical consultants on this matter or whether, as Alexander suggests, they simply followed judicial custom by limiting their opinion to the facts of the case at bar.

The Medical Research Council of Great Britain took the position in 1963 that young children should not be subjects of "nontherapeutic" research if that research "may carry some risk of harm."[4] Their general rule is that if a child is under 12 years of age:

> information requiring the performance of any procedure involving his body would need to be obtained incidentally to and without altering the nature of a procedure intended for his individual benefit.[5]

If the child is over age 12, his or her consent should be obtained, and its validity would depend upon a showing that the child understood the implications of the procedures involved.

The Declaration of Helsinki,[6] published by the World Medical Association in 1964, provides, with respect to "nontherapeutic" research, that "if [the subject] is legally incompetent the consent of the legal guardian should be secured."* The acceptance of this code by the American Society for Clinical Investigation, the American College of Physicians, the American College of Surgeons, and particularly the American Medical Association[7] resulted in the general acceptance throughout this country of third-party permission for research employing interventions that are not for an incompetent subject's direct benefit.

The 1971 Institutional Guide to DHEW Policy for the Protection of Human Subjects required the consent of a subject "or his authorized representative." It did not define "authorized representative," but cautioned that:

> The review committee should consider the validity of consent by next of kin, legal guardians, or by other qualified third parties representative of the subjects' interests. In such instances, careful consideration should be given by the committee not only to whether these third parties can be presumed to have the necessary depth of interest and concern with the subjects' rights and welfare, but also to whether these third parties will be legally authorized to expose the subjects to the risks involved.[8]

---

* The 1975 revision states, as a basic ethical principle, that: "When the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation."

DHEW invited comments in 1973 on the proposal that parental or guardian consent be supplemented both by the judgment of a consent committee and by requirements for the assent of the child or incompetent.[9] The following approach was taken regarding the refusal and consent of children:

> 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 unlawful to proceed merely with the consent of the child, but without consent of the parent or legal guardian, the reverse should also hold.[10]

This proposal to require assent of the child was adopted for intramural research by the NIH Clinical Center on July 14, 1975.[11]

Current DHEW regulations provide that consent may be obtained from an individual's "legally authorized representative," which is defined as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to such subject's participation in the particular activity or procedure."[12] Strictly construed, this provision would permit third-party permission only in those jurisdictions which specifically authorize a third party to consent for another's participation in research. While parental authority to consent for medical care is clear, there is no statute or judicial decision granting such authority for nonbeneficial procedures. (See the discussion in Chapter 7 of this report.)

Ethical Positions in Recent Literature. At least five different positions on the involvement of children in research can be found in recent literature.

(1) The most restrictive position is found in the writings of Paul Ramsey. He argues that research which does not directly benefit individual children is always ethically impermissible. His argument rests on the general viewpoint that "nontherapeutic" research should never be performed without the informed consent of the subject. Since young children are not capable of giving informed consent, it is a short step to the conclusion that no research ought to be performed on them unless the research holds out the possibility of direct benefit. In his book, The Patient as Person, Ramsey argues as follows:

> A parent's decisive concern is for the care and protection of the child, to whom he owes the highest fiduciary loyalty, even when he also appreciates the benefits to come to others from the investigation and might submit his own person to experiment in order to obtain them.
>
> This is simply the minimum claim of childhood upon the adult community, whose members may make themselves joint adventurers or partners in the enterprise of medical advancement at cost to themselves if they will.[13]

Ramsey distinguishes "beneficial research," for which parental consent is a proper fulfillment of the fiduciary duty, from "nonbeneficial research," for which he considers third-party permission a breach of the fiduciary duty. It is not merely the exposure to possible risk that he finds unacceptable. Rather, it is the abrogation of "the right of each of us to determine for ourselves, not alone the extent to which we will share ourselves with others, but the timing and the nature of any such sharing."[14] It is thus a claimed violation of respect for persons (by treating others as a means to one's own end) which is morally unacceptable to Ramsey: "where there is no possible relation to the child's recovery, a child is not to be made a mere object

in medical experimentation."[15] Still, Ramsey is concerned with the risk of harm as well as with the violation of autonomy. He argues that the imperative to avoid evil has a moral primacy in biomedical research over the imperative to do good, and he takes this priority as one more support for his general position.[16] Nonetheless, it is the alleged use of human beings merely as means to others' ends that most deeply informs Ramsey's polemic against "nontherapeutic" research.

Ramsey proposes to give ethical primacy to the protection of nonconsenting subjects against wrongful treatment. While this general position must be commended, Ramsey's views are subject to a number of objections. First, it is important to distinguish those who refuse to consent to participation in research from those who are not fully qualified to consent to participation. It would be generally conceded that children who refuse to agree to participate in "nonbeneficial" research should not be involved. But it appears to be increasingly the case that most children are willingly involved in research and give their assent (when capable). Second, Ramsey neglects discussion of the low level of risk involved in most research involving children. His conclusions (though not his actual arguments) would be more supportable if there were a widespread risk of serious harm. In fact, however, much biomedical and behavioral research involves no more risk to children than those risks encountered in their daily lives. Ramsey's proposals for curbing research in general, if acted upon, would render impermissible research that is only observational, or merely uses questions, or involves only paper and pencil tests or procedures of a routine medical

examination. While everyone would agree that the line specifying permissible risk must be drawn somewhere, Ramsey's absolute prohibition seems too restrictive. Ramsey's argument is internally consistent on these matters, in that he would prohibit all research without regard to risk or to the assent of children. It is his treatment of these relevant factors (risk and assent) as irrelevant which is unacceptable.[17]

Third, Ramsey's position rests on a false dichotomy between research intended to benefit subjects directly -- which he concedes is permissible -- and research intended to develop more knowledge. Much research does not fit neatly into either category, since the outcome is uncertain and the research may or may not benefit the subjects involved. Research on chronic diseases, for example, may or may not directly benefit those involved in the research, contingent upon the results of the research. Indeed, the possibility of (even remote) future benefits for the subjects can seldom be ruled out from the beginning.[18]

This problem introduces a further problem about the meaning and scope of the term "research," as Ramsey employs it. Research, by definition, is intended to develop general knowledge. Therapy, by definition, is for the benefit of an individual and therefore does not inherently involve any generalizable component. The term "therapeutic research" thus mixes together two quite different ingredients, and it remains unclear what "therapeutic research" could mean. There are dangers in this unclarity. On the one hand, there is the danger that simply because a benefit (therapy) is included in a "therapeutic" research protocol, all sorts of additional interventions

not germane to the therapeutic intervention but useful for general knowledge can be regarded as justified (under Ramsey's scheme). On the other hand, if a quite narrow but nonetheless reasonable interpretation of "research" is accepted, then one literally could never do any "research" at all, because the research itself (e.g., data analysis) is not therapeutic. Ramsey can perhaps introduce further distinctions to handle some of these problems -- for example by arguing that "therapeutic research" is a certain kind of mixture of controlled studies of alternative therapies, when all treatments are thought to be equally efficacious. But as his work now stands there remain conceptual unclarities which introduce needless confusion.

Ramsey at one point acknowledges that even if there were powerful moral reasons for doing "nontherapeutic research with uncomprehending subjects" such as children, "it is better to leave [this] research imperative in incorrigible conflict with the principle that protects the individual human person from being used for research purposes without either his expressed or correctly construed consent."[19] Ramsey argues that it would be "immoral" either to do or not to do the research, but he maintains that one should "sin bravely" in the face of this dilemma by sinning on the side of avoiding harm rather than attempting to promote welfare. But why must a calculation of benefits and harms always fall on the side of preventing research? In those cases where potentially great therapeutic benefits may well result from research and only minimal risk is involved, it may be reasonably argued that the calculus of morally right actions has shifted.

Ramsey attempts to support his view by appeal to the Kantian maxim that persons ought to be treated as ends only, and never merely as means. But what is it, in the context of research, to be treated merely as a means? When a soldier is conscripted, he is treated as a means (even against his will, in some cases). But he is not treated merely as a means, for none in the military hierarchy is free to do anything with a soldier he wishes. Similarly, a child involved in research may be used as a means, but not merely as a means; for no investigator is free to use a child in any way he wishes. The question remains whether the child is being used in such a way that the treatment qualifies as immoral treatment. And if the child is exposed only to minimal risk (with judicious parental permission and the child's agreement), while substantial benefit may accrue to others, it is far from obvious that any immoral treatment is present. If there were some reason for supposing that children would regard themselves as being violated or as being used as mere means, Ramsey's argument would be strengthened; but in a world where many adults feel themselves morally obliged to help those in need, there is no reason to attribute an unduly selfish attitude to children, as Ramsey's argument often seems to presuppose. Moreover, as Benjamin Freedman has argued, even if children occupy a dependent, morally different status from that of adults -- as Ramsey contends -- it does not follow that parents are derelict in their duty in consenting for children to participation in research. Even though children have some claims upon us for protection, participation in research does not seem to violate their rights unless such participation constitutes a harmful invasion.[20]

(2) The fact that some research on children involves minimal risk and holds out the prospect of benefit for the class of children (but presumably not direct benefit to the research subjects themselves) has been the decisive factor in motivating some writers to accept less stringent criteria than Ramsey's. One example is Richard McCormick, who has written in opposition to Ramsey from the perspective that children have obligations to participate in research. McCormick employs a natural law foundation for his arguments. He maintains that a child ought to do something if that action is expressive of basic values of human nature or purposes of human life. In the case of therapy, for example, it is a reasonable presumption that the child would consent because (in light of the normative ideal of health) the child ought to promote his own health. Similarly in the "nontherapeutic" case, according to McCormick, it is a reasonable presumption that the child would consent because (in light of the normative ideal of contributing to the health of others) the child ought to choose to participate in research. There is a general moral obligation to help others when there is little cost to oneself. Because children (like all individuals in society) ought to benefit others by their actions and would so act if they had a proper moral perspective, it is legitimate to involve them in research (provided it is of no more than minimal risk). McCormick's presumption is not that someone would actually act in a certain way but only that another may validly presume consent because the act is right. Parental consent is said to be morally valid for both "therapeutic" and "nontherapeutic" contexts, because it is based on a reasonable presumption of the child's obligations:

> . . . there are things we ought to do for others simply because we are members of the human community. . . . 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.[21]

In sum: the parent is the vehicle for choosing what the child should rightly chose if he were so situated that he knew what he ought to do.

McCormick's position is subject to a variety of objections. There are at least two possible problems with his claim that we can presume consent because a child ought to consent. First, natural law arguments have been subjected to sharp criticism in ethical theory. In particular, one common objection to natural law theory is that it does not follow from the wide or even universal sharing by human beings of certain values or purposes (e.g., health, happiness, etc.) that human beings ought to promote those values or purposes. For example, from the value human beings place on propagation of the species it does not follow that all persons ought to propagate at will or even that they should propagate at all. It does not follow even if such a value is basic to human nature. This apparent deficiency in McCormick's position is important, since if his natural law foundation is unsupportable, the entire position on children is groundless.

A second possible problem with McCormick's position resides in the claim that consent may validly be presumed where there is an underlying obligation. There are probably numerous activities in which adults ought to participate, but to which many would not consent. The whole point of

obtaining a person's consent is to protect his autonomy. What one person will consent to may vary significantly from what another will consent to because of basic differences of value. To respect persons is to respect their right to their own evaluative choices, including their right not to perform certain actions which other persons believe, with some justification, that they ought to perform. While we have a moral right to demand that individuals fulfill their obligations, some obligations are created only by an individual's own commitments, and we often have no right to demand the commitment itself. Consent is such a commitment, and absent the commitment no valid consent can be presumed (this much is true in Ramsey's position).

Accordingly, it seems certain that we could never validly presume consent on the part of a competent adult subject merely because the person ought to consent. How, then, can consent of the child be validly presumed? As Ramsey has argued, McCormick's position "amounts to the destruction of the protections consent-language was designed to afford."[22] Consent can rarely be presumed, and there seems no way it can be presumed on the part of a child. In short, perhaps the gravest deficiency in McCormick's position is its very core: the notion that the child's consent can be validly presumed.

Ramsey has generalized this conclusion in the following way: if McCormick's standard is used,

> . . . then anyone -- and not only children -- may legitimately be entered into human experimentation <u>without</u> his will or unwillingly. . . . If a child may be treated as

> an adult who would will what he should, then any other nonvolunteer may be treated simply as a child who . . . would will what he should. Any nonvolunteer may be treated as a child who does not will as he ought.[23]

Ramsey's point is that if consent can validly be presumed because of what persons ought to do, then (1) it is hard to find a principled basis for the claim that there is any morally relevant difference between adults and children, and (2) it would follow that the general conscription of adults is permissible. Ramsey's argument does not constitute an objection to McCormick, from one perspective, since McCormick actually favors the conscription of adults. The pertinent point, however, is about consent, not about conscription. The form of McCormick's argument is: if one ought to do it, then consent may be validly assumed. But consent is precisely what may not be assumed even if one ought to do it. One reason why the requirement of informed consent has become so important in recent years is that the consent of some subjects was never solicited, because a prior judgment had been made that they ought to participate.

Moreover, it is not even clear, based on McCormick's arguments, that consent should be a relevant consideration. If a child ought to do something and the obligation justifies the child's doing that thing, then the consent of his parents could neither validate nor invalidate his participation. Parental consent is simply irrelevant to the justification for involving the child in research. To put this point another way, McCormick operates with two levels for the justification of involving children: natural law and consent by

third parties. If the natural law justification is correct, it actually undermines the consent model by rendering it gratuitous.

A possible response by McCormick to some of these arguments is considered at the end of the next section (3). But it is worth mentioning at this point that an alternative interpretation of McCormick's arguments to the one presented above might be offered. In his later writings McCormick's major conclusions appear anchored in the argument that all members of society, including children, have minimal obligations to benefit other members of society. These obligations are created by social circumstances (rather than by some general property of human nature). Among these obligations is that of participating in minimal risk biomedical or behavioral research. Because of these social obligations the child should be willing to participate in research; and parents may be empowered to consent for the child's participation whenever the child <u>should</u> be willing to be involved in the research if the child <u>could</u> comprehend and consent. On this alternative interpretation, "proxy consent" is merely a device to protect the child, and plays no more substantive role in the argument. That is, the obligations children have justify using them, and consent is merely a protective device that plays no role in the justification. McCormick's position is thus turned into a "presumed duty" rather than a "presumed consent" position. If this alternative reading of McCormick is preferable, then his position is perhaps closer to the one that is presented in section (5), below.

(3) A variant of McCormick's stance might be developed along lines proposed by Stephen Toulmin[24] in the course of considering the justification of fetal research. He suggests that instead of beginning with what children ought to do, we might ask whether it may be presumed that they could not reasonably object if they were capable of understanding what is at stake and of making a decision in their own right. This strategy is thought by Toulmin to free the theory of the objection of imputing obligations to children and to reconcile McCormick's approach with common public policy judgments about the validity of involving children in research. Toulmin's proposal is distinguishable from the two positions previously outlined by its philosophical basis. Rather than using a theory of informed consent or natural law, Toulmin makes an appeal to what the reasonable person would agree to choose -- or, as he states it negatively -- what the child could not reasonably object to.

A roughly parallel view, but with an emphasis on the problem of consent, has been advanced by Victor Worsfold.[25] As is common, he distinguishes between those children who have attained the age of reason and those who have not. For those who have not -- the class discussed by Toulmin -- Worsfold suggests that the absence of the ability to make judgments justifies decisions by others (parents), although these must "be guided by the individual's own settled preferences and interests insofar as they are not irrational, or failing one's knowledge of these, by [some] theory of primary goods."[26] In judging the right course, he says, "We must be able to argue that with the development or the recovery of his rational powers the individual in question

will accept our decision on his behalf and agree with us that we did the best thing for him."[27] This position is the positive side of the one proposed by Toulmin. Rather than holding that the child could not reasonably object, Worsfold's criterion is that the reasonable child would approve, in retrospect, an invitation to be involved in research. Additionally, Worsfold holds that children of sufficient understanding have the right to make their own decisions; and he proposes that younger children who are incapable of making judgments entirely on their own nevertheless should be listened to and their preferences taken into account by those who decide on their behalf.

Several possible responses to these theories may be mentioned. In a paper written for the Commission on "Rights, Duties, and Experimentation on Children: A Critical Response to Worsfold and Bartholome," Stanley Hauerwas challenges the current preoccupation with the notion of children's rights. The language of "rights," Hauerwas suggests, is not entirely appropriate to, and in fact is misleading for, an ethical analysis of the place of children as research subjects, although such language may facilitate a formulation of appropriate policy. He argues that "rights language," as applied to the family, inclines us to conceptualize the family as a contractual society of individuals -- which he believes it is not. As a substitute, Hauerwas proposes that the idea of parental duties and responsibilities toward their children (i.e., to love, protect and educate them) provides a better ethical framework on which to base such policy. He focuses on the historical view that being a parent involves an obligation to care for

and to educate one's child in a manner appropriate to making the child a full participant in the community. His central argument is that the child ought to be conceptualized as a family member, and because of this special position the consent and guidance of parents is relevant to the participation of children. For Hauerwas, accordingly, making a case for children's "rights" as Worsfold does runs the risk of destroying what being a child means, by ignoring that a child's need is not for "rights," but rather for trust, love and care.

Whatever the merits of Hauerwas' arguments, perhaps the major problem with the reasonable consent theory resides in the flexible and ambiguous term "reasonable." The reasonableness of nonparticipation in an activity that is primarily charitable or for the benefit of others can be judged only by reference to a person's reasons for nonparticipation. In the case of children, possible reasons for nonparticipation must be projected by others, and a decision about the reasonableness of these reasons must be made by others. This judgment does not centrally involve inferring what a child would do if he could consent. It is a judgment of reasonableness based on a standard that is not the child's, and hence is external to the standard of what the child would do if he could choose. But what precisely is that standard? Is it reasonableness in light of the importance of the knowledge to be gained? Reasonableness in light of the values of the research community? Reasonableness in the eyes of the parents?

Even more problematic is the very justification of the use of children by appeal to reasonableness. Many things might be done to nonconsenting

subjects which they cannot reasonably (in the eyes of most) object to, and yet we would not permit such actions to be performed. The mere lack of a reasonable objection does not justify appropriating others. It seems, moreover, that the reasonable consent position encounters some of the same problems as McCormick's position because it is too broad in scope. If lack of a reasonable objection or reasonable presumption of a later agreement justifies appropriation, then it justifies drafting adults as well as children.

Presumably Toulmin, McCormick and others would argue that the morally relevant difference between a competent adult and a child is that the adult can informedly consent and the child cannot. But why should refusals to consent by adults override drafting them if their refusal is not "natural" or reasonable? The answer must be that we would be exhibiting a lack of respect for them by violating their autonomy and that this disrespect is not being exhibited toward the child, because he cannot express autonomy. While this reply is no doubt correct, it fails to exhibit why mere absence of a reasonable objection justifies any use of another person. Or, to put the point another way, it may be that the absence of a reasonable objection by another person is a necessary condition of using the other person for research, but it is not sufficient. And if it is an insufficient reason, then the reasonable consent position only tells us one condition that must be satisfied if we are to do research on children. It does not tell us that we may do the research if there is an absence of a reasonable objection; yet this conclusion is what is primarily desired in a principled justification.

(4) Some writers have attempted to mediate between Ramsey's entire exclusion of the class of children and McCormick's (and others') apparent entire inclusion of the class. These writers have suggested that children old enough to be educated can be aided in their education by participation in research, but not at earlier ages. The justification for participation, then, is moral development; and if there can be no moral development through participation, the justification is lost. Perhaps the first to suggest this approach was Henry Beecher. In Research and the Individual he suggested, without further elaboration, that

> Parents have the obligation to inculcate into their children attitudes of unselfish service. One could hope that this might be extended to include participation in research for the public welfare, when it is important and there is no discernible risk.[28]

This kind of position has been defended in a paper written for the Commission by William Bartholome.[29] He discusses the involvement of children from age five to seven through age 14 to 16 in research activities. He criticizes Ramsey's total exclusion of children from "nontherapeutic" research as harsh, and suggests that to focus exclusively on informed consent (as Ramsey does) as the moral basis for including subjects in research is to prejudge the answer to the question whether children may participate in "nontherapeutic" research. At the same time Bartholome agrees with Ramsey that interventions in the lives of children can be justified only if they are to benefit the child. These two authors largely differ over what shall count as a benefit. While Ramsey considers only therapy to be beneficial, Beecher and Bartholome consider improved moral character to be a benefit.

Bartholome criticizes McCormick for presuming that adults are able to know what a child should want and rejects McCormick's suggestion that there are certain things a child "ought to do." Children are not morally "transparent," he argues, and thus no adult can know what a particular child should choose. And since it cannot be asked what they would choose, only their needs should be considered in asking about their participation in research. Even if there are certain things that a child ought to want to do for others, Bartholome claims, no one has the right to determine how, when and in what manner such obligations should be fulfilled. Bartholome also disputes what he takes to be McCormick's argument that we owe to future generations the cure or prevention of certain diseases and that, in general, involvement in "nontherapeutic" research is obligatory for everyone. Bartholome prefers to see such rewards for future generations as "gifts" rather than as obligations required by justice or by social need.

To resolve the conflict between the two polar positions exemplified by the writings of Ramsey and McCormick, Bartholome suggests that children may be assisted in their moral education by participating in "nontherapeutic" research, once (at age five to seven) they are able to appreciate the importance of helping others. As part of their general obligation to enhance the moral development of such children, parents should encourage them to take advantage of opportunities for moral growth; and Bartholome contends that involvement in research is one of many activities which parents might select to this end. He distinguishes between the parental

duty to encourage such behavior and McCormick's notion that parents have a right to force children to engage in charitable acts. Bartholome disagrees both with Ramsey's position that "children are not capable by nature or grace of charitable acts" and with McCormick's position that parents have a right to see that their children undertake such acts. Instead, Bartholome considers the parental obligation to be one of moral instruction, which may include encouragement but also requires that the child be a willing participant. Assent by the child should be mandatory, he maintains, and parents should be involved in the process both by deciding whether or not participation in research would be a beneficial learning experience for their child and by participating with their child as "joint-subjects" when the experimental design provides an opportunity for such collaboration.

In an accompanying paper on "The Infant as Person," Bartholome takes the position that infants (i.e., children below the age of understanding) have a right to be treated as persons but, because they have no awareness even of themselves, do not have a moral obligation to the human community. For this reason he would reject "nontherapeutic" research involving infants below the age of five, at least where research requires serious invasive procedures.

In the aforementioned paper by Hauerwas, Bartholome's position is criticized in two respects: first, because informed consent is taken as a primary issue and a necessary ingredient in respect for persons, and second, because it is thought necessary that children be "persons" in order to have

rights and to merit protection. Hauerwas argues that third-person consent, which Bartholome regards as an attempt to protect the child, might more correctly be viewed as an attempt to protect the integrity of the family unit by ensuring that whatever is done to a child is consistent with the moral convictions and traditions of the child's family. Hauerwas argues that children are deserving of care not because they are "persons," but because they are children with a special position in a family unit. Their rights, if they can be said to have rights, are claims against parents and society for the provision of such care. For Worsfold and Bartholome to insist that children be "persons" in order to participate in research, he contends, is to make the mistake of requiring them to be adults in order to be respected, which is to fail to treat them for what they are -- children.

Hauerwas' argument, however, fails to appreciate either the merit or the central problem in the moral instruction position promoted by Beecher and Bartholome. The merit of the position on moral instruction proposed by Bartholome is that it attempts a justification of research by appeal to an actual contribution made to children. It is not implausible to suppose that altruism can be cultivated in children by such "instruction," and these arguments are useful reminders that psychological and moral benefits may be derived from participation in research (a type of benefit apparently overlooked by Ramsey). On the other hand, these positions (Bartholome's, anyway) seem subject to the objection that whenever it could not reasonably be said that a child would be instructed, the research could not be justified. This position seems objectionable for some of the reasons

already mentioned in discussing Ramsey, since the argument partially resembles Ramsey's highly restrictive position. Ramsey argues against allowing research unless there is "therapeutic" benefit, whereas this position stands against doing research unless there is moral benefit to the child. As Bartholome correctly points out, even his own position would exclude the entire class of "uninstructable" children. Unfortunately, his contentions leave unanswered why it would be immoral or otherwise wrong to involve uninstructable children such as infants. In short, while this position may have merit by providing at least a partial justification for certain research, it fails to show that some research on classes of children such as infants cannot be justified on a different basis.

(5) A position with a conclusion similar to the presumed consent and reasonable consent positions, but with a somewhat different theoretical foundation, is that some research on children is justified because of the beneficial consequences to the class of children in general. If this position were stated in extreme form, it would be the unqualified utilitarian position that such research ought to be done whenever-it maximizes social welfare to do so (whether or not the subjects assent or dissent). While no writer seems to hold this unqualified position, two papers done for the Commission give weight to the consideration of benefit to others as the theoretical justification for research. The first paper was done by H. Tristram Engelhardt, Jr.,[30] and the second by Robert Veatch.[31] (Neither paper, however, deals solely or even primarily with research involving children.)

Engelhardt recognizes the absolutely fundamental character of both the principle of respect for individual human subjects and the principle of beneficence (which involves the concern to maximize benefits for society in general), though he considers the protection of autonomy and promotion of individual self-determination to be primary. Accordingly, he rejects the involvement of unwilling subjects in research, even if the results of the research would be of considerable utility.[32] With respect to children clearly too young to consent, he argues that "infants, though often willful, have no free will and are not the object of respect as adults are." Since infants are nonautonomous, there is no obligation to respect autonomy; there is only an obligation to protect them from harm. He further contends that the function of third-party consent in such contexts is not to respect the child as an autonomous moral agent but to safeguard the child's best interest by preserving his or her physiological and psychological integrity. But he regards the notion of third-party consent to be less appropriate than other substitute language might be, since the third-party feature contravenes the purpose of consent. The point of informed consent, he argues, is to respect the freedom of individuals by asking their permission before involving them in research, yet for many children such treatment is impossible and inappropriate.

Engelhardt advances two sorts of arguments bearing on the use of children in research. He first argues that research is nonallowable if it would leave a residual amount of damage to the child. This argument stakes out his restraining conditions on appeals to beneficial consequences. Although his argument justifies research by appeal to beneficial consequences,

Engelhardt also advances one consequentialist argument which actually restricts research. He contends that investigators and parents should always act in the best interest of children in order to provide general support for social practices of attention and kindness to the defenseless and powerless (a larger class than the class of children). Nonetheless, Engelhardt concludes that experiments which may involve minor discomforts but which would not expose children to physical or psychological risks greater than "in the usual ambience," are justifiable "in terms of an appeal to the minimal duties that each of us owe(s) to society."[33] In this argument, his usually strong emphasis on individual self-determination does not apply, and his argument turns on the duties owed to society. These duties are grounded in beneficence rather than respect for persons.[34]

Veatch agrees that "for the most part, it is a mistake to speak of proxy consent for experiments in children";[35] however, parents may approve a child's participation in "therapeutic" research because, as guardians, they rightly serve to protect the best interests of the child, and as parents they are given limited authority to exercise their own self-determination about their offspring, to the extent that their determination does not substantially deviate from the social consensus.[36] He argues that parents may also encourage their children to make minor contributions to the general welfare or to the welfare of specific others. He further maintains that if "the individual is seen as a member of the social community, then certain obligations to the common welfare may be presupposed even in

cases where consent is not obtained." [37] This formulation expresses the common thread of argument from beneficence running through the positions of McCormick, Engelhardt and Veatch. This condition would apply, he says, only in very special cases where there would be no risk or only minimal risk to the subject and when the information to be obtained would be of great social value and could be obtained in no other way. The subject's participation in such research is justified, he contends, because of the substantial contribution to the general welfare which may be made -- a contribution which, even without consent, the "reasonable person would find required." [38] (Veatch, however, adds that proceeding without consent is valid only in the case of very young children where self-determination is impossible. And he is always careful to add that his position does not entail that social benefits can be used to justify a cancellation of individual rights.) Veatch also argues in favor of retaining age 18 as the age of consent for medical treatment, and favors adjudicating on a case-by-casebasis when, in the case of "therapeutic" research, children and their parents disagree. Finally, he proposes that a national committee review all research protocols involving children, using the same review criteria applied by IRBs. [39]

The qualified beneficial consequences position taken by Veatch and Engelhardt would obviously be found deficient by Ramsey and Bartholome, for example, on grounds that it justifies too much. In particular they would argue that it fails to respect persons by subjecting them to risk without consent and without obvious beneficial consequences for the subjects. However, perhaps the largest potential deficit in the positions

taken by Veatch and Engelhardt rests in the lack of specificity concerning the scope of research justified by their principles. For example, how much research (if any) which involves more than minimal risk is acceptable in "nontherapeutic" cases? It is hard to see how an answer could be derived from their theory. Without further argument minimal risk seems a purely arbitrary cut-off point when, in very special cases, substantial benefit for others is in prospect. Both Veatch and Engelhardt are appropriately engaged in the attempt to balance the obligation to protect individuals against the obligation to provide substantial social benefits. While this balancing must be done, it is doubtful that their theories satisfactorily show how and at what point the individual rights of children properly limit their social obligations. Relatedly, it is one thing to argue that some research on infants may be allowed, and another to develop the precise conditions under which it is justified. Neither Veatch nor Engelhardt delineates a rigorous set of such conditions.

Among the well known dangers of social benefit approaches is that they may justify so much on grounds of the principle of beneficence that the principle of respect for persons fails to be applied.[40] That is, the obligation to benefit others (perhaps by developing therapies which avoid harm to them) might be employed in such a way that the obligation to protect subjects is not fulfilled. Both Veatch and Engelhardt attempt to guard against this possibility, because, as Veatch puts it, there are such "great dangers" in unqualified appeals to the benefit of others. Accordingly, what must be said to be lacking in the Veatch and Engelhardt papers is not that they

make no appeal to the principle of respect for persons. What seems in need of development is an explanation of the proper balance to be struck between the competing obligations to respect persons and to benefit those in need of help.

REFERENCES

1. Trials of War Criminals Before the Nuremberg Military Tribunals, U.S. v. Karl Brandt, vol. II, U.S. Government Printing Office, 1949, p. 181.

2. Leo Alexander, Psychiatry: Methods and Processes for Investigation of Drugs, 169 Annals N.Y. Acad. Sci., 1970, p. 347.

3. Andrew Ivy, The History of the Use of Human Subjects in Medical Experiments, 108 Science 1948, p. 1. For an extended discussion of this matter see Beecher, Research and the Individual: Human Studies, Little, Brown & Co., Boston, 1970, p. 277.

4. Medical Research Council, Great Britain, Responsibility in Investigations on Human Subjects (1963) in Beecher, op. cit., pp. 262, 265.

5. Ibid.

6. World Medical Association, Declaration of Helsinki, 1964, in Beecher, op. cit., p. 277.

7. Ibid., p. 279.

8. DHEW, The Institutional Guide to DHEW Policy on Protection of Human Subjects, DHEW Publication No. (NIH) 72-102, December 1, 1971, p. 7.

9. DHEW, Protection of Human Subjects, Policies and Procedures, 39 Federal Register 31742, November 16, 1973.

10. Ibid.

11. Policy and Communications Bulletin, The Clinical Center, No. 75-5 (July 14, 1975).

12. 45 CFR § 46.103 (1975).

13. Paul Ramsey, The Patient as Person, Yale University Press, New Haven, 1970, p. 25.

14. Ibid., p. 39 (quoting Oscar M. Ruebhausen, Experiments with Human Subjects, 23 Records of N.Y. Bar Association, Feb., 1968, p. 93).

15. Ibid., p. 12.

16. Ramsey, Children as Research Subjects: A Reply, Hastings Center Report, April 1977, pp. 40f.

17. See Chapter 3 of this report.

18. Ramsey does say, however, that benefits are sometimes unclear and would make a difference in emergency situations. Cf. The Patient as Person, p. 15.

19. Ramsey, The Enforcement of Morals: Nontherapeutic Research on Children, Hastings Center Report, August 1976, p. 21.

20. Benjamin Freedman, A Moral Theory of Informed Consent, Hastings Center Report 5, August 1975, pp. 29–39. Cf. esp. p. 38.

21. Richard McCormick, Experimentation on the Fetus: Policy Proposals, Report Submitted to the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1975. In Appendix: Research on the Fetus, DHEW Publication No. (OS) 76–128, 1976, pp. 5–3 and 5–4. For a fuller discussion by the same author, see Proxy Consent in the Experimentation Situation, 18 Perspectives in Biology and Medicine, Autumn, 1974, and Experimentation in Children: Sharing in Sociality, Hastings Center Report, December 1976.

22. Children as Research Subjects: A Reply, p. 40.

23. The Enforcement of Morals: Nontherapeutic Research on Children, p. 24.

24. Stephen Toulmin, Fetal Experimentation: Moral Issues and Institutional Controls, Report to the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1975. In Appendix: Research on the Fetus, DHEW Publication No. (OS) 76–128, 1976, pp. 10–7 and 10–8.

25. Victor Worsfold, A Philosophical Justification of Children's Rights, Harvard Educational Review, vol. 44, no. 1, February 1974.

26. Ibid., p. 154, quoting Rawls, A Theory of Justice, Harvard University Press, 1971, p. 249.

27. Ibid.

28. Boston: Little, Brown & Co., 1970, p. 63. Cf. W. J. Curran and H. K. Beecher, Experimentation with Children, JAMA 10 (October 10, 1969), pp. 77ff.

29. The Ethics of Non–Therapeutic Clinical Research on Children.

30. Basic Ethical Principles in the Conduct of Biomedical and Behavioral Research Involving Human Subjects (December 1975).

31. Three Theories of Informed Consent: Philosophical Foundations and Policy Implications (February 2, 1976).

32. Engelhardt, p. 7.

33. Ibid., pp. 36–37.

34. Ibid., pp. 35–37.

35. Veatch, p. 35.

36. Ibid., p. 36.

37. Ibid., p. 37.

38. Ibid., p. 38.

39. Ibid., p. 49.

40. This form of reply to the Veatch and Engelhardt type of approach is found in Hans Jonas' essay, Philosophical Reflections on Experimenting with Human Subjects, in Paul A. Freund, ed., Experimentation with Human Subjects, George Braziller, Inc., New York, 1970. He construes such research as a duty only in emergency situations.

CHAPTER 9. DELIBERATIONS AND CONCLUSIONS

The Commission's recommendations on research involving children were adopted unanimously with the exception of Recommendation (5), from which Commissioners Cooke and Turtle dissented. Various members of the Commission preferred different statements (or supported more than one statement) of the rationale for their recommendations, and three such statements are included below. Statements explaining the two dissents are also included.

Statement of Commissioners Height, King, Louisell, Ryan and Seldin

The Commission has identified three ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects: beneficence, respect for persons and justice. In the case of research involving children, as in other difficult cases, the challenge is to find a proper balance in applying these principles and to establish priorities among the principles when they appear to be in conflict.

Beneficence. Beneficence requires both the provision of benefit and the avoidance of harm. This principle is applied to research involving children in several ways. The promotion of health, by improving methods to prevent or treat a disease or abnormal condition and to foster optimal growth and development, is a benefit that serves as a general justification of research. Similarly, the imperative to avoid harm may serve as a justification for research designed to evaluate the safety and efficacy of procedures in standard

practice. Avoidance of harm also requires that risk to human subjects be reduced or eliminated in the actual conduct of research.

In order to promote the health of both children and adults, the participation of children in research is needed. In many cases, children are the only possible subjects for research designed to study the nature of childhood disorders, some precursors of adult disorders, and the normal physiological, psychological and social development of children. The benefits from such research may accrue to the individual research subjects or to children as a class.

Research also makes possible the avoidance of harm that may result from the application of routine practices. This benefit is illustrated dramatically in the case of infants, who cannot survive without the intervention of others and for whom some previously accepted procedures have been proven dangerous. Research has been required, for example, to learn the correct levels of oxygen, fluids and nutriments that are necessary to sustain the life of newborns without harming them. On grounds of beneficence, therefore, the Commission considers the conduct of certain research involving children to have strong ethical justification (Recommendation (1)).

The conclusion that research involving children may generally be justified on the grounds of beneficence does not mean that all such research is therefore justifiable. The principle of beneficence also requires that those who conduct or sponsor such research protect children from harm by limiting the risk to which children may be exposed as research subjects. In Recommendation (2) the Commission applies the principle of beneficence by delin-

eating general conditions that all research involving children should meet. In Recommendations (3), (4), (5) and (6), the Commission addresses the problem of determining the proper balance between the importance of conducting research in order to promote health and the imperative to avoid harm to the children who are subjects of that research. These considerations are reflected in provisions regarding the nature of anticipated benefit that may justify the involvement of children in research.

The Commission has concluded that problems related to two kinds of research are comparatively straightforward. Where the risk of harm presented to children by a research project is no more than minimal (Recommendation (3)), no particular problems are presented so long as general provisions are fulfilled (Recommendation (2)), and so long as appropriate provisions are made for soliciting and receiving both parental permission and the assent of the children who may be asked to participate (Recommendation (7)).

The second kind of research that presents relatively few ethical problems is that in which the risk is related to an intervention that holds out a reasonable promise of benefit for the individual subjects. The acceptability of the risk presented by such an intervention should be determined in the same way that the acceptability of risk is determined for interventions that are applied in standard practice. Risk may be justified by an avoidance of greater harm or by the provision of an important anticipated benefit to the individual exposed to risk. Thus, if the anticipated benefit to the children for whom the intervention is proposed is greater than the attendant risk, the intervention is justified; and if the risk-to-benefitratio of the proposed

intervention is at least as good as that of other available approaches (including refraining from any intervention), then the study of that intervention is ethically acceptable even if the risks are more than minimal (Recommendation (4)). The benefits that are expected to be derived from a therapeutic, diagnostic or preventive intervention, however, justify only the risk associated with that intervention (including such procedures as may be necessary, for reasons of safety, to monitor the effects of the intervention). Risk associated with other procedures, performed purely for the purpose of acquiring generalizable knowledge, cannot be justified merely by inclusion in a protocol that also includes procedures from which subjects may derive direct benefit.

The most difficult ethical issues for the Commission arose with respect to research presenting more than minimal risk but no immediate prospect of direct benefit to the individual children involved. Some members of the Commission urged that the limit for such research remain at the level of minimal risk; others pointed out that such a limit might eliminate much research that has great scientific significance and the promise of substantial long-term benefit to children in general, while possibly avoiding only minor additional risk to the research subjects. Much of the Commission's later debate was focused on this class of research projects. The Commission was seeking to determine the circumstances (if any) under which such research might be ethically acceptable, and, if so, what review procedures would be appropriate to assure proper protection of the research subjects.

In their resolution of this question, the Commission relied largely upon two considerations. It noted, first, that the scope of parental authority

routinely covers a child's participation in many activities in which risk is more than minimal, and yet benefit is questionable. (Involvement in skiing and contact sports are two examples among many.) The Commission was also impressed by reported examples of diagnostic, therapeutic and preventive measures that might well have been derived from research involving risk that, while minor, would be considered more than minimal.

Ultimately, the Commission decided (with two members dissenting) that if three additional conditions are satisfied, research in this most difficult class of cases could be justified (Recommendation (5)). First, the risk involved must be only a minor increment beyond minimal. In addition, the procedures to be used must be reasonably commensurate with (similar to) those with which prospective subjects have had experience. Further, the research must be likely to yield generalizable knowledge important for the understanding or amelioration of the subjects' specific disorder or condition. Thus, foreseeable benefit in the future to an identifiable class of children may justify a minor increment of risk to research subjects.

In exceptional situations, dangers to children or the community resulting from a failure to involve children in research might exceed whatever risk is presented by that research. For instance, the threat of an epidemic that could be offset by developing a safe and effective vaccine might justify research involving risk greater than otherwise acceptable to establish safety, efficacy and dosage levels for children of different ages. The outright prohibition of such research on grounds of risk might constitute an exception to the general rules enunciated above, however, the

decision to permit its conduct should be made at the national level, with opportunity for public participation. In Recommendation (6), the Commission suggests procedures by which this goal may be accomplished. The same procedures should be invoked to review any research that cannot be approved by an IRB under the guidelines set forth in this document, whenever a review board considers that for urgent or unique reasons the research should be permitted.

Respect for persons. This principle requires that the choices of autonomous individuals be respected. It is applied in the conduct of research by asking permission of autonomous individuals before involving them as subjects of research. Problems arise, however, regarding individuals with diminished autonomy and thus diminished capacity to consent; and objections to the involvement of children in research have been based on children's incapacity, or lesser capacity, to give valid consent to their participation as subjects. Indeed, most of the literature has focused on this problem, and the most restrictive position (exemplified by Ramsey) is that children should not be involved in any research unless it is reasonably expectable that they will derive some direct benefit from their participation.

The Commission considered seriously the arguments presented by those engaged in the current debate about the legitimacy of third-party consent (see Chapter 8 of this report). The Commission concluded that the incapacity of children to consent is one aspect of a more general condition of dependency on adults who are responsible for their care. The permission that parents give for children's participation in research can be accepted as

an exercise of their general role, as caretakers, to guide decisions affecting their children's lives and activities. Although some critics have challenged the right of parents to make decisions for their children to participate in research, the Commission is persuaded that the practical need for parents to manage the details of the child's life legitimately extends to such decisions.

One consideration that does justify the placing of limits on parental or guardian authority is respect for the developing autonomy of children. The Commission has concluded that any child capable of some degree of understanding (generally, a child of seven or older) should participate in research only if the child assents. Even the objection of a very young child should be binding except for situations in which the research involves a therapeutic intervention that is unavailable outside the research context. This conclusion is consistent with a recent trend in both law and philosophy to respect the rights of children and to encourage their development toward assuming responsibility for their decisions. It is also consistent with the reported ability of children of school age to make decisions concerning their activities (see Chapter 6), and with the practice of investigators in pediatric research who commonly seek the assent of children at seven years of age and older before accepting them as research subjects (see Chapter 3).

Recognition of the capacity and the right of children to make their own determination regarding participation in research resolves important ethical problems about third-party consent. By respecting the developing

autonomy and moral responsibility of children (as proposed by Worsfold and Bartholome and to some extent by Engelhardt and Veatch), the problem of involving children in research against (or without) their will is avoided. This conclusion does not resolve the considerable difficulties that may arise in determining how informed and responsible some children are, and thus is not to be construed as an unrealistic application of the principle of respect for persons. One unresolved area concerns the involvement of infants and children who are incapable of assenting or of objecting to their participation. For this class of children, the Commission believes (as anticipated by Veatch and Engelhardt) that benefits either to the subjects or to the class of children may justify the involvement of children who are unable to indicate willingness or unable to object, provided their parents (or some other appropriate third party) protect their physical and psychological integrity throughout the research project, and provided further that strict limitations are placed on the risk to be permitted.

It must be recognized that there may be occasions when parental or guardian interests are at odds with the best interests of their children. When parental permission cannot be relied upon as a protective mechanism (as in cases of child abuse, for example), alternative mechanisms should be set in place to protect the health and welfare of the children. In other instances (for example, when the research involves treatment of conditions such as venereal disease or drug abuse) a requirement for parental permission may actually jeopardize the health or welfare of a child. In the latter cases, the assent of the child should be sufficient as it now is in those

jurisdictions where children may consent on their own to treatment of such conditions. (The Commission's conclusions regarding consent are reflected in Recommendations (7) and (8).)

There are several additional conditions that respect for persons requires in the conduct of research: e.g., that the time and inconvenience requested of subjects be justified by the importance of the research and by the soundness of its design, even if no more than minimal risk is involved; that the privacy of children and their families be protected; and that the confidentiality of data be maintained. (These conditions are set forth in Recommendation (2).)

Justice. Justice is a moral principle that requires a fair distribution of burdens and benefits in a given population. In research contexts this principle requires that the burdens of being involved in research should be fairly distributed and that the benefits produced by the research also should be fairly allocated. There are at least two dangers of injustice that might result from the involvement of children in research. First, certain groups of children may be overutilized as research subjects due to their ready availability. For example, there are manifest dangers that children living in orphanages or in special training facilities might be exploited for purposes of research. Given their dependent status and their diminished capacity to consent, it is important that children be protected against selection solely because of administrative convenience or because their illness or socio-economic condition render them especially vulnerable. It does not follow that such groups of children can never be involved in research. The point is that since there is a relevant inequality in their situation, they should not be

treated in the same way all other children are treated; rather, they should be afforded additional protection. However, it may be justified to involve that class of children in research concerning their specific condition. This conclusion is an application of the formal principle of justice that equals should be treated equally, while those unequal in morally relevant respects may be treated unequally.

Second, wherever appropriate, animal and adult studies should be conducted prior to the involvement of children in a research project. Studies on older children should also be conducted prior to the involvement of younger children and infants. This distributive principle is itself justified by certain conclusions already derived from the principles of respect for persons and beneficence. Respect for persons requires obtaining informed consent whenever possible. Since informed consent is far more likely to be obtained in a meaningful way from the adult population, and since older children can be more easily informed than younger ones, respect for persons dictates that adults and older children be respectively first and second in the order of persons selected as subjects of research. Beneficence also plays a role because it is easier to avoid doing harm to adults and older children than to younger ones. Young children often do not accurately report their feelings or physiological responses, and investigators are thus not likely to know if something unusual occurs. Accordingly, infants might be at greater risk than adults participating in the same research. In short, beneficence and respect for persons provide a dual justification for the claim that, as a matter of distributive justice, research risks should be allocated to adults rather than to children whenever feasible. Justice also

requires that special classes of children not be inequitably selected as research subjects -- no matter how significant the research may be (Recommendations (2), (9) and (10)).

Statement of Commissioners Brady, Jonsen, Lebacqz, Louisell, Ryan and Stellar

During the course of its deliberations, the Commission has recognized that biomedical and behavioral research brings about certain benefits for individuals and society. Discovery of new information, improved understanding of the human condition and the environment, better treatment of disease or other disorders: these are the obvious benefits to individual subjects and to society that have resulted and continue to result from research. Insofar as research is directed to these goods, it manifests the ethical principle of conferring benefit and avoiding harm. This is the first of the ethical principles that the Commission has identified as underlying the conduct of research.

In the case of research with children, it is obvious that significant benefits for individual subjects and for society have been produced. Participation of children in research has led to many discoveries that have improved the health of children. Children are often the only possible subjects in those investigations studying the normal physiological, psychological and social development of children, the nature of diseases peculiar to children, and the childhood precursors of disorders that are manifest only during adult years. In addition, research uncovers, and makes it possible to prevent, harm that results from some common and routine practices of dealing with children.

This benefit is dramatically illustrated in the care of infants, who cannot survive without the intervention of others and for whom some standard medical procedures have been proved dangerous. Research has been required, for example, to learn the correct levels of oxygen, fluids and nutriments that are necessary to sustain the life of newborns without harming them. In the light of such evidence, it is obvious that biomedical and behavioral research involving children conforms to one essential ethical principle: it contributes to the good of individuals and, consequently, to society while also contributing to the avoidance of harm.

However, it is also obvious that research involving children encounters major ethical objections, for, while much of such research involves nothing more than observing and recording the activities of children, some investigations seek information that can be obtained only by exposing the subjects to some risks that would not otherwise be part of their lives or their care. That same principle of conferring benefits also requires, not only that harmful current practices be revealed, but that harm to individuals be avoided. Thus, research with children, to the extent that it involves any exposure to otherwise nonexistent risks, raises a serious ethical question and calls for particular ethical justification. In addition, some assert that even where harm is not an issue, the researcher breaks into the privacy of the child in a way that is not ethically justified. For example, one author asserts that "children can be wronged, without being harmed."

In the case of research with adults, the problem of risk and the problem of privacy, as a rule, can be answered by insisting on the free consent and

informed consent of the participant in research. The practice of generally requiring free and informed consent of adult subjects, which is recognized by all recent codes of ethics of research, rests upon the second major principle that the Commission has identified as underlying the ethical conduct of research: the principle of respect for persons. This principle can be understood as the source of the obligation that all persons be allowed to select and follow those courses of action which they judge good for themselves, unless their activities cause harm to others. In accordance with this principle, research participation ought never to be imposed on individuals against or without their willingness, provided they are capable of expressing their willingness. However, the principle of respect for persons can be stated in a more fundamental manner. It established the obligation that each person be acknowledged as a unique being, and dealt with in terms of his or her own desires, needs and purposes. If the person is capable of communicating those unique desires, needs and purposes, that expression becomes the first and, in most cases, the final and deciding factor in how others ought to act toward them. Children are often absolutely incapable of such communication; when they can communicate, they may do so only imperfectly. Children's desires, needs and purposes are imperfectly developed, their self-understanding and understanding of the world is incipient, and their judgments, when formulated, are limited. Still, the ethical principle of respect extends to them: it demands respect for their reality as children. This respect requires protection of their evolving autonomy, a protection which should lead them toward maturity and, at the same time, shelter them from harm which they cannot themselves ward off.

Finally, whatever benefits issue from the research should be distributed throughout the society in ways that are fair, and the burdens of any research that is permitted should not fall unduly on certain persons or groups. Thus, the principle of justice, identified by the Commission as the third ethical principle, supplements the principles of respect and conferral of benefits.

The Commission considers that all of these principles must be taken together as the necessary and sufficient conditions for the ethical conduct of research regarding children. Unless research can be designed which reflects all three, it cannot be called ethical. However, the Commission admits that the production of benefit, the avoidance of harm, respect for persons, and justice are complex notions that must be refined in ways which, on the one hand, make them more specific and, on the other, remain true to their essential meaning. Its deliberations were directed toward an attempt to view research with children within the perspective of all these ethical considerations. Its conclusions reflect the difficult effort to interpret these principles and to make appropriate distinctions in their application to the variou general situations found in research involving children.

Recommendation (1) states the Commission's conclusion that the evidence bears out the social value of research with children. It also states that the Commission is satisfied that the benefits of research can be sought in ways that meet the ethical standards that ought to underlie the conduct of all research. Recommendation (2) proposes that reasonable and informed persons, in judging whether any proposal for research with children meets ethical standard should invariably demand assurance on several points. Considerations of pro-

viding benefit and avoiding harm are reflected in the provisions that research be scientifically sound and significant and that its risks be minimized. Considerations of respect are reflected in the provisions about protection of privacy and confidentiality. Considerations of justice are reflected in the provisions to conduct studies first on animals or adults and to select subjects equitably.

Recommendation (3) applies the principle that harm should be avoided. It acknowledges that where no risk at all or no risk that departs from the risk normal to childhood (which the Commission calls "minimal risk") is evidenced, the research can ethically be offered and can ethically be accepted by parents and, at the appropriate age, by the children themselves. The Commission has taken this position because it has concluded that the scope of parental responsibility includes the right to choose activities and to define a manner of life for their children. It is inevitable that many activities and events of childhood involve some risks. No one suggests that parents must shield their children from all risks; some propose that permitting only those risks of activities likely to benefit the child lies within the parental prerogative. The Commission considers this position too stringent and artificial, since many of the experiences which parents generally allow to their children are somewhat risky and cannot be said, without forcing the case, to involve particular benefits. The Commission, then, has concluded that, when risks entailed in research are equivalent to normal risks of childhood, parents may properly permit these risks.

Recommendation (4) applies the principle of conferral of benefits to the situation in which a particular child is the intended beneficiary of an in-

tervention which does entail risks "more than minimal." Whenever benefits and harm may accrue to the same person and when that person has some needs that require remedy, it has long been considered ethically appropriate to "balance" the risks and benefits and to proceed on the showing that "benefits outweigh the risks." The Commission has taken this concept a step further. It has decided that the justification of the contemplated course of action on the basis of the risks and anticipated benefits associated with it should be at least as strong as the justification on the basis of risks and anticipated benefits of any other course of action (or nonaction). Unquestionably, this sort of calculation is a matter of discretion. It cannot easily be expressed in quantitative terms, although in some cases statistical data about possible benefits and risks can be adduced as evidence. In the last analysis, the concerned parties, namely, the researchers, the reviewers, the parents and, if possible, the child, must attempt to form a judgment of acceptability.

Recommendations (5) and (6) represent the most difficult problem in reconciling all appropriate ethical principles. This problem arises when interventions dictated solely for research purposes, with no intention of benefiting the subject, present more than minimal risk. Some members of the Commission urged that the limit for risks of any interventions not intended to benefit the subject be held to the conservative level of "minimal risk"; others pointed out that such a limit would proscribe much research that promises substantial future benefits to many children. Much of the Commission's later debate centered on this class of research projects.

Most of the Commissioners agreed that a minor increase in risk would be permissible in order to attain substantial future benefits to children other than the subject. "Minor increase" refers to a risk which, while it goes beyond the narrow boundaries of minimal risk determined by the Commission, poses no significant threat to the child's health or well-being. Moreover, the Commission requires that the research activities presenting such risks be similar to the experiences familiar to the children who would be the subjects of the research. Such activities, then, would be considered normal for these children. Given this conservative limit, the Commission concluded that promise of substantial benefit does justify research which goes beyond, but only slightly beyond, the minimal risk. The Commission considers that, as in the question of "no more than minimal risk," permission to allow such research lies within the scope of parental responsibility. In addition, children capable of more mature judgment may wish to volunteer for research of this sort.

Ultimately, the Commission decided (with two members dissenting) that if three conditions are satisfied, research in this most difficult class of cases could be justified (Recommendation (5)). First, the risk involved must be only a minor increment beyond minimal. In addition, the procedures to be used must be reasonably commensurate with (similar to) those with which prospective subjects have had experience. Finally, the research must be likely to yield knowledge important for the understanding or amelioration of the subject's specific disorder or condition from which the subject suffers, even though the subject may not actually benefit. Thus, foreseeable

benefit to an identifiable class of children may justify a minor increment of risk to research subjects.

The Commission acknowledged that exceptional situations may arise in which considerable dangers to children or to the community at large might be avoided or prevented by exposing children to research attended by more than minimal risk. Some might offer the ethical argument that avoidance of great danger or disaster outweighs the injunction against exposing children to risk of more than minimal harm. For instance, they may say the threat of an epidemic that could be offset by developing a safe and effective vaccine might justify research involving risk greater than otherwise acceptable to establish safety, efficacy and dosage levels for children of different ages. The outright prohibition of such research on grounds of risk might have consequences which themselves appear unethical.

Faced with such a hypothetical situation, the Commission found itself confronted by a common dilemma: regardless of whatever course is chosen, some benefit may be foregone and some harm may be done. Rather than attempt to resolve the dilemma in the abstract, the Commission has chosen to recommend that the ethical argument should be made, not over a hypothetical case, but over an actual situation, in which the real issues and the likely costs of any solution can be more clearly discerned. The ethical principles at stake are the moral obligation to protect the community or to come to the aid of certain sufferers within it and the moral prohibition against using unconsenting persons, at considerable risk to their well-being, for the promotion of the common good. These principles are of such moment and their

observance so basic to a just and humane society that any debate about their application should be held at the most public level of discourse. Thus, Recommendation (6) urges that should such a situation occur, it be defined in the most stringent way and determined by those at high levels of public accountability.

The central point of contention in the debate over the ethics of research involving children is the question of consent. The codes of ethics of experimentation and almost all commentators agree that free and informed consent of the subject should be required for participation; however, as we have noted in Chapter 8, they are ambiguous regarding children. When they do admit the participation of children, they do so on condition that proxy consent is granted by parents or guardians. Proxy consent, of course, is not free and informed consent of the subject, but rather the permission of another.

Recommendations (7) and (8) deal with issues related to "informed consent." As noted above, the requirement to seek informed consent derives from the principle of respect for persons. This principle means both that the free choices of persons should be respected and that their individual needs, desires and life situations be acknowledged and honored. The Commission admits that infants are quite incapable of consent and that children exhibit in varying degrees the activities which can be recognized as understanding and consent. Since children are not autonomous, that is, fully capable of informed, reflective decisions, other aspects of their life situation besides autonomy are important in determining what "respect for persons" requires. The Commission decided that the dependence of children on adults, which is both the

condition for their growth and the source of their vulnerability, is ethically relevant. Moreover, the Commission acknowledges and affirms the importance of the family in the child's life: to be a child is, generally, to be a member of a family. Respect, then, requires that children be protected from influence and circumstance that would (in the case of children, at least) impede their growth or compromise their health, safety or future well-being. In the case of children, this calls for an awareness of the limits and the potentiality of childhood, at varying steps in its development, as well as acknowledgement of the social milieu in which children live.

The Commission reached the conclusion that, as a rule, decisions about the participation of children in research should reflect a combination of respect for the general prerogatives of parents in protecting the health and safety of their children and respect for the maturing autonomy of the child. The Commission, therefore, recommends that the IRB assure adequate provisions are made for soliciting assent and permission (Recommendation (7)). It also suggests that the objection of a child to an intervention imposed for research purposes alone should generally be binding. In so doing, it permits the child to protect itself from unpleasant experiences and respects the maturing autonomy of the child. In view of the presumption that very small children are specially vulnerable and that parents are generally the best protectors of their children, the Commission also recommends that the IRB consider whether parents should be intimately involved, sometimes even present, in research activities that may disturb very young children or infants.

The Commission also notes that childhood is a changing state and that children become progressively more capable of reflective choices. Empirical studies have revealed the maturation, at particular ages, of children's ability to make ethical judgments. While there is debate about precise ages, the Commission has selected age seven as the age that may be considered as the time when children become capable of some reflective judgment. For procedural purposes, it imposes this age as the suitable time to consult the child about research. Since some research bears no benefit to such child, the Commission has decided that, in such cases, the child's refusal to participate should be determinative. In those cases where investigational procedures are being done with specific therapeutic intent and hold out the prospect of benefit that is available to the child only in the context of research, the Commission, recognizing the imperfect nature of a child's assessment of circumstances, allows the parental judgment to be final.

The Commission notes that the growing autonomy and privacy of children is recognized by some jurisdictions, where older children are permitted to give consent for specific medical interventions. Moreover, Commissioners were aware that informing some parents of proposed research involving their children might jeopardize rather than contribute to the child's welfare (e.g., in cases of venereal disease or child abuse). Thus, the Commission recommends that whenever parental permission is not a reasonable requirement to protect the well-being of the child, alternatives should be required by the IRB (Recommendation (8)). Here, it operates under the general moral principle to avoid harm as well as to respect the autonomy of older children. In addition, the Commission recognizes that some parents are unsuited to

care well for their children, and that some children are without caring parents. In these situations, the Commission requires an advocate for the child, to take the place of a parent (Recommendation (9)).

Finally, Recommendation (10) requires that additional special protections be invoked where children are institutionalized.

Statement of Commissioner Louisell

I hope that the alternative ethical rationalizations of the Commission's recommendations will not produce confusion. Each I think is an acceptable position paper so far as it goes. The assumed need for both reflects, I believe, the grave and inherent difficulty occasioned by Recommendation (5), which deals with potentially nontherapeutic experimentation involving more than minimal risks. Such experimentation on children can be morally justified, if ever, only to fulfill an essential social need analogous to that involved in the drafting of youth for national security purposes. Resolution of this kind of a moral dilemma in a democracy at a minimum requires decision by society's highest political voice, and that is why I have insisted upon Congressional review as a condition of this type of experimentation.

Caution respecting experimentation on children can hardly be excessive, especially in an era when new inhibitions on the power of government to protect children are surprisingly found in the Constitution itself. Carey v. Population Services International, 97 Sup. Ct. 2010 (1977).

Dissenting Statement of Commissioner Cooke

Recommendation (5) permits the involvement of infants and children who are unable to consent in research which is highly important to reduce harm to other individuals with similar conditions at some subsequent time, but which offers no prospect of immediate or delayed benefit to the subjects despite the confusing implication of section (C) that the subjects' disorder might be ameliorated. If the subjects were truly able to volunteer rather than parents volunteering them, such a recommendation would be acceptable even though the risk exceeds minimal. Further, if the risk were no more than what is commonly understood to be "minimal" -- that is, only a slight additional risk beyond that of everyday life -- parental permission would be acceptable if the parents (one or both) also participated in the research and could withdraw the infant or child if discomfort seemed excessive.

By the designation of acceptable risk as that beyond minimal even to a "minor" degree, the Commission transfers to each Institutional Review Board the decision regarding the limits of "minor." Although a process is provided for judging "minor," no traditional guidelines exist nor are any examples provided. Considerable disparity can then be expected in such determinations by one IRB or another.

This recommendation does avoid the cumbersome transfer of much research approval to a National Ethical Advisory Board, but because of the differences in IRB performance it is likely that ethical review will be carried out by the NIH study sections, which will be forced to operate as a surrogate National

Ethical Advisory Board, but without public debate or exposure as required in Recommendation (6).

In the ethical justification of its recommendation the Commission can invoke only the principle of utility. This in itself does not constitute any breach of ethics, but it does indicate the perilous nature of the recommendation and the ethical uncertainty of the Commission.

Dissenting Statement of Commissioner Turtle

Preliminary Statement

Throughout the Commission's deliberations, I have expressed many reservations about the involvement of children as research subjects. My fellow Commissioners have heard me out in each instance and accommodations have been reached in all areas* except one -- the special status, if any, to be accorded sick children with regard to their potential involvement as research subjects where no foreseeable benefit will accrue to the subject.

I believe that the substantial majority of the Commission (9—2) has committed clear error in approving Recommendation (5), potentially subjecting

---

* My problems with "proxy consent" have been dealt with by obtaining parental permission and children's assent and in recognizing that a child's objection at any stage of the project is determinative. This protection is similarly afforded to infants through encouragement of the participation of a parent in those situations in which the child is clearly dependent (Recommendation (7)). The problem of an Executive "kiddie draft" for more than minimal risk research in response to another "swine flu" scare is ameliorat by the requirement for Congressional notification and real opportunity for debate and action (Recommendation (6), Comments).

sick children to greater risks than other children without regard to foreseeable benefit, and thus, I must register this dissent to that Commission recommendation.

Conclusions

1. Sick children cannot be deemed to be a morally relevant separate class for purposes of relaxing protective measures and mechanisms.

2. Sick children, if capable of being placed into a morally relevant separate class, would require even greater protection than that afforded to children in general.

3. The distinctions attempted in both sets of deliberations* are shams and there is no legal, ethical or social basis for subjecting sick children risks merely because a foreseeable benefit might accrue to more than minimal to an identifiable class of children in the future.

Argument

1. Sick Children Cannot be Deemed to be a Morally Relevant Separate Class for Purposes of Relaxing Protective Measures.

Only one set of deliberations presents any argument for affording less protection to sick children than to all other children. It posits that sick children are by the very nature of their condition subject to certain unique

* The Commissioners have presented two sets of deliberations, the rationale for the majority position on Recommendation (5) is found at pages 126 through 127 and 138 through 140 of this report.

risks and experiences, and relies on the limitation that added research "risks be similar to the risks and experiences familiar to certain classes of children" to conclude that the added research risks "are normal for these children." This rationale is a perversion of the Commission's attempt to define "minimal risks" as relating to the ordinary everyday risks of childhood.

Children, who through no fault or choice of their own, are subjected to greater risks incident to their condition or necessary treatment, cannot ethically be assumed to qualify for additional increments of risk. To do so, is to add to the potential burdens that result, directly or indirectly, from the child's illness. This is especially true when the Commission places more restrictive limits on the involvement of normal children (Recommendation (3)). The natural and intended consequences of providing restrictive limits on one subject group, and relaxing limits on another, is a direction to researchers to involve more sick children as research subjects. Nowhere is such a direction countered by any requirement that research projects not involve sick children if normal children would likewise be scientifically appropriate subjects.

Taken as a whole the Commission's recommendations mandate that research involving more than minimal risk will be carried out on sick children, simply because they already are subject to similar or greater risks. The aggregate impact of risks is ignored and the burdens of research "fall unduly" on the sick child in clear violation of the Commission's own formulation of the principle of "justice."

The aggregation of risks concept and the impact of sickness on other protective mechanisms would, if properly assessed, require that sick children be segregated from others for purposes of special protection as described below.

2. Sick Children, if Capable of Being Placed into a Morally Relevant Separate Class, Would Require Even Greater Protection Than Others.

a. The Principle of Beneficence Must be Applied. The Commission has adopted as one of its basic ethical principles the principle of beneficence. This principle which directs, at the least, that we do no harm requires that those who, by virtue of their condition already experience greater than normal risks, should be protected against any increment of risks, no matter how slight. Thus, in assessing risks to a subject in both a legal and ethical sense, it is necessary to take into account the known fragility of the subject as a result of his existing conditions before creating a situation in which any increment of risk, no matter how minimal, can be added. There are some societies which do not grant equal value to the sick and the healthy. It has always been my assumption that our society was not among them and that we considered that we had a special need to protect and assist those, who through no fault of their own, might be at a disadvantage or most vulnerable. The Commission's Recommendation (5) is directly contrary to my understanding of the principle of beneficence as it is applied in our society.

b. Other Protective Mechanisms Which Generally Supplement the IRB May be Adversely Affected in the Case of a Sick Child. The Commission has

recognized that IRB review is not the only protective mechanism which is available to children. Specifically, we have required parental permission, children's consent and have given the child a veto with regard to involvement in a research project.

The Commission did not specifically assess how well these other protective mechanisms would work with sick, as opposed to normal children. However, evidence in the record tends to support the general proposition that such protective mechanisms are not enhanced, but rather are diminished, when the prospective subject is a sick child.

First with regard to the child, the illness itself may be such as to interfere with normal cognitive and physical functions involved in the ability to assent meaningfully and even more important the ability to object at any stage of the project. This is especially true of children who are suffering from some form of mental retardation or are under the influence of some drug or sedative necessary to their therapy at the time that their participation is both solicited and effected.

Second, children who suffer long bouts with illness develop a special relationship with their therapist and the medical staff. To a certain extent because of their separation from their normal parents, the therapists and staff themselves often become surrogates for parental authority. When those therapists and medical staff are involved in a research project, the child's assent or failure to object may be influenced by the surrogate parent relationship.

With regard to parents there are certain obvious impacts on both the family unit and the parent that result from a child's illness. First, the emotional impact of a serious illness in the family may lead to a breakdown of the judgmental and perceptive relationships within the normal family unit. To a certain extent, the sick child becomes a burden that parents may not be capable of assuming without some diminishing of normal parental judgment and discretion. This is especially true in situations in which the child must be confined to an institution in order to obtain therapy or treatment. It is also true of those situations in which therapy or treatment at home is especially difficult and disruptive. Second, the parent of the sick child will in most instances have a long, intimate, and even emotional involvement with those who provide therapy for the child. As amply demonstrated in some of the filmed informed consent sequences presented to the Commission, that emotional involvement with the therapist may well have a severe and in fact even overriding impact on the parents' judgment with regard to granting permission for the participation of their child in a research project.

In conclusion then both the principle of beneficence, and the adverse impact on the other protective mechanisms require that this Commission afford sick children greater protection than that afforded to children at large.

3. <u>The Distinctions Attempted in Both Sets of Deliberations are Shams and There is No Legal, Ethical or Social Basis for Subjecting Sick Children to More Than Minimal Risk Merely Because a Foreseeable Benefit Might Accrue to an Identifiable Class of Children in the Future</u>.

In its two sets of deliberations, the Commission has attempted to present a shopping list of reasons in support of Recommendation (5). Each of these shall be dealt with separately, below.

First, the Commission notes that "the scope of parental authority routinely covers a child's participation in many activities in which risk is more than minimal, and yet benefit is questionable (involvement in skiing and contact sports are two examples among many)." Without concurring in the judgment of the Commission that benefit in skiing and contact sports is questionable, it is clear to me that this same rationale holds true for normal children as well as sick children. Thus, I perceive no basis for making any distinction between the two classes of children on the basis of that state ment.

Second, the Commission notes that it was "impressed by reported examples of diagnostic, therapeutic and preventive measures that might well have been derived from research involving risks that, while minor, would be considered more than minimal ." Again, that rationale provides no basis for segregating children into separate classes. The rationale is strictly utilitarian and, is not specifically supported in the record. Moreover, at no point does the Commission require that such research be carried out only if normal children would not be scientifically appropriate subjects. In the absence of such a limitation, I do not believe a strictly utilitarian rationale can provide adequate justification for a policy creating a doubly disadvantaged class of children.

Third, the Commission suggests that more than minimal risk is a condition that is "normal" for sick children. My problems with that characterization have been expressed above and will not be repeated here.

Finally, both sets of Commission deliberations conclude that "foreseeable benefits in the future to an identifiable class of children may justify a minor increment of risk to research subjects." That statement can be used to justify large quantities of applied research utilizing sick as opposed to normal children. The statement itself is without legal, ethical or social justification. If such justification did exist, it could be applied equally as well to normal children. In a situation in which "conservative" limits are placed on the participation of normal children, relaxation of those limits for sick children constitutes a specific mandate and direction to shift the risks and burdens of research from children in general to those who, by nature of their illness, are least, and not most, appropriate research subjects.

Comment by Dr. Ryan, Chairman of the Commission

In spite of the diversity of views reflected in the foregoing statements, our recommendations were adopted almost unanimously. The dissenting statement of Commissioner Turtle reflects a sharp disagreement, however, and requires some comment since it is based, I believe, on a misunderstanding of Recommendation (5).

The Commission has adopted a conservative definition of "minimal risk," i.e., the risk of harm that is normally encountered in the daily lives, or in

the routine medical or psychological examination, of healthy children. Virtually the entire Commission is in agreement that a "minor" or "slight" additional risk over that normally encountered may ethically be presented in very limited circumstances by research not intended to benefit directly the children who are subjects. These limited circumstances are commensurability of experience, likelihood of yielding generalizable knowledge about the subjects' disorder, and importance of that knowledge for understanding or treating such disorder. Further, provision must be made, when appropriate, for the participation of parents in such research involving their children.

Recommendation (5) contemplates research into the nature and treatment of disorders that specifically afflict children. The limited circumstances under which such research may be approved under Recommendation (5) clearly indicate that the research must be related to the disorder or condition affecting those subjects who are involved. Such research cannot by its very nature be conducted on normal subjects. Accordingly, Mr. Turtle's statement that the Commission's recommendations require research presenting more than minimal risk to be carried out on sick children merely because they are already subject to such risk, and his contention that the recommendation would shift involvement in such research from normal to sick children, are both incorrect. The Commission's intention in Recommendation (5), and the likely effect of this recommendation, are clearly not to encourage any unnecessary involvement of sick children in research, but rather to permit the conduct of research intended to develop important knowledge of disease states from which certain children suffer and for which research they are the only appropriate subjects.

☆ U.S. GOVERNMENT PRINTING OFFICE 1977 O—441—101

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND
DHEW PUBLICATION NO. (OS) 77-0004