Commentary

Constraints on Experimentation: Protecting Children to Death

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Why are so many adolescent girls becoming pregnant even though contraception is available? What is the best technique for repairing the congenital heart defects that still kill many newborns? Is it possible to develop a drug that will slow or stop progression of brain tumors in children? These questions are among those being asked today by researchers.

Although presumably everyone wishes that these and other questions had answers, the notion of finding answers by performing research on adolescents and children, especially infants, still meets with strong resistance in some segments of our society.[1] Often this resistance is unwarranted. For instance, if a two-year-old boy needs a haircut, his mother takes him to a barbershop, sits him in a chair, and regardless of objection, forces him to get a haircut. Few, if any, advocates of children's rights would consider this haircut a threat to the child's welfare. If a medical researcher, in contrast, wants to study children's hair and the same two-year-old is brought by the same mother to have a piece of hair snipped by a physician instead of a barber, some people would argue that the child's fundamental

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1. Research is a class of activities solely designed to develop or contribute to generalizable knowledge. Practice refers to a class of activities designed to enhance the well-being of an individual.

By definition, research is never intended to benefit the particular subject. If benefit is intended, the intervention is practice. The category of practice consists of two subsets. "Customary practice" is the currently accepted method of treating the patient's problem. "Non-validated practice" may include the application of novel procedures or interventions performed in the course of rendering treatment.

For general reading on the legal, ethical, and regulatory aspects of research on human subjects, see R.J. Levine, Ethics and Regulation of Clinical Research (2nd ed. 1986) (Chapter Nine discusses research on children); Levine, Clarifying the Concepts of Research Ethics, Hastings Center Report 21 (June 1979); J. Katz, Experimentation with Human Beings 999-1011 (1972).

rights are being violated, and that the child himself is being abused, because he cannot give legally binding consent to the haircut.[2]

Current federal regulations, which took effect in 1983,[3] now permit most, if not all, research that responsible pediatricians conceivably might wish to perform on children. Yet ethical objections from some influential commentators continue to have a substantial negative effect on researcher interest and funding, particularly in the area of pediatric drug development. The politicians, journalists, and physicians who equate pediatric research with child abuse exert a strong influence over researchers, who are often unaware or reluctant to take advantage of the latitude permitted for research under current regulations. As a result of this prejudice, internists are more likely to do important low-level drug testing on adults than pediatricians are to do similar testing on children. Many drug companies seem hesitant to sponsor potentially beneficial pediatric research because they fear tort liability and negative publicity.

Psychologists and sociologists are also often reluctant or unable to study, among other subjects, the psychosocial causes of adolescent pregnancy, the effects on adolescent behavior of providing contraceptives, and research on the prevalence and prevention of AIDS among adolescents. Social prejudice against research on these critical adolescent issues stems from a fear not that the research will threaten the physical health of the subjects, but that it will threaten their spiritual health. Because such studies are viewed in some political circles as fostering immoral adolescent behavior,[4] they generate little interest or funding.

The prejudice against medical and public health research on children and adolescents means that even those research projects that are valuable, responsible, and permissible under current federal regulations are not being initiated—and children are suffering as a result.[5]

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2. *See, e.g.*, Langer, Medical Research Involving Children: Some Legal and Ethical Issues, 36 Baylor L. Rev. 1, 28-34 (1984), for a defense of this argument.

3. 48 Fed. Reg. 9814-20 (Mar. 8, 1983).

4. 1 Risking the Future: Adolescent Sexuality, Pregnancy, & Childrearing 248-49 (1987) (discussion of public policy issues relating to research involving adolescents). The same fears behind the public prejudice against research on adolescent sexual behavior also affect the provision of sex education for minors. *See* Editorial, New York Times, Mar. 15, 1985, at 26, col. 1 (criticizing the tendency of many Americans to oppose sex education for their children out of reluctance to accept responsibility for the "sexual revolution").

5. One glaring example is the failure to date of any drug company to test improvements in the diptheria-pertussis-tetanus [D.P.T.] vaccine. At present, these shots occasionally cause convulsions and death in children. Fears about these potential side effects

Medical research on adult subjects cannot serve as an adequate substitute for medical research on children. Children are physiologically quite different from adults in many medically significant ways. Answers to biomedical or psychosocial questions about adult conditions and behavior may not apply to children; in some cases, in fact, drugs developed to treat a disease successfully in adults may do permanent harm to children with the same condition. For example, tetracycline is an antibiotic commonly prescribed for adults who have many types of infections, but it can cause permanent tooth damage if given to small children.

Moreover, lack of adequate research on children may actually endanger their health. For instance, because critics of research on children argue that children should be "protected" from the "dangers" of being research subjects, there have been few, if any, trials of drugs on sick children. Consequently, few results are available to establish boundary levels in children, making maximum dosages uncertain. In addition, because new drugs may not be tested on children in "Phase One" drug trials,[6] a great many drugs, some of which may be quite helpful in the treatment of children, are labeled "Not for pediatric use" or "This drug has not been tested and approved for use on children and infants." Pediatricians treating sick children with these drugs in the course of ordinary clinical practice are in effect conducting drug trials, whether or not they consider themselves researchers. When harm caused by these drugs occurs outside the setting of a clinical trial, reports of their side effects may be sporadic or delayed. Side effects may, in fact, go unrecognized by physicians caring for sick children. Meanwhile, children all over

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are so great that parents sometimes refuse to allow children to be vaccinated at all, leaving them vulnerable to whooping cough. Testing on children to develop a safer D.P.T. vaccine would be permissible under the current federal regulations, but corporate concerns about tort liability have sapped the incentive to initiate this valuable research. As a result, to date no safer vaccine has been developed.

6. An "investigational drug" is one not yet approved for use by the federal Food and Drug Administration [FDA]. In the process of drug development, the investigator must submit basic scientific and animal data to the FDA. If the FDA finds the data satisfactory, the developer receives an Investigational New Drug Application [IND] and may then administer the drug to human subjects in trials.

"Phase One" trials are almost always conducted on healthy volunteers; they establish the safety of the drug. "Phase Two" trials involve a very small number of patients with the disease that the drug is designed to alleviate; they establish the efficacy of the drug. "Phase Three" trials further establish the safety and efficacy of the drug by involving a wider sample of patients and a larger number of physicians.

When these trials are completed, the developer then applies to the FDA for a New Drug Application [NDA]. If this is granted, the drug can be made available for prescription by any licensed physician.

the country may be having the same unrecognized problem, causing some of them to be protected to death.

Adolescents suffer from the results of overprotection from research as well. In the current political climate, in fact, psychosocial research is considered as much, if not more, of a threat to their well-being than medical research. Adolescents are certainly different psychologically and socially from younger children and from adults, and the results of research on them will differ from the results of research on adults and children. We will never learn much more about adolescents if researchers continue to be prevented or discouraged from conducting research on them.

Such discouragement may take the form of hospital requirements that researchers obtain parental permission before administering questionnaires to adolescents about such subjects as their sexual activities. Federal regulations, however, do not require parental involvement in such cases, and with good reason. Troubled adolescents will often refuse to participate in research studies if participation will lead their families to find out about their problems. Study of these problems will continue to be impossible so long as there is a requirement for parental involvement.

In this Comment, I will examine concerns about experimentation on children and adolescents and will show how they are addressed by federal guidelines and local research review boards. I will argue that, with some modification, existing regulations and protocols provide ample safeguards for young subjects of medical research. Medical researchers often misunderstand or ignore the latitude offered by these guidelines, retarding our progress in understanding—and solving—important health and social problems.

I. Concerns About Research on Children

A central issue in debates about experimentation on humans, particularly children, has been consent. Those who object to the use of minors as research subjects often cite Supreme Court dicta in *Prince v. Massachusetts*:

> Parents may be free to become martyrs themselves but it does not follow that they are free in identical circumstances to make martyrs of their children before they have reached the age of full and legal discretion when they can make the choices for themselves.[7]

7. 321 U.S. 158, 170 (1944).

Some authorities, both legal and ethical, have taken the position that a parent cannot give valid consent for any medical procedure on a child that is not for the direct benefit of that child because the child lacks the legal capacity to give consent.[8]

Paul Ramsey, a noted ethicist, has asserted that even in the absence of risk, an unconsented touching is a moral wrong.[9] Donald T. Chalkley, former Director of the Office of Protection from Research Risks of the then-Department of Health, Education and Welfare, wrote in 1973, "A parent has no legal right to give consent for the involvement of his child in an activity not for the benefit of that child."[10] Advocates of this view would rule out even harmless research on children, not only research with the potential for harm.[11]

A. A "Worst Case" Scenario

Opponents of research on children were inflamed by the notorious "Willowbrook Experiment" in the 1950s and 1960s. Willowbrook is a large state institution, then overcrowded and understaffed, for the severely retarded in New York City. Conditions at the hospital were so filthy that hepatitis was endemic among its patients. Researchers in the Willowbrook Experiment vaccinated children on their admission to the hospital, then infected them with a mild dose of hepatitis to test the effectiveness of the vaccine against the disease. Most parents consented to this experiment on their children when the researchers told them that the children, even if not the subjects of experimentation, would inevitably develop more serious cases of hepatitis once they mingled with the institution's general population.[12]

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8. *See, e.g.*, P. Ramsey, The Patient as Person 17 (1974); McCormick, Proxy Consent in the Experimentation Situation, 18 Persp. in Biology & Med. 2 (Autumn 1974).

9. Ramsey, *supra* note 8, at 17.

10. Human Experimentation, Med. World News, June 8, 1973, at 41 (quoting Chalkley).

11. The contrary view, that parents may consent to research if the minor is exposed to no discernible risk, was presented as early as 1969 in an article in *JAMA*, the journal of the American Medical Association, Curran & Beecher, Experimentation in Children, 210 JAMA 77 (1969). It was also the position taken by the American Academy of Pediatrics in 1977, Comm. on Drugs, American Academy of Pediatrics, Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations, 60 Pediatrics 91 (July 1977), and by the American Medical Association in 1966, McCormick, *supra* note 8, at 4 (containing American Medical Association, Ethical Guidelines for Clinical Investigation, Nov. 30, 1966 (unpublished)).

12. For further reading on the Willowbrook case, see J. Katz, *supra* note 1, at 1007-10; D.J. & S.M. Rothman, The Willowbrook Wars (1984); Student Council, New York Univ. School of Medicine, Proceedings of the Symposium on Ethical Issues in Human Experimentation: The Case of Willowbrook State Hospital (1973).

The adults who worked at Willowbrook and who were exposed similarly to the disease, however, were never used as subjects.[13] Standard sanitation procedures and isolation of those children suffering from hepatitis could have cleared the institution of the disease. Although the vaccine proved to be a significant achievement that subsequently saved countless lives, the researchers did not know what harm might occur when they tested it on the Willowbrook children.

When the Willowbrook research was published, many commentators felt that the physicians involved had violated ethical standards.[14] Willowbrook became a symbol for the view that *all* research on children presented ethical problems of such magnitude that it should not be performed.

B. Contemporary Protections Against Abuses

The serious ethical questions raised by the Willowbrook Experiments have largely been resolved today by case law, state statutes, and federal regulations against child abuse. Today courts would presumably take a very cautious view of the validity of a parent's consent to research conducted on a child if there were any element of coercion involved in that consent, as there was in the Willowbrook case. Admission to Willowbrook was at one point restricted to children whose parents consented to their participation in the hepatitis research projects. Due to the enormous burdens on a family presented by a severely retarded child and the need to place some of these children in institutions, no court today would uphold parental consent under these conditions as free and voluntary. Today we assume that where admission to treatment facilities is restricted to children whose parents agree to their participation in research studies and where the children, if not admitted, would otherwise be denied standard treatment for financial or other reasons, the voluntary nature of parental consent to the research is questionable.[15]

Although it was not an issue in the Willowbrook case, offering payment to parents for allowing their child to participate as a re-

13. Ramsey, *supra* note 8, at 48.

14. *See, e.g.*, Goldy, Experiments at the Willowbrook State School, 1 Lancet 749 (1971).

15. This dilemma does not occur in those rare situations in which the child suffers from a condition for which there is no known treatment and the sole potential therapy for his problem is available only as part of a study. In such cases, a parent who consents to a child's admission to a hospital for non-validated therapy and research studies presumably is not coerced in the normal sense of the word.

search subject would introduce another potentially coercive element into a research design.[16] In the absence of an inherently coercive element, such as extreme poverty, payment of adult volunteers for their inconvenience, discomfort, and risk appears to be ethically acceptable and is clearly legally permissible. Offering payment to a person for consenting to a procedure on behalf of another, especially a child, however, is now deemed ethically unacceptable.

Today most courts would hold that, even if there were a therapeutic justification for a particular project using children as subjects, a parent could not give valid permission for dangerous non-validated therapy on a child where there was available a standard, effective, and less potentially dangerous non-experimental therapy for treatment of the child's complaint. As a hypothetical example, suppose a physician noticed that highly toxic chemotherapy that was effective against some form of childhood cancer but caused severe side effects also seemed to stop itching when the children undergoing cancer treatment encountered poison ivy. Whatever the therapeutic justification might be, prescribing the chemotherapy instead of standard remedies to an otherwise healthy child with poison ivy would be clearly unethical—and legally might constitute child abuse.

The problems for children have changed since the Willowbrook era. Children are clearly protected by law from such excesses as occurred at that institution. If parents today consented to, and physicians performed, a dangerous intervention where an effective and demonstrably safer therapy existed, as they did at Willowbrook, they would probably be found in violation not only of state, but also of federal, law.

II. The Federal Regulatory Scheme

Federal regulations establish a set of requirements that protect child research subjects from abuses while allowing all children to benefit from research uses. The Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the Commission), established by the National Research Service Award Act of 1974,[17] provided recommendations for nearly all aspects of ethical standards for con-

16. Capron, Legal Considerations Affecting Clinical Pharmacological Studies in Children, 21 Clin. Res. 141, 146 (1973).

17. Pub. L. No. 93-348, 88 Stat. 342 (codified as amended in scattered sections of 42 U.S.C.).

ducting research on children.[18] The Department of Health and Human Services (HHS) incorporated these recommendations into agency regulations (the Regulations) in 1983.[19]

The Regulations form a web of rules indicating the permissible boundaries for government-sponsored or -funded research and for research to be submitted to federal agencies. Most universities require that all research projects undertaken by faculty, staff, or students, regardless of their funding sources, comply with the federal regulatory scheme. Thus the Regulations function as a set of national ethical standards, affecting most major research conducted today.

The Regulations, detailed in this section, took significant steps toward expanding the role of necessary medical research on children while providing careful protections for child research subjects. The Regulations resolve, at least in theory, the dispute between those who fear the harm of research on children and those who seek its benefits. Unfortunately, the Regulations have not achieved this resolution in practice. If properly clarified and followed, though, I believe that they would achieve their purpose.

A. Minimal Risk Projects

In building the regulatory scheme, HHS endorsed the basic building-block rule of child research: The Department agreed to conduct or fund research that poses no greater than "minimal risk" to children.[20] Local Institutional Review Boards (IRBs) were required to review all proposals for research on human subjects and to validate the existence of adequate provisions for soliciting children's assent and parental permission.

The Regulations do not provide a definition of "minimal risk," creating uncertainty for medical researchers and divergent standards among the various IRBs. Other federal guidelines clearly define minimal risk as "those [risks] ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[21] Pricking a child's finger for a drop of blood would constitute a minimal risk, by this definition, since it is

18. Research Involving Children: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 43 Fed. Reg. 2084 (1978).

19. The Regulations are codified as: Additional Protections for Children Involved as Subjects in Research, 45 C.F.R. § 46.401-.409 (1986).

20. 45 C.F.R. § 46.404 (1986).

21. Basic HHS Policy for Protection of Human Subjects, 45 C.F.R. § 46.102(g) (1986).

routinely done at physical examinations; drawing a large amount of blood would not meet the definition.

The Regulations do not offer a definition of "material risk" either. A material risk of harm to a child subject should certainly include any procedure that, although not physically harmful, may frighten or upset the child. Psychological tests that involve misleading or deceiving a child may also be found to constitute a serious risk to some children and may be ethically deplorable for all. In addition, any genuine pain, as opposed to momentary minor discomfort, to a child clearly constitutes harm.

B. "Anticipated Benefit" Projects

If an intervention or procedure holds out the prospect of direct benefit for the individual subject, HHS will approve research that leaves the child open to more than a minimal risk only if three conditions are met: (1) the risk is justified by the anticipated benefit to the subjects; (2) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and (3) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.[22]

In using the terms "permission" and "assent," instead of "consent," the Commission clarified legal nuances that are often misused, particularly by lawyers. "Consent" is an active, comprehending agreement, always on one's own behalf and never on behalf of another. "Assent" has two quite separate meanings. When a person who is legally capable of giving consent gives assent instead, the word means passive acquiescence—a "going along with."[23] The

22. 45 C.F.R. § 46.405 (1986). The Commission abandoned the term "consent" to research except in those situations in which an autonomous adult may make decisions on his or her own behalf. In its discussions of research on children, the Commission instead used the term parental or guardian "permission." It concluded that the "assent" of the child, if he or she is old enough to give it, should also be obtained with a form analogous to the consent form used for adult subjects. *See generally* Ackerman, Moral Duties of Investigators Toward Sick Children, 3 IRB: A Review of Human Subjects Research [hereinafter IRB] 1 (June/July 1981); Schoeman, Children's Competence and Children's Rights, 4 IRB 1 (June/July 1982); Weithorn, Children's Capacities to Decide About Participation in Research, 5 IRB 1 (Mar./Apr. 1983); Keith-Spiegel, Children and Consent to Participate in Research, in Children's Competence to Consent (G.B. Melton, G.P. Koocher & M.J. Saks eds. 1983) for discussions of children's rights to make decisions in the research context.

23. *See* Levine, The Nature and Definition of Informed Consent in Various Research Settings, in The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (Appendix, Volume I) 3-6, DHEW Publication No. (OS) 78-0013 (1975).

second meaning of assent is more relevant to the Commission's recommendations: agreement by a person who is perhaps only technically incapable of giving a legally valid consent. A person who is not legally capable of giving "consent" may in fact give fully informed, active agreement. Just as a 25-year-old competent person may give consent to a medical researcher to draw a blood sample, an intelligent 12-year-old may understand just as clearly why the researcher wishes to draw the blood, may realize just as completely that it will produce momentary discomfort, and may wish just as actively to agree. Because the legal system holds that children as a class, without regard to individual capacity to understand, are ruled incapable of consent, the 12-year-old's agreement is termed "assent."

C. More Risky Projects

In some circumstances, HHS will conduct or fund research where more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject or by a monitoring procedure that is not likely to contribute to the wellbeing of the subject. This process will only be approved if an IRB finds that: (1) the risk represents a minor increase over minimal risk; (2) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; (3) the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and (4) adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.[24]

The definition of "a minor increment over minimal risk" is left to the discretion of the IRB reviewing the research study. The IRB at Yale University, for example, has approved bone marrow aspirations in adolescent leukemia victims, who are already familiar with the procedure, and single spinal taps on those adolescent patients who have already experienced the procedure during diagnostic evaluations for various illnesses. The IRB would not permit such an intervention on healthy children or pre-adolescent patients.

HHS will also conduct or fund research that the IRB does not believe meet other regulatory requirements if:

24. 45 C.F.R. § 46.406 (1986).

(1) the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(2) the Secretary of HHS, after consultation with a panel of experts in pertinent disciplines (such as science, medicine, education, ethics, and law) and after opportunity for public review and comment, has determined either that:

(a) the research in fact satisfies the conditions of other regulatory sections, or

(b) the proposed research will meet the following three tests:

(i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) the research will be conducted in accordance with sound ethical principles; and

(iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.[25]

Unfortunately, HHS did not renew the charter or funding of the panel of experts in related fields, known as the Ethics Advisory Board, when they expired in 1980.[26] As a result, no mechanism exists today for approval of federal funding for studies involving more than minimal risk, and no such studies are funded.

D. Responsibilities of the IRBs

The Regulations often require IRBs to determine that adequate provisions are made for soliciting the assent of competent children. In determining whether children are capable of assenting, an IRB must take into account the age, maturity, and psychological state of the children. This judgment may be made for all children involved in research under a particular protocol, or on an individual basis. If the IRB determines that: (1) the capability of some or all of the children is so limited that they cannot reasonably be consulted, or (2) the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or wellbeing of the children and is available only in the context of the re-

25. 45 C.F.R. § 46.407 (1986).
26. R.J. Levine, Ethics and Regulation of Clinical Research 319 (2nd ed. 1986).

search, the assent of the children is not a necessary condition for proceeding with the research.[27]

Under the Regulations, the IRB must make adequate provision for soliciting the permission of each child's parents or guardians. Under 45 C.F.R. §§ 46.404 and 46.405, the IRB may find that permission of one parent is sufficient for research. Where research is covered by §§ 46.406 and 46.407 and permission must be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or only one parent has legal responsibility for the care and custody of the child.

If an IRB determines that a research protocol is designed for a subject population for which parental or guardian permission is not a reasonable requirement (for example, neglected or abused children), it may waive the consent requirements, provided an appropriate mechanism for protecting the children is substituted. For example, the IRB may appoint one of its members to interview the child and make an independent determination that the child wishes to participate. The choice of an appropriate mechanism depends on the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and the children's age, maturity, status, and condition.

Children who are wards of the state or any other agency, institution, or entity can be included in research approved under 45 C.F.R. §§ 46.406 or 46.407 if the research is: (1) related to their status as wards, or (2) conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. If the research meets these requirements, the IRB must appoint an advocate for the best interests of the child. One individual may serve as advocate for more than one child; the advocate must be unrelated to the research group or the guardian agency.[28] This section serves to protect children who are available in public institutions and whose families may or may not be situated to consider their participation. If parents whose children live at home allowed them to participate in a particular research project, this section would permit institutionalized children to participate in the project.

27. 45 C.F.R. § 46.408 (1986).
28. 45 C.F.R. § 46.409 (1986).

III. Analysis of Parental Consent

Section 46.408 of the Regulations sensibly relies on parental permission as an important protection for children who are research subjects. As a matter of public policy, it is difficult to argue that a parent should be denied the right to consent to his or her child's participation in even harmless research. There are thousands of harmless procedures that provide valuable and necessary information when performed on normal children as controls for research. Examples of such research include noninvasive procedures like psychological or intelligence tests, physical examinations, regulation of diet (so long as the child is not deprived of necessary nutrition), and studies of urine or blood samples. Society should be willing to permit parents to accept the relatively low risks involved in this type of research, which is necessary to improve the medical treatment of children.

The daily lives of any normal children include many physically risky activities. Yet no one questions the right of a parent to consent to his or her child's participation in such normal activities as, for instance, riding a bicycle in a city or climbing mountains in an Outward Bound program. In fact, some child custody cases indicate that a parent who *prevents* a child's participation in normal activities in order to shelter the child from injury or germs is likely to lose custody on the ground that such overprotection is harmful to the child.[29] The ironic extension of the anti-research logic is that while a parent may consent to a child's participation in football, which might result in a variety of serious injuries or even death, that same parent has no authority to allow that child to have a blood sample drawn by a physician if the blood will be used in research of no direct benefit to the child.

Given the necessity of experimental controls for successful research, a competent parent should be able to consent to research so long as the risk of harm to the child is less than that to which a child of that age is reasonably likely to be exposed in daily life. To return to the football analogy, if participation is encouraged because the child learns sportsmanship and other values, a child who is encouraged to donate a small sample of blood for the benefit of other children may be learning altruism and empathy.

29. Holder, Mental Illness and Parental Rights, 216 JAMA 575, 576 (1971) (citing Ericson v. Ericson, 195 P. 234 (Wash. 1921) (holding that a mother's refusal to let her children play outside is one ground requiring rehearing of petition claiming she was unfit)).

This is not to suggest that parents *must* consent to their children's participation in *all* harmless research procedures. Parents retain the right to withhold consent, as they may not agree with the purpose of the research. The possibility of a disagreement with the purpose of the study, even though the child would obtain a direct benefit, might well arise in some psychological, sociological, or behavioral research projects. For example, research on children who have reading disabilities could conceivably benefit the particular child-subject, but the data might also be used to "prove" that the child's social or ethnic group is inferior or superior to other groups in reading aptitude as well as achievement. Recent studies, for example, indicate that comparing mathematical aptitude levels of boys and girls "proves" that boys are clearly superior to girls in mathematical reasoning abilities.[30] Many women's groups objected to the research that led to this conclusion as biased.

When parental permission is requested for comparative studies of children based on hypotheses that one group may be superior or inferior to another in some respect, the purposes of the studies must be explained to parents. The potential uses of an investigation may be of equal or greater concern to parents than the immediate benefit that they hope will accrue to their child from it, and they should be permitted to refuse their permission.

The Regulations on the elements of informed consent to research of course include the right to refuse to participate.[31] Although there have not yet been any cases on the subject, the following situation may arise at any time: A child has a disease, such as leukemia or bone cancer, and her parents wish to reject standard medical therapy and have her take laetrile or another substance. Welfare officials obtain a court order to have the child treated.[32] Standard

30. *See, e.g.*, Benbow & Stanley, Sex Differences in Mathematical Reasoning Ability: More Facts, 222 Science 1029 (1983).

31. 45 C.F.R. § 46.116 (1986).

32. All state courts interpret willful refusal to provide a child with necessary medical care as a violation of child neglect laws. "Neglect" may include failure to take a sick child to the physician, *see, e.g.*, In re Tolbert, 378 N.E.2d 565 (Ill. 1978) (children removed from mother's care because they suffered from untreated malnutrition and worm infections); In re D.L.E., 645 P.2d 271 (Colo. 1982); and In re Hamilton, 657 S.W.2d 425 (Tenn. 1983); failure of parents for religious reasons to permit children to receive blood transfusions during necessary surgery, *see, e.g.*, Jehovah's Witnesses of Washington v. King County Hospital, 390 U.S. 598 (1968); Muhlenberg Hospital v. Patterson, 320 A.2d 518 (N.J. 1974); In re Sampson, 278 N.E.2d 918 (N.Y. 1972); and Holder, Circumstances Warranting Court-Ordered Treatment of Minors, 24 Proof Of Facts 2d 169 (1980); a wish to use laetrile or some other medically unaccepted remedy, *see, e.g.*, In re Custody of a Minor, 379 N.E.2d 1053 (Mass. 1978), *aff'd*, 393 N.E.2d 836 (Mass. 1979); or a simple lack of compliance with necessary medical care, *see, e.g.*, In re Welfare

therapy fails. The physician caring for the child wishes to use an investigational drug that is on a protocol pending approval by the Food and Drug Administration. The parents, still adamant in their opposition to the administration of chemotherapy, refuse permission for the child to enter the study. The physician asks the judge to order it. There is no medical disagreement that the drug might cause a remission or that the child would die without it. Yet under the Regulations, so long as parents have custody of the child, they have the right to refuse administration of an investigational substance.

Forced participation in a drug trial asks the unwilling adolescent patient or parent of a child patient to assume the risks of unknown side effects or other problems with the drug. Since there is always a risk that an investigational substance will not work as well as standard therapy, no parent should ever be required to permit his or her child to participate in any research.

IV. Analysis of Children's Assent

Although the Commission report recommended that children be given a "right to dissent" from participating in research that would not directly benefit them, the final version of the Regulations did not include such a provision. The omission is a surprising and disturbing one, in light of the recognition of children's rights in other areas. For instance, although the Supreme Court has recognized a teacher's right to spank a misbehaving child, it also has held that the discomfort must be administered in a manner that does not violate minimal constitutional guarantees of due process.[33] For instance, the child has a right to protest the administering of a physical punishment before it takes place.[34] Adopting this principle in a research context, any child who is to be subjected to any discomfort in a nontherapeutic context should have a clear right to object to par-

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of Wachlin, 245 N.W.2d 183 (Minn. 1976) (child with neurological disfunction found to be neglected because mother refused to cooperate with efforts to provide speech therapy).

Most cases in which courts order treatment involve life-threatening illnesses, but courts have gone so far as to order treatment when its absence would cause permanent psychological disability. *See, e.g.*, In re Sampson, 278 N.E.2d at 918. Courts will not intervene, however, when parents are taking a child to a licensed physician and complying with his or her instructions, even if most other physicians and/or the public welfare department disagree with the physician's views. *See, e.g.*, In re Hofbauer, 393 N.E.2d 1009 (N.Y. 1979); In re Doe, Order by Circuit Court for Monroe County, Indiana, No. GU-8294-004A (Apr. 12, 1982) (reprinted at 47 Conn. Med. 409 (July 1983)).

33. Baker v. Owen, 395 F. Supp. 294, *aff'd*, 423 U.S. 907 (1975).

34. 395 F. Supp. at 302.

ticipation. "I don't want to be stuck with a needle" should be a sufficient objection.

If the child agrees to a minor discomfort once it has been explained, if he or she is not afraid, and if the parents concur, such an intervention is—and should be—legally permissible. Since adults have the right to refuse to participate as a research subject for any reason, and since children deserve the same respect that researchers accord an adult, a child's withholding of assent should also suffice to eliminate his or her participation as a research subject where he or she will not directly benefit. While the IRBs retain discretion to require investigators to respect children's refusals, it would seem that the Regulations should be amended to allow such dissents.[35] Where the child is too young to communicate, the parent alone may withhold consent.

V. Adolescent Assent or Consent?

The murky legal status of adolescents—i.e., should the courts treat them as children or as adults?—has posed special problems in determining their capacity to consent to participation in research. Similarly, it poses problems in determining their capacity to consent to medical treatment. During the past few decades, courts have substantially broadened the right of adolescent patients to consent to medical treatment without parental knowledge.[36] Even in the absence of specific treatment statutes permitting adolescents to consent, courts in all states have adopted what is known as the "mature minor rule." This jurisprudential doctrine permits teenagers who are capable of understanding a procedure and its risks to give informed consent in the same way that adult patients do. Teenagers in all states may make their own health care decisions, at least where the procedure can be characterized as "minor" in nature.[37]

In the relatively few cases in which the issue of a minor's refusal of treatment has been litigated, courts have held that if a minor has the

35. In some cases, treatment for the child's medical problem is only possible within a study designed to determine the safety or efficacy of a non-validated practice. A child may, for example, have a disease for which the only possible treatment is a drug on investigational status. In this case, the legal rules applying to the limitations of a minor's rights to refuse treatment in the context of medical practice should be applied.

36. *See* A. Holder, Legal Issues in Pediatric and Adolescent Medicine (1985) (Chapter Five); Holder, Minors' Rights to Consent to Medical Care, 257 JAMA 3400 (1987).

37. Pilpel, Minors' Rights to Medical Care, 36 Alb. L. Rev. 462 (1972); Wadlington, Minors and Health Care: The Age of Consent, 11 Osgoode Hall L.J. 115 (1973); Munson, Toward A Standard of Informed Consent by the Adolescent in Medical Treatment Decisions, 85 Dick. L. Rev. 431 (1981); Ewald, Medical Decisionmaking for Children: An Analysis of Competing Interests, 25 St. Louis U. L.J. 689 (1982).

right to consent to treatment, he or she has the right to refuse it.[38] The question of whether to extend a mature minor's right, without permission of his or her parents, to consent to treatment to the right to consent to minimal-risk research is one that has engendered much debate among lawyers and ethicists since the Commission's report was issued.[39] Section 46.408(c) of the Regulations does extend adolescents' right to consent, dispensing with the necessity of parental permission for participation in research equivalent to most treatment interventions for which the adolescent may consent.

Although the Regulations provide that prior parental approval requirements may be waived when such permission is not a reasonable requirement for the protection of subjects, the scope of this waiver has yet to be defined. No IRB is likely to waive permission for any research involving more than minimal risk of physical harm.

Under § 46.408(c) of the Regulations, the IRB must make judgments about waiving parental permission requirements in four situations in which questions about participation by adolescents in research typically arise.

(1) *Adolescence is relevant to the condition studied.* An example would be a survey of attitudes of teenagers who have had abortions. In this context, not only would it be an imposition on a teenager whose parents did not know that she had had an abortion to get their permission to ask her questions about it, but she would undoubtedly decline to participate in the survey on this basis. Requiring parental permission to participate in such a survey would run counter to the purpose of the Regulations that permission be sought for the protection of subjects. These adolescents have already exercised their right to choose an abortion. Forbidding them to decide independently whether they want to answer questions about this decision illustrates the potential for these Regulations to be read in an overprotective manner. It certainly seems appropriate to dispense with parental permission in these cases.

(2) *Adolescence is irrelevant to the research.* For instance, a medical researcher posts notices in undergraduate dormitories that he or

38. Since a younger child cannot consent and may only assent, he or she presumably also lacks the right to refuse. A parent might give permission for research activities for a small child receiving investigational chemotherapy even if the child objected. *See, e.g.*, In re Smith, 295 A.2d 238 (Md. 1972); Melville v. Sabbatino, 313 A.2d 886 (Conn. 1973); In re Mary P., 444 N.Y.S.2d 545 (1981).

39. *See* Holder, Can Teenagers Participate in Research Without Parental Consent?, 3 IRB 5 (Feb. 1981); Herceg-Baron, Parental Consent and Family Planning Research Involving Minors, 3 IRB 5 (Nov. 1981); Levine, Teenagers, Research, and Family Involvement, 3 IRB 8 (Nov. 1981).

she will pay research subjects five dollars to donate a tube of blood. One of the volunteers is a 16-year-old freshman. Most IRBs would waive parental permission only where there is little or no risk involved.

(3) *The research involves an attempt to recruit subjects from a variety of age groups.* For example, a political scientist wishes to survey a variety of people in the community to find out how many of them recognize the Bill of Rights. She wants to include a group of 16-year-old "candy stripers" at the local hospital. If the information is not particularly sensitive, there seems no reason to require parental permission before it can be solicited.

(4) *The research is not related to the patient's age, but an adolescent patient has a disease that a clinical researcher wishes to study or an investigational drug that the researcher wishes to prescribe.* For example, a hematologist treating a 16-year-old who has leukemia that is not responsive to standard therapy wishes to enroll the adolescent in a protocol for an investigational drug. Investigational therapy with a risk of serious side effects is reserved for conditions that are themselves serious, regardless of the patient's age. Since it is not very likely that a teenager with leukemia is being treated without parental knowledge, protocols of this sort are most unlikely to present an ethical issue of a waiver of parental permission. If they do, however, parental permission should almost always be required, due to the great risk of side effects from the investigational drug.

An IRB's decisions in these four situations must be based on its interest in protecting the adolescent subject. Any waiver of parental permission must also be accompanied by the enactment of a substitute mechanism for the protection of the adolescent subjects. As the above examples show, interpretation of § 46.408(c) requires flexibility on the part of the IRB. The board must be sensitive to research needs as well as to the dangers of too much or too little protection of adolescent subjects. Protection mechanisms should reflect these considerations.

VI. Exempted Psychological Research

In one area, the Regulations may not go far enough. Research in schools involving normal educational practices, such as studies of the effectiveness of instructional techniques or classroom management methods, are often exempted under the HHS regulations from

IRB review and from any parental permission requirements.[40] While requiring IRB review and/or parental permission for research in the classroom might be unnecessary in most cases, such review or parental consent may be vital for some psychological research requiring children to be asked personal questions about themselves or their families that may violate customary standards of privacy.[41] The psychological research exception should be narrowed.

The results of such research may harm children as well as violate family privacy. Classification of children who are research subjects by labels such as "gifted," "slow," "hyperkinetic," "depressed," or "uncoordinated," may be entered on school records and follow the children throughout their educational careers.[42] Unproven test instruments, which may provide inaccurate results, have the potential for even greater harm to children who are the subjects of this research. Although HHS may have exempted educational research from consent and review requirements on the ground that it is innocuous, this sort of research may be potentially far more damaging to a child than a minimal-risk activity conducted in the context of biomedical research. It should be covered by consent and review requirements in the same manner as medical research.

VII. Child Research Abuse: A False Threat

Although there is a potential for child abuse in research as in other settings, reported cases of such exploitation are now rare. Medicine's view of children has changed since 1722, when Queen Caroline ordered an experimental smallpox vaccination program for 10 orphans to see what would happen before she would consent to vaccinating the royal offspring.[43] The work of the Commission and the Regulations that resulted have encouraged safer pediatric research, particularly in the area of drug development, than ever before.

One recent study demonstrates the current cautious approach toward pediatric research. Researchers who sought to study certain mechanisms of diabetes in the healthy siblings of children with the

40. 45 C.F.R. § 46.101(b)(1) (1986).

41. Merriken v. Cressman, 364 F. Supp. 913 (D.Pa. 1973); Sherrer & Roston, Some Legal and Psychological Concerns About Personality Testing in Public Schools, 30 Fed. B.J. 111 (Spr. 1971).

42. Kirp, Schools as Sorters: The Constitutional and Policy Implications of Student Classification, 121 U. Pa. L. Rev. 705 (1973).

43. Mitchell, The Child and Experimental Medicine, 1 Brit. Med. J. 721, 722 (1964); Moros, The Philosophy of Medicine: Clinical Science and Its Ethics, 31 Persp. in Biology & Med. 134 (1987).

disease needed to identify changes in their blood glucose levels.[44] The healthy children were to be admitted to the hospital for 48 hours to allow blood to be drawn at frequent intervals. (Only one needle stick was required, and blood was drawn thereafter without discomfort.)

The IRB that reviewed the study was very concerned about the effects of hospitalization on healthy children. After exhaustive discussion, it approved the protocol. The researchers discovered that the children were made uncomfortable by the IV boards, so they removed the boards. The worst problem thereafter was boredom, since the children were effectively immobilized by the IV lines. Because no one wished to continue a study on bored or unhappy children, a VCR was brought onto the pediatric research unit. The only harm from the study was reported to be to the researchers' sanity—in their efforts to protect the children, they had to suffer through repeated showings of *Raiders of the Lost Ark.* Such are the "dangers" of pediatric research as it is being conducted today.

Conclusion

It is unfortunate that many politicians, journalists, and some physicians still equate pediatric research with abuse. Pediatric researchers and drug companies who fail to appreciate the extent of the research permitted under, and the protections offered by, existing government regulations are afraid to commit funding and reputations to research that still inspires fear and prejudice. Progress in gaining knowledge of children's diseases and potential treatments is slowed as a result. Protection of the rights of children participating in medical research is vitally important, but ironically, the overcaution prevalent in research institutions today hurts children's interests more than it protects them.

44. Amiel, Pediatric Research on Diabetes: The Problem of Hospitalizing Youthful Subjects, 7 IRB 4 (Jan./Feb. 1985).