

Nontherapeutic Research on Children

IN the late 1940s and again in the early 1950s, Massachusetts Institute of Technology scientists conducting research fed breakfast food containing minute amounts of radioactive iron and calcium to a number of students at the Walter E. Fernald School, a Massachusetts institution for "mentally retarded" children.¹ The National Institutes of Health, the Atomic Energy Commission, and the Quaker Oats Company funded the research, which was designed to determine how the body absorbed iron, calcium, and other minerals from dietary sources and to explore the effect of various compounds in cereal on mineral absorption.

In 1961, researchers from Harvard Medical School, Massachusetts General Hospital, and Boston University School of Medicine administered small amounts of radioactive iodine to seventy children at the Wrentham State School, another Massachusetts facility for mentally retarded children. With funding from the Division of Radiologic Health of the U.S. Public Health Service, the scientists conducting this experiment used Wrentham students to test a proposed countermeasure to nuclear fallout. Specifically, the study was meant to determine the amount of nonradioactive iodine that would effectively block the uptake of radioactive iodine that would be released in a nuclear explosion.

Recently, these two studies have received con-

siderable media attention, and an official Massachusetts state task force has reported on both episodes in some detail.² Although they represent special cases because they involve institutionalized children, the Fernald and Wrentham experiments nonetheless are the most widely known examples of a category of research that raises particular concerns for the Committee: nontherapeutic experimentation on children.

Experiments involving children are important to the Committee for two reasons. First, children are more susceptible than adults to harm from low levels of radiation, and thus as a group they are more likely than adults to have been harmed as a consequence of their having been subjects of human radiation experiments. Second, an evaluation of research with children is critical to determining whether any former subjects of radiation experiments should be notified in order to protect their health, one of our specific charges.³ Subjects who were children at the time of their exposure are more likely than adults to be candidates for such notification, both because of their increased biological sensitivity and because they are more likely to still be alive. (See chapter 18 for the Committee's recommendations with respect to notification and follow-up.)

We elected to focus on pediatric research that offered subjects no prospect of medical benefit, so-called nontherapeutic research, because it is

this kind of research that has generated the most public concern and is the most ethically problematic. This is not to say, however, that experiments on children in which the children stand to benefit medically never raise ethical issues; such research certainly can and does. But in deciding how to allocate our limited resources, we chose to concentrate where the issues are mostly sharply drawn. Also, because most nontherapeutic research with children involved tracer doses of radioisotopes, focusing on this work allowed us a window into radioisotope research generally.

We begin the chapter by setting the context for nontherapeutic radiation experiments on children. We review those factors that make nontherapeutic research on children ethically problematic and how such research has been viewed historically. We next consider what the practices and standards were for research on children in the 1940s, 1950s, and 1960s. This is a continuation of the discussion in chapter 2, which focused on professional standards and practices for human research.

The next three sections address human radiation experiments in terms of the central ethical issues raised by nontherapeutic research involving children—level of risk, authorization for the involvement of children, and selection of subjects. To address the question of risk, we analyzed twenty-one nontherapeutic radiation experiments with children conducted during the 1944–1974 period. The focus of this analysis is whether it is likely that any of the subjects of these experiments was harmed or remains at risk of harm attributable to research exposures. A table summarizing these experiments and our risk estimates can be found at the end of this chapter. The twenty-one experiments were selected from eighty-one pediatric radiation research projects identified by the Committee from government documents and the medical literature. Although these eighty-one by no means constitute all the pediatric radiation research conducted during this time, they include what are likely fairly typical examples of such research. Of the eighty-one, thirty-seven studies were judged to be nontherapeutic, and twenty-one of these were conducted or funded by the federal government and thus fell under

the charge of the Committee. Included within these twenty-one studies were the two nutrition experiments conducted at the Fernald School and one fallout-related study conducted at the Wrentham School discussed in the introduction to this chapter. All twenty-one studies employed radioisotopes to explore human physiology and pathology.

We turn next to a consideration of how authorization for the inclusion of the children in these experiments was obtained and who these children were. Unfortunately, for most of these experiments, little is known about either of these issues. The last section of the chapter focuses specifically on the experiments at the Fernald School where, thanks to the work of the Massachusetts Task Force on Human Subject Research, relevant information is available. Throughout the chapter, we focus only on research in which children could not have benefited medically. The Committee did not have the resources to pursue two related areas of research—nontherapeutic research on pregnant women and therapeutic research on children. We include two capsule descriptions of examples of these types of research at the end of this chapter.

THE CONTEXT FOR NONTHERAPEUTIC RESEARCH WITH CHILDREN

Children as Mere Means

In both law and medical ethics, it has long been recognized that children may not authorize medical treatment for themselves, except in special circumstances.⁴ Instead, authorization must be sought from the parent. Historically, the source of this respect for parental authority rested upon the view that children were the property of their parents, and thus parents had the right to determine how their "property" was to be treated. Today, we still speak of parental rights, although the justification for these rights no longer rests on an analysis of children as property. Instead, respect for the rights of parents is viewed as a mechanism for valuing and fostering the institution of the family and the freedom of adults to perpetuate family traditions and

commitments. Another important line of justification for respecting the authority of parents relies not on a recognition of parental rights but on the view that the interests of the child are generally best served by ceding decisional authority to the parent. The parent is thought not only to be in the best position to determine what is in the interests of the child but is also thought to be generally motivated to act in the child's best interests.⁵

When research involving children offers a prospect of medical benefit to the child-subject, the application of the above analysis is straightforward. Parents are generally thought to have the authority to determine whether their children should be made subjects of such research. Certainly today, any use of a child in research would not be ethically acceptable or legally permissible without the parent's permission.⁶ Where the research does not offer any prospect of benefit to the child, however, the legitimacy of the parent as authorizer is less clear.

Respect for the authority of parents to make decisions for their children and otherwise control their children's lives is not without bounds. The law recognizes several exceptions, designed primarily to protect the child from what society at large considers to be unacceptable or unjustifiable harm or risk of harm.⁷ Laws against the physical abuse of children are perhaps the most obvious example of such limitations on parental authority. In the context of research, the question arises of whether a parent has the authority to permit a child to be put at risk of harm in an experiment from which the child could not possibly benefit medically. In this case, the child is to be used as a means to the ends of others. Children are not in a position to determine for themselves whether they wish to agree to such a use and thus cannot themselves render the use morally acceptable. Should parents have such authority? Should anyone?

This question was resolved as a matter of public policy in the 1970s through the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and the subsequent adoption, in 1983, of federal regulations governing research involving children that were guided by the recommendations of the National Commission.⁸ These

regulations state that children can participate in federally funded research that poses greater than minimal risks to the subject if a local review committee (an institutional review board, or IRB) finds that the potential risk is "justified by the anticipated benefit to the subjects"; "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 "adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians."⁹ The word *consent* is purposely avoided in these regulations to distinguish parental *permission* and minor *assent* from the autonomous, legally valid *consent* of a competent adult.

Federal regulations do allow nontherapeutic research on children if an IRB determines that the research presents "no greater than minimal risk" to the children who would serve as subjects, although no clear definition of what constitutes minimal risk is provided.¹⁰ As with therapeutic pediatric research, parents or guardians must grant "permission" and children who are deemed capable must offer "assent."

The regulations also allow for nontherapeutic research with children that *does* present more than minimal risk, again with parental permission and assent of the child (as appropriate), *but only if* the risk represents a minor increase over minimal risk, the procedures involved are commensurate with the general life experiences of subjects, and the research is likely to yield knowledge of "vital importance" about the subjects' disorder or condition.¹¹ Research with children that is not otherwise approvable may be permitted, but only under special, and presumably rare, circumstances. In addition to local IRB review, such research must withstand the special scrutiny of the secretary of the agency sponsoring the research, who is to be advised by a special IRB.¹² The secretary must also allow the opportunity for "public review and comment" on a proposed nontherapeutic research project that is not otherwise approvable.

The regulations thus draw a sharp distinction between therapeutic and nontherapeutic research. Nontherapeutic research, while severely restricted, is not banned. The decision to permit parents to authorize the use of their children in nonthera-

peutic research reflects both the recognition that some important advances in pediatrics could come only from research with children that was of no benefit to them and the recognition that we all—as parents, as potential future parents, and as members of society—share in the interest of advancing the health of the young. At the same time, however, parental authority to permit such use of a child is generally restricted to research judged to pose little risk; as important as it is to promote the welfare of children (as a class), this interest justifies only minor infringements of the principle not to use people as mere means to the ends of others.

These 1983 regulations, and the reasoning behind them, were the culmination of considerable public debate and scholarly analysis, much of which occurred in the 1970s. To situate properly the experiments of interest to the Committee, it is necessary to examine the social and professional roots of the issues and arguments that ultimately led to the federal regulations.

Public Attitudes, Professional Practices

Attitudes and Practices Prior to 1944

There was significant research interest in infants and children as early as the eighteenth century, as scientists began to experiment with vaccines and immunization. Children were particularly valuable subjects for this type of research because in general, they were less likely than adults to have been exposed to the disease being studied.¹³ A child's response to immunizations was also of great interest because most immunizations are performed during childhood.

During the nineteenth century, the Industrial Revolution greatly increased the number of child laborers, and the public began to acknowledge the need for laws to protect children from abuse.¹⁴ Physicians started to specialize in pediatrics, studying specifically the health problems and diseases that afflicted children. Simultaneously, as social reformers were creating a wide range of institutions for children, such as orphanages, schools, foundling homes, and hospitals, scientists recognized the value of research conducted in these types of institutions. In the

late nineteenth and early twentieth centuries, Alfred F. Hess, the medical director of the Hebrew Infant Asylum in New York City, conducted pertussis vaccine trials and undertook extensive studies of the anatomy and physiology of digestion in infants at the asylum. According to Advisory Committee member and historian Susan Lederer, Hess sought to take advantage of the conditions in the asylum as they approximated those "conditions which are insisted on in considering the course of experimental infection among laboratory animals, but which can rarely be controlled in a study of infestation in man."¹⁵

Although many shared Hess's laudable goal of improving the health of asylum children, many people drew the line at the pediatrician's investigations of scurvy and rickets. In order to study the disease, Hess and his colleagues withheld orange juice from infants at the asylum until they developed lesions characteristic of scurvy. Responding to the public discussion of the ethics of using children in such nontherapeutic experiments, the editors of one American medical journal insisted that such investigations gave the children an opportunity to repay their debt to society, even as they conceded that experimentation on human beings should be limited to "children as may be utilized with parental consent."¹⁶

Hess's work was not the only case in which experiments involving children attracted negative public opinion. In 1896, for example, American antivivisectionists attacked a Boston pediatrician, Arthur Wentworth, who performed lumbar punctures on infants and children in order to establish the safety and utility of the procedure. The antivivisectionists were particularly alarmed because this procedure, which caused pain and discomfort, did not confer any benefits to the subjects. John B. Roberts, a physician from Philadelphia, labeled Wentworth's procedures "human vivisection," saying that "using the children in the hospital without explaining his plan to their mothers or gaining their permission intensified public fear of hospitals."¹⁷

The twentieth century brought new drugs and advanced technologies, which allowed for increased research on children. The conduct of this

experimentation, however, was largely left to the individual investigator. When his experimental gelatin injections provoked "alarming symptoms of prostration and collapse in three normal children (including a 'feeble-minded' four-year-old girl), the physician Isaac Abt stopped his pediatric experiments and began experimenting on rabbits."¹⁸ Meanwhile, legislation was being proposed throughout the country to protect children and pregnant women from experimenting physicians. Two proposals were introduced in the U.S. Senate in 1900 and 1902; proposals "to prohibit such terrible experiments on children, insane persons and pregnant women . . . , and to ensure 'that no experiment should be performed on any other human being without his intelligent written consent' were introduced in the Illinois legislature" in 1905 and 1907; in 1914 and 1923, the New York legislature considered bills that prohibited experimentation with children.¹⁹ Although these bills did not become law, it is clear that some unease concerning nontherapeutic research on children existed among the public and elected officials.

Reaction to the polio vaccine trials conducted during the 1930s further demonstrated the growing discomfort over pediatric experimentation as thousands of American children were involved in what some considered at the time to be premature human trials of the polio vaccine. Although it appears that parental consent was obtained for a number of these studies, the controversy over these trials stalled polio vaccine research for almost two decades and generally made investigators ambivalent about the use of human subjects.²⁰

Although there are no legal cases that bear directly on nontherapeutic research with children during this period, an appellate court ruling in 1941, *Bonner v. Moran*, involving the performance of a nontherapeutic medical procedure on a child without parental consent, suggests how such a case might have been decided.²¹ John Bonner, a fifteen-year-old African-American boy from Washington, D.C., had undergone an experimental skin graft for the benefit of Clara Howard, a cousin suffering from severe burns. When he discovered that John Bonner had the same blood type as the burn victim, Howard's plastic surgeon, Robert Moran,

persuaded Bonner to allow him to fashion "a tube of flesh" by cutting from the boy's "arm pit to his waist line."²² This procedure, however, was conducted without the consent of a parent, as "his mother, with whom he lived, was ill at the time and knew nothing about the arrangement."²³ Moran then attached the free end of Bonner's flesh tube to Clara Howard, hoping that the flesh-and-blood link would bring benefit to the burned girl. Due to poor circulation in the tube, the procedure did not help the burn patient and put the healthy boy, who was required to stay in the hospital for two months, at significant risk (and left him with permanent scars). Bonner's mother brought suit against Moran for assault and battery.

The appellate court based its ruling against Moran on what it perceived as a disturbing combination of a lack of direct benefit for John Bonner and a lack of permission from the boy's mother:

[H]ere we have a case of a surgical operation not for the benefit of the person operated on but for another. . . . We are constrained, therefore, to feel . . . that the consent of the parent was necessary.²⁴

The court did not refer to the episode as an instance of experimentation, but the parallels between this novel procedure performed for the benefit of another and a nontherapeutic medical experiment are quite powerful.²⁵

Attitudes and Practices 1944-1974

As best the Committee can establish, there were no written rules of professional ethics for the conduct of research on children prior to 1964. Taken literally, the Nuremberg Code, which requires that all subjects of research "have legal capacity to give consent," precludes all research with children.²⁶ There is no reason to believe, however, that the judges at Nuremberg meant to impose such a prohibition, and the Nuremberg Code did not result in a ban on research with children.

Pediatric research flourished after World War II, as did biomedical research in general. What is less clear is how this research was conducted, and on whom. One source of evidence about legal thinking on pediatric research, if not actual

practice, is the writings of Irving Ladimer, a lawyer who, in 1958, was completing a doctoral degree in juridical science at the same time he was employed as an administrator at the National Institutes of Health. Ladimer concluded his doctoral dissertation, "Legal and Ethical Implications of Medical Research on Human Beings," with an appendix devoted to the issues surrounding "Experimentation on Persons Not Competent to Provide Personal Consent," whom he defined broadly as minors and mental incompetents.²⁷ Ladimer argued that it was "permissible to employ minors and incompetents as subjects of medical investigations . . . where there is informed consent by a parent or guardian (including the state) for procedures which also significantly benefit or may be expected to benefit the individual."²⁸ Ladimer was less sanguine, however, about nontherapeutic research with these populations. He expressed particular concern about the use of institutionalized children—even with proxy permission—in research that did not hold the possibility of personal benefit: "Permission given by parents or the state to utilize institutionalized children, without any suggestion of benefit to the children, may well be beyond the ambit of parental or guardianship rights."²⁹

Ladimer did, however, leave open a window for the use of legally incompetent subjects in nontherapeutic research, but he clearly harbored great discomfort with his own suggestion:

[T]he availability of certain persons, not able to consent personally, may constitute a strategic resource in terms of time or location not otherwise obtainable. It must be remembered, however, that the Nazis hid behind this rationalization in explaining certain highly questionable or clandestine medical experiments. Such justification should not even be considered except in dire circumstances. If ever employed, it should not be assimilated into the concept of personal benefit, else there may be no legal or ethical control for the protection of both prospective subject and investigator and their individual integrity.³⁰

As part of the Committee's Ethics Oral History Project, we interviewed two pediatricians who were beginning their careers in academic medicine in the late 1940s. One of these respondents, Dr. Henry Seidel, had some research experience with institutionalized children. He

noted that "we got access [to the children] very easily," and although his research was merely observational, it was "not hard to imagine" that experimental research with these children could have been conducted.³¹ When asked about the studies conducted by Dr. Saul Krugman on institutionalized children at the Willowbrook State School (discussed later in this chapter), Seidel observed, "I didn't have any problem imagining that possibility. In retrospect, I'm sure it could happen, you know. There was something about those reports that rang true. . . ."³² William Silverman, the other pediatrician interviewed, had clear recollections of how research was conducted in pediatrics at that time. He recalled that, in the 1950s, many pediatricians, including himself, believed that it was not necessary to obtain the permission of parents before using a pediatric patient as a subject in research—even if the research was nontherapeutic (he has since become a strong proponent of the parental permission requirement in pediatric research).³³ He also asserted that performing nontherapeutic experiments on children without authorization from parents was part of a broader "ethos of the time" in which "everyone was a draftee" in a national war on disease.³⁴ Dr. Silverman's account squares with the picture that emerged in chapter 2 of practices in research with adults, in which it was not uncommon to use adult patients as subjects of research without their knowledge or consent.

Silverman was among the researchers invited by Boston University's Law-Medicine Research Institute (LMRI) to participate in a conference on "Social Responsibility in Pediatric Research" held in May 1961.³⁵ This meeting was one in a series of closed-door conferences organized by LMRI to investigate actual practices among clinical researchers. The transcripts of the conference provide an important window onto practices and attitudes of the time; in large measure, they confirm Silverman's recollection of his own position some thirty-five years ago. Early in the meeting, Silverman asserted that "there is an unwritten consent by being a living person at this time to participate in this kind of advancement of knowledge [that is, nontherapeutic pediatric research]."³⁶ Some of the other participants employed the same analogy to the military draft

that Silverman recently used to relate his recollections.

However, there was by no means unanimity about the appropriateness of this view:

Dr. A: [Dr. B] says that this [research without consent] is like military conscription.

Dr. C: Not comparable. We voted to do military conscription.³⁷

The proceedings of the conference suggest that while it may not have been uncommon for pediatric patients to be used as subjects of nontherapeutic research without the permission of their parents, at least some physician-investigators, including investigators who followed this practice, thought it was morally wrong to do so. Consider, for example, a story relayed by one pediatrician-investigator at the conference who seemed to embrace with particular earnestness the desire of the conference organizers to learn the unvarnished reality of clinical research. In the opening minutes of the meeting, this researcher reminded his colleagues that "the question for us to discuss here today is how we operate on a daily basis."³⁸ He offered for discussion a provocative case from his personal experience in which he and his associates "wanted [to do] lumbar punctures on newborns."³⁹ He explicitly noted that "this study [was] not of benefit to the individual; it was an attempt to learn about normal physiology."⁴⁰ One of the other conferees asked, "Did you ask [parental] permission?" The researcher responded, "No. We were afraid we would not get volunteers."⁴¹ The case prompted a great deal of discussion at the conference, but perhaps most tellingly this researcher frankly acknowledged toward the end of the discussion—in a meeting that had begun with an assurance of confidentiality from the organizers—that he had "sinned" in carrying out these lumbar punctures in "normal infants" without parental permission.⁴²

The proceedings of the conference also suggest that at least some pediatrician investigators routinely obtained the permission of parents before embarking on research with their children. It is perhaps significant that the pediatric researcher who articulated this position at the conference was from Canada—and the conference transcript seems to suggest that he was pro-

viding a general characterization of practices in his country:

Dr. A: Let's ask [Dr. B] from Canada.

Dr. B: We have been quite sticky on consent. If we want a biopsy or a radioactive exposure and the parent says "no" then we don't do it. . . . The question of morals is too valuable.⁴³

If this statement represents the sensitivity of Canadian pediatrician-investigators to issues of parental permission (which this single quotation does not prove), there is no obvious explanation as to why many of their colleagues in the United States behaved differently.

The LMRI conference is noteworthy not only for what it reveals about the range of views and practices concerning parental permission for nontherapeutic research, but also for the unanimity expressed about the importance of obligations to prevent or minimize harm to pediatric subjects of research. Minimizing risk was recognized by those at the conference as the most important (and, for some participants, the only) moral duty of pediatric investigators.⁴⁴

Three years after the LMRI conference, in the summer of 1964, the World Medical Association ratified a code of ethics for human experimentation at a meeting in Helsinki. Unlike the Nuremberg Code, this statement, known as the Declaration of Helsinki, recognizes that research may be conducted on people with "legal incapacity to consent."⁴⁵ The Declaration distinguishes between two kinds of research: "Clinical Research Combined with Professional Care" and "Non-therapeutic Clinical Research."⁴⁶ It permits the use of people with legal incapacity to consent as subjects in both kinds of research, provided that the consent of the subject's legal guardian is procured.

Subjects of the first kind of research are referred to as patients; disclosure to and consent from patient-subjects are required by the Declaration, "consistent with patient psychology."⁴⁷ The Declaration does not specify whether considerations of "patient psychology" also could justify not obtaining the consent of the guardian where the subject does not have the legal capacity to consent.

The subjects of "non-therapeutic clinical research" are not referred to as patients but

as human beings who must be "fully informed" and whose "free consent" must be obtained.⁴⁸ The Declaration also requires that nontherapeutic research be discontinued if in the judgment of the investigators to proceed would "be harmful to the individual."⁴⁹ Thus, although the Declaration permits parents to authorize the use of their children as subjects in nontherapeutic research, such research is not intended to be "harmful" to the subjects.

The language and reasoning of the Declaration was unclear and confusing with regard to clinical research, both therapeutic and nontherapeutic, on legally incapacitated individuals. It was revised in 1975, at a time when the ethics of research with human subjects was receiving considerable public attention in the United States (see chapter 3).

Both in the 1960s and early 1970s, public controversies erupted about several cases of research involving human subjects, controversies that led to the establishment of the National Commission and publication of the federal regulations (see chapter 3). One of the most well known of these cases involved research on institutionalized children. During the 1950s and 1960s, Dr. Saul Krugman of New York University conducted studies of hepatitis at the Willowbrook State School, an institution for the severely mentally retarded.⁵⁰ To study the natural history, effects, and progression of the disease, Krugman and his staff systematically infected newly arrived children with strains of the virus. Although the investigators did obtain the permission of the parents to involve their children in the research, critics of the Willowbrook experiments maintained that the parents were manipulated into consenting because, at least in the later years of the research, the institution was overcrowded and the long waits for admittance were allegedly shorter for children who were entering the research unit. Henry Beecher, a Harvard anesthesiologist whose impact on the history of research ethics is detailed in chapter 3, condemned Krugman and his staff for not properly informing the parents about the risks involved in the experiment.⁵¹ Beecher also challenged the legal status of parental consent when no therapeutic benefit for the child was anticipated. A New York state senator, Seymour R.

Thaler, criticized the Willowbrook research on the pages of the *New York Times* in 1967, only to come to its defense later in 1971. Also in the early 1970s Willowbrook became the subject of a heated debate in the medical literature.⁵²

Interestingly, Dr. Krugman was one of the participants at the LMRI "Social Responsibility in Pediatric Research" conference where he expressed pride that he routinely obtained permission from the parents of the children in his studies. In that group in 1961, Krugman was thus among those pediatric investigators most sympathetic to the position that children could not be used as mere means to the ends of the researcher without the authorization of the parent.

AEC Requirements for Radiation Research With Children

Although in the 1940s and 1950s there were apparently no written rules of professional ethics for pediatric research in general, there were guidelines for the investigational use of radioisotopes in children. In 1949, the Subcommittee on Human Applications of the Atomic Energy Commission's Isotope Division established a set of rules to judge proposals submitted by researchers for the use of radioisotopes in medical experiments with human subjects, including "normal children."⁵³ These standards appeared in the fall 1949 supplement to the AEC's isotope catalogue and price list. Under the heading "Normal Children" the isotope catalogue offered the following statement:

In general the use of radioisotopes in normal children is discouraged. However, the Subcommittee on Human Applications will consider proposals for such use in important researches, provided the problem cannot be studied properly by other methods and provided the radiation dosage level in any tissue is low enough to be considered harmless. It should be noted that in general the amount of radioactive material per kilogram of body weight must be smaller in children than that required for similar studies in the adult.⁵⁴

These guidelines did not mention consent—of parents, guardians, or children.⁵⁵ Instead, this statement simply discouraged nontherapeutic experiments with children. The guidelines did not, however, suggest that the practice was completely inappropriate; the subcommittee asserted

that "important" research using "harmless" levels of radiation dosage with children was acceptable. The crucial terms *important* and *harmless* were left undefined.

It seems reasonable to expect that "important" pediatric research would address a significant medical problem affecting children or would explore key aspects of normal human physiology—relevant to health promotion or disease prevention—for which research on children is indispensable. By these standards, the twenty-one nontherapeutic radiation experiments with children whose risks we review in the next section of this chapter could all be said to address important questions relevant to pediatric health care. This judgment is not based on a determination of whether a given study proved important in the subsequent development of a particular field. Such retrospective analysis would place an unreasonable burden on investigators of the past, as research is an inherently speculative enterprise. Many experiments that prove to be of little value in the advance of medical knowledge are, at the time they are implemented, well designed and appropriate attempts to address important research questions.

It is easier to infer what the members of the AEC Subcommittee on Human Applications would have considered "important" research than what the subcommittee would have considered "harmless" radioisotope research. Acute toxicity is not seen following administration of nontherapeutic (tracer) doses of radioisotopes. Thus, the principal potential harm from radiation exposure at lower doses is the subsequent development of cancer. In the 1940s and 1950s, some in the field apparently discounted the risk, while others were wary of a prevailing uncertainty. Dr. John Lawrence, an early radioisotope researcher at the University of California, described how some researchers conducted public demonstrations of tracers, using an "unsuspecting physician out of the audience to act as the guinea pig," presumably to reassure the audience that tracers were innocuous.⁵⁶ By contrast, other investigators focused on the tragedy of the radium dial painters, concerned that this might be repeated with man-made radionuclides.

Evidence of how well the AEC enforced its 1949 guidelines with respect to research on chil-

dren is elusive (see chapter 6). AEC correspondence with researchers at the Fernald School suggests that in at least one case there was oversight of research in which children were administered radioisotopes.⁵⁷

RISK OF HARM AND NONTHERAPEUTIC RESEARCH WITH CHILDREN

The Twenty-One Case Examples

During the 1944–1974 period, there was an explosion of interest in the use of radioisotopes in clinical medicine and medical research, including pediatrics. The twenty-one research projects we review here include only a small number of all those that were likely conducted. These twenty-one do include, however, every nontherapeutic study that was funded by the federal government and fell into our original group of eighty-one pediatric radiation experiments. The table that appears at the end of the chapter provides information about the number of children involved in each of the experiments, the radioisotopes used, and risk estimates for cancer incidence. These twenty-one represent a subset of eighty-one studies identified in documents of the Atomic Energy Commission and a review of the medical literature that met the criteria described above.⁵⁸

All twenty-one projects analyzed in detail involve the administration of radioisotopes to children in order to better understand child physiology or to develop better diagnostic tools for pediatric disease. In this respect, the studies supported by the federal government do not differ from those reviewed that had other funding sources. With the exception of the study at the Wrentham school to evaluate protective measures for fallout, none of the twenty-one experiments reviewed was related to national defense concerns. Seventeen of the twenty-one experiments involved the use of iodine 131 for the evaluation of thyroid function.

Three examples of research reviewed by the Committee will help illustrate the nature of the experiments and the risks posed to children. In the first example, investigators at Johns Hopkins in 1953 injected iodine 131 into thirty-four chil-

dren from ages two months to fifteen years with hypothyroidism and an unknown number of healthy "control" children in order to better understand the cause of this disease.⁵⁹ Iodine is normally taken up and used by the thyroid gland for hormone production. In this experiment, a radiation detector was placed over the thyroid to detect the amount of iodine 131 taken up. Most children with hypothyroidism have an underdeveloped thyroid gland, in which case only very low levels of iodine 131 uptake will occur. Indeed, this is what the investigators found in this experiment, which was one of the first projects to use iodine 131 uptake as a measure of thyroid function in children. Hypothyroidism is a relatively common condition (1 per 4,000 births) that can cause profound mental retardation if untreated. Today, better diagnostic tests for thyroid function including radioimmunoassay and effective thyroid hormone replacement have virtually eliminated hypothyroidism as a cause of mental retardation in the developed world.

A second example of research reviewed by the Committee is an experiment by investigators at the University of Minnesota in 1951 in which four children with nephrotic syndrome were injected with an amino acid labeled with sulfur 35, along with two "control" children hospitalized for other conditions.⁶⁰ Nephrotic syndrome is a serious pediatric condition in which protein is excreted by the kidneys in large quantities. There was controversy at the time over whether children with nephrotic syndrome have low blood protein levels solely because of renal losses or whether they also have impaired protein production. This experiment looked at the incorporation of the radioisotope-labeled amino acid into protein, and the results suggested that the protein production in children with nephrotic syndrome is normal.

A third example of research reviewed by the Committee is a study of iodine 125 and iodine 131 uptake by eight healthy children performed at the Los Alamos Laboratory in 1963.⁶¹ The purpose of the study was to evaluate the use of radioisotopes in very small doses (nanocurie levels) as a measure of thyroid function. The study demonstrated that the technique was scientifically valid and exposed the children to smaller radiation doses than earlier methods.

Estimating Risk

How can the risks posed to children in these types of experiments be estimated? The primary risk posed by the administration of radioisotopes is the potential development of cancer years, even decades, after the exposure. As will be discussed further, the risk of cancer following external radiation exposure was not well documented until the late 1950s and the early 1960s. Thus, the published reports of research projects prior to that time rarely discuss the issue of long-term risks.

The principles of risk assessment for radioisotopes are laid out in "The Basics of Radiation Science" at the end of "Introduction: The Atomic Century."⁶² To review: the increased risk of cancer is generally assumed to be proportional to the dose of radiation delivered to the various organs of the body. This dose depends upon a number of factors, including the amount of radioactivity administered, its chemical form (which determines which organs will be exposed), and how long it stays in the body, which in turn depends upon the radioactive decay rate and the body's normal excretion rate for that substance. For many radioisotopes, the overall personal dose can be derived by the "effective-dose method," in which the doses to the ten most sensitive organs are computed and added together, weighting the various organs in proportion to their radiosensitivity. Thus, this effective dose can be thought of as producing the same excess risk of cancer (all sites combined) as if the whole body had received that amount as a uniform dose. This risk is then computed by multiplying the effective dose by established risk estimates per unit dose for various ages. For this chapter, the Advisory Committee has adopted the effective doses and risk estimates tabulated by the International Commission on Radiation Protection and the National Council on Radiation Protection.⁶³ The lifetime-risk estimate used in this chapter is 1/1,000 excess cancers per rem of effective dose for children and fetuses exposed to slowly delivered radiation doses, like those from radioactive tracers.

The risks of thyroid cancer following exposure to radioactive iodine (generally I-131) represent a special case for three reasons. First, use of the

effective-dose method is inappropriate because the dose is much greater to the thyroid than for other organs, and the lifetime risk is therefore dominated by the thyroid cancer risk. Therefore, risk is best calculated using only the thyroid dose and its associated risk. Second, the thyroid cancer risk varies even more by age than for other cancers. Third, the risk for iodine 131 has not been measured directly, but several lines of evidence suggest that it may be substantially lower than for external radiation. For this chapter, the Advisory Committee has adopted estimates provided by three follow-up studies of external irradiation of the thyroid by x rays or gamma rays in childhood: 2,600 children who received x-ray treatment for enlarged thymus glands in the first year of life;⁶⁴ 11,000 children who were treated by x rays in Israel for ringworm under age ten;⁶⁵ and Japanese atomic bomb survivors under age twenty.⁶⁶ The risk estimates from these studies were divided by three to convert them to internal iodine 131 exposures.⁶⁷ The estimates from these studies are for cancer incidence; for mortality we have divided them by 10, since 90 percent of thyroid cancers are curable. The resulting estimates are summarized in table 1. These are the same estimates used by the Massachusetts Task Force, which investigated the Fernald and Wrentham experiments.⁶⁸

We can use data from the previously described Johns Hopkins iodine 131 study as an example. In this study, the amount of radioactivity administered was 1.75 microcuries per kilogram body weight; equivalent to 44 microcuries in a seven-year-old child weighing 25 kilograms. Based on interpolation of the tables in ICRP 53, and assuming a 13 percent thyroid uptake, this would produce a thyroid dose of 115 rem to a child aged seven. In this age range (5-9), the lifetime risk of developing thyroid cancer would be calculated by multiplying this dose by 20 per million person rems to produce an estimate of 2.3 cases per 1,000 exposed individuals, or 0.23 percent for a particular child. The risk of dying of thyroid cancer would be one-tenth of this, or 0.023 percent.

The twenty-one experiments subjected to the Committee's detailed risk analysis included approximately 800 children. Eleven of the studies produced estimates of average risk of cancer in-

cidence within the range of 1 and 0.1 percent; eight studies ranged within 0.09 and 0.01 percent, and the remaining two studies produced average risk estimates of 0.001 percent. The maximum potential risk estimate was 2.3 percent in a few children aged one to two years at the time of exposure. The average risk of cancer incidence for the Fernald radioiron and radiocalcium studies were 0.03 percent and 0.001 percent respectively, and for the Wrentham fallout (iodine 131) study, 0.10 percent. All of the highest-risk experiments involved iodine 131, and hence the risks of dying of cancer would be about ten times smaller. (See table 2 at the end of this chapter for further details.)

Based on the average risk estimate for each of the twenty-one experiments, we would estimate an excess cancer incidence of 1.4 cases for the entire group of 792 subjects. However, given the uncertainties built into the risk analysis, it is also possible that no excess cases resulted. Furthermore, since most of that excess would have been thyroid cancer, it is particularly unlikely that any cancer deaths would have been caused. Finally, as thyroid cancer does occur in the general population, it would be difficult to attribute these cases to an individual's involvement in research. In addition, any cases of thyroid cancer among former subjects attributable to their participation in research conducted in the 1940s and 1950s are likely to have occurred already, although there is little long-term follow-up data to know for certain what the ultimate lifetime risk might be.

How do these risk figures compare with what is acceptable in nontherapeutic research today? As noted earlier in this chapter, the contemporary regulatory standard permits children to be involved in nontherapeutic research if the research poses no more than "minimal risk" to the subjects. "Minimal risk" is defined by analogy only: "A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological tests."⁶⁹ The regulations also allow for nontherapeutic research with children that *does* present more than minimal risk, *but only if* the risk represents

Table 1. Summary of Risk Estimates for Thyroid Cancer from Iodine 131

EXPOSURE AT VARIOUS AGES				
Age	0-4*	5-9 [†]	10-14 [‡]	15-19 [§]
Lifetime risk of cancer incidence per million exposed per rem				
Males	27	13	6.7	1.9
Females	53	27	13	3.7
Both	40	20	10	2.8
Lifetime risk of cancer mortality per million exposed per rem				
Males	2.7	1.3	0.7	0.2
Females	5.3	2.7	1.3	0.4
Both	4.0	2.0	1.0	0.3

* From R. E. Shore et al., "Thyroid Tumors Following Thymus Irradiation," *Journal of the National Cancer Institute* 74 (1985): 1177-1184, based on 2.9 cases per million person-year-rem.

† From E. Ron and B. Modon, "Thyroid and Other Neoplasms Following Childhood Scalp Irradiation," in J. D. Boice, Jr. and J. F. Fraumeni, Jr., eds., *Radiation Carcinogenesis: Epidemiology and Biological Significance* (New York: Raven, 1984), 139-151, based on the risk in this age group being half that in the 0-4 age group.

‡ From R. L. Prentice et al., "Radiation Exposure and Thyroid Cancer Incidence Among Hiroshima and Nagasaki Residents," *National Cancer Institute Monographs* 62 (1982): 207-212, based on the risk in this age group being one-third of that in the 0-9 age group.

§ Ibid. based on 0.21 per million person-year-rem.

|| Based on an assumed forty-year period at risk from five to forty-five years after exposure and assuming females have twice the excess risk of males.

a minor increase over minimal risk, the procedures involved are commensurate with the general life experiences of subjects, and the research is likely to yield knowledge of "vital importance" about the subjects' disorder or condition.⁷⁰ The regulations do not specify what would count as a minor increase over minimal risk. With this general guidance, it is the obligation of individual institutional review boards (IRBs) to determine whether a nontherapeutic study involving children is acceptable.⁷¹ It is likely that a cancer risk of greater than 1 per 1,000 subjects would be considered by most, if not all IRBs to be unacceptable by a minimal-risk standard, even for nonfatal cancers. It is less clear whether this risk would be considered unacceptable by the "minor increase over minimal risk" standard (assuming the research satisfied the "vital importance" condition). The difficulty of establishing an acceptable level of risk in nontherapeutic radiation research with children is currently being

debated in the medical literature,⁷² a debate that will likely continue at least until federal guidelines become more specific.

What Was Known at the Time About Risk in Children

Assuming that any study that posed risks of greater than 1 excess case of cancer per 1,000 subjects would be judged to be more than minimal risk, eleven of the twenty-one research projects reviewed by the Committee exposed children to higher risk than is acceptable today for nontherapeutic experiments. From a moral perspective, a crucial question is whether investigators at the time could or should have known that they were putting their pediatric subjects at greater than minimal risk. If they could have known, then, arguably, these investigators were not conforming to the AEC's requirement permitting nontherapeutic research in children pro-

vided that "the radiation dosage level in any tissue is low enough to be considered harmless."

It is clear that the medical community's understanding of the nature and magnitude of risks posed to children by radiation exposure is not what it is today. Researchers did not positively associate prior exposure to external radiation with an increased risk of cancer until the mid to late 1950s. In 1950, Duffy and Fitzgerald raised the question as to whether there might be cause to investigate a possible association between therapeutic thymic irradiation during childhood and subsequent development of thyroid or thymic cancers:

To pose a cause and effect relationship between thymic irradiation and the development of cancer would be quite unjustified on the basis of data at hand when one considers the large number of children who have had irradiation of an "enlarged thymus." However, the potential carcinogenic effects of irradiation are becoming increasingly apparent, and such relationships as those of thymic irradiation in early life and the subsequent development of thyroid or thymic tumors might be profitably explored.⁷³

By 1959, several studies had reported an association between radiation exposure and the subsequent development of leukemia.⁷⁴ Saenger et al. performed an epidemiologic study of several thousand children in 1960 to evaluate the association between radiation exposure and cancer.⁷⁵ They stated:

The question of whether or not radiation can be indicted as the principal causative factor in the induction of neoplasia following radiation exposure for either diagnostic or therapeutic purposes has been of increased interest over the past several years.⁷⁶

In completing their analysis, they concluded: "It remains a fact, indisputable in all respects, that the rate of thyroid cancers in the irradiated group is disproportionately high."⁷⁷

In 1961, Beach and Dolphin prepared a detailed analysis of the literature on the relationship between radiation and thyroid cancer in children.⁷⁸ They reported:

The thyroid has always been considered to be an organ comparatively radio-resistant to alteration and subsequent tumor development. Although no definite development of radiogenic tumor has been reported in adults after therapeutic administration of iodine-

131, Jelliffe and Jones (1960) discuss a total of 10 cases of thyroid cancer reported in the literature in persons treated early in life by x-ray irradiation in the neck region. [T]he total of malignant thyroid tumors which develop in children given a dose of x-radiation to the thyroid that is of the same order of magnitude as the incidence estimated for other tumors if a linear dose-response relationship is assumed. No biologic significance is attached to this point, apart from noting the fact that the child's thyroid appears to be more radio-sensitive than an adult's but not more sensitive than some adult tissues.⁷⁹

This lack of appreciation for the potential long-term effects of radiation in children is further reflected in institutional policy development for use of radioisotopes at the time. The Massachusetts General Hospital developed standards for tracer doses of radioisotopes in May 1949. Dr. Shields Warren, director of the AEC Division of Biology and Medicine, assisted in the development of the MGH standard:

Tracer doses in humans will always be kept to the absolute minimum required to make the observation.

Adult humans who are ill and who are expected to benefit from the procedure, shall not receive tracer doses of radioactive material giving off radiation in excess of a total of 4 rep. Children (all patients below 15 years of age) shall not receive more than a total of 0.8 rep.⁸⁰

In any other cases, tracer doses will be limited to radioactive material giving off radiation in an amount less than a total of 1 rep.

In the case of iodine, the thyroid, which retains most of the radioactivity, is radioresistant. In this case, the permitted dosage may be increased by a factor of 100.⁸¹

Despite the cautious tone of this document, the policy illustrates the complete lack of understanding of the true radiosensitivity of the thyroid gland, especially in the pediatric population. Further allowances must be made with regard to what was known about the distribution of radioisotopes in children at the time. It is evident that investigators using radioisotopes in children were not employing available information on organ weights in children to calculate tissue exposures at least until the mid-1960s. When "standard man" assumptions were used to calculate pediatric exposures before pediatric standards were developed, investigators may

have significantly and systematically underestimated effective tissue dosages in children. It is notable that the highest levels of risk posed in the experiments reviewed were to infants administered iodine 131.

Iodine 131 was routinely used for diagnostic procedures in the pediatric population until the 1980s, when it was replaced by I-123, a newly available radioisotope with a significantly shorter half-life, which reduced the thyroid dose markedly. The Wrentham fallout study, performed in 1961, employed doses of iodine 131 that resulted in an average dose of 44 rad to the gland, slightly less than the dose that would have been received for a diagnostic thyroid scan during this time.

Although the doses of radioisotopes subsequently declined during these years for both therapeutic medicine and nontherapeutic research, these guidelines were not based on long-term outcome studies of exposed individuals but rather on conservative extrapolations from high-dose studies and on the dosages necessary to enable detection with the available equipment.

The debate over the potential risks of low-dose exposure continues today, as epidemiological studies of thyroid cancer incidence subsequent to iodine 131 administration in both the diagnostic as well as therapeutic dose range have been largely negative. Risks as a result of iodine 131 exposure are still unclear, and risk analyses for exposure to radioisotopes are thus based on extrapolations from studies involving external irradiation.

In summary, during the period in which children were exposed to the highest levels of risk from nontherapeutic research involving radioisotopes, investigators had a limited understanding of the potential long-term risks of low-dose radiation and of methods to accurately calculate the tissue doses in children. Today, we cautiously assume that any exposure to radiation likely produces some small increase in cancer risk, so that no exposure is absolutely harmless. Instead, the concept of minimal or acceptable risk is commonly used, as discussed earlier. Some of the studies during this period involved risks that would be judged as minimal even today, whereas others would be clearly viewed as unacceptable today. Should the investigators then

have viewed any of these studies as harmless? Though an understanding of the association between exposure to external radiation and subsequent development of cancer was emerging during this time, a similar association had not been made for exposure to low dose levels of radioisotopes. In addition, the relative radiosensitivity of many pediatric tissues, including thyroid, had not been established, and most researchers during this period subscribed to the "threshold" theory of risk, which assumed that sufficiently low doses were probably harmless. In the face of such widespread factual ignorance, it is difficult to hold these investigators culpable for imposing risks on their subjects that were not appreciated at the time.

BEYOND RISK: OTHER DIMENSIONS OF THE ETHICS OF NONTHERAPEUTIC RESEARCH ON CHILDREN

The level of risk to which children are exposed is critical in evaluating the ethics of nontherapeutic research on children. Also important, however, is whether and how the authorization of parents was solicited, and also which children were selected to be so used. For nineteen of the twenty-one studies reviewed by the Committee, we know almost nothing about whether the permission of parents was sought or what the parents were told about their children's involvement. Two of the studies conducted at the Fernald School were the exceptions, as a result of extensive historical and archival research by the Massachusetts Task Force on Human Subjects Research.

There is a reference to parents in the published literature on only one of the remaining nineteen studies, a 1954 iodine uptake experiment at the University of Tennessee. This paper included the following line: "The procedure was described to the mothers of the infants studied, and the mothers gave consent for the study before the tests were made."⁸² (The inclusion of this line is noteworthy for it suggests that at least some investigators thought parental permission was worth mentioning in published reports of their research.)

If the Committee had devoted extensive investigatory resources to these nineteen studies, it is likely we would have learned more about whether or how parental authorization was obtained in at least some cases. It is also almost certain that even the deepest archival digging would have produced no useful information about parental authorization for some of these experiments. The recent experience of the Massachusetts Task Force demonstrates the possibility of both outcomes: for some of the experiments conducted at the Fernald School, the task force's diligent historical research uncovered a variety of documents that shed important light on what both parents and children were told; for the experiments at Wrentham, similar efforts did not produce any significant information on questions of parental authorization.

Again with the exception of the experiments conducted at Fernald and Wrentham, we know almost nothing about who the children were who served as subjects in these experiments. The journal articles on these remaining studies do not describe the sociodemographic characteristics of the subjects. They do sometimes mention whether the subjects had relevant medical conditions and usually that the children, including the "control" subjects, were hospitalized patients. In some of the experiments reviewed by the Committee, the scientific research questions of interest could have been pursued only in children who were ill and hospitalized. In other instances, however, the hospitalized children were likely samples of convenience. This is particularly plausible in the case of control subjects, when a sample of healthy, nonhospitalized children might have made a better control group from a scientific perspective. As we saw in chapter 2, hospitalized patients were often viewed by physician-investigators as a convenient source of research subjects.

Because so little is known, the Committee cannot draw conclusions about the ethics of most of the nontherapeutic studies involving children we reviewed, apart from the important issue of risk of harm to the children involved. We turn now to an analysis of the studies where relevant information about parental authorization, disclosure, and subject selection is available: the studies conducted at the Fernald School.

THE STUDIES AT THE FERNALD SCHOOL

Researchers from the Massachusetts Institute of Technology, working in cooperation with senior members of the Fernald staff, carried out nontherapeutic nutritional studies with radioisotopes at the state school in the late 1940s and early 1950s. The subjects of these nutritional research studies were young male residents of Fernald, who were members of the school's "science club." In 1946, one study exposed seventeen subjects to radioactive iron. The second study, which involved a series of seventeen related subexperiments, exposed fifty-seven subjects to radioactive calcium between 1950 and 1953. It is clear that the doses involved were low and that it is extremely unlikely that any of the children who were used as subjects were harmed as a consequence. These studies remain morally troubling, however, for several reasons. First, although parents or guardians were asked for their permission to have their children involved in the research, the available evidence suggests that the information provided was, at best, incomplete. Second, there is the question of the fairness of selecting institutionalized children at all, children whose life circumstances were by any standard already heavily burdened.

Parental Authorization

The Massachusetts Task Force found two letters sent to parents describing the nutrition studies and seeking their permission. The first letter, a form letter signed by the superintendent of the school, is dated November 1949.⁸³ The letter refers to a project in which children at the school will receive a special diet "rich" in various cereals, iron, and vitamins and for which "it will be necessary to make some blood tests at stated intervals, similar to those to which our patients are already accustomed, and which will cause no discomfort or change in their physical condition other than possibly improvement." The letter makes no mention of any risks or the use of a radioisotope. Parents or guardians are asked to indicate that they have no objection to their son's participation in the project by signing an enclosed form.⁸⁴

The second letter, dated May 1953, we quote in its entirety:

Dear Parent:

In previous years we have done some examinations in connection with the nutritional department of the Massachusetts Institute of Technology, with the purposes of helping to improve the nutrition of our children and to help them in general more efficiently than before.

For the checking up of the children, we occasionally need to take some blood samples, which are then analyzed. The blood samples are taken after one test meal which consists of a special breakfast meal containing a certain amount of calcium. We have asked for volunteers to give a sample of blood once a month for three months, and your son has agreed to volunteer because the boys who belong to the Science Club have many additional privileges. They get a quart of milk daily during that time, and are taken to a baseball game, to the beach and to some outside dinners and they enjoy it greatly.

I hope that you have no objection that your son is voluntarily participating in this study. The first study will start on Monday, June 8th, and if you have not expressed any objections we will assume that your son may participate.

Sincerely yours,

Clemens E. Benda, M.D.
[Fernald] Clinical Director

Approved: _____

Malcom J. Farrell, M.D.

[Fernald] Superintendent⁸⁵

Again, there is no mention of any risks or the use of a radioisotope. It was believed then that the risks were minimal, as indeed they appear to have been, and as a consequence, school administrators and the investigators may have thought it unnecessary to raise the issue of risks with the parents. There was *no basis*, however, for the implication in both letters that the project was intended for the children's benefit or improvement. This was simply not true.⁸⁶

The conclusion of the Massachusetts Task Force was that these experiments were conducted in violation of the fundamental human rights of the subjects. This conclusion is based in part on the task force's assessment of these letters. Specifically, the task force found that

[t]he researchers failed to satisfactorily inform the subjects and their families that the nutritional research

studies were non-therapeutic; that is, that the research studies were never intended to benefit the human subjects as individuals but were intended to enhance the body of scientific knowledge concerning nutrition.

The letter in which consent from family members was requested, which was drafted by the former Fernald superintendent, failed to provide information that was reasonably necessary for an informed decision to be made.⁸⁷

Fairness and the Use of Institutionalized Children

The Fernald experiments also raise quite starkly the particular ethical difficulties associated with conducting research on members of institutionalized populations—especially where some of the residents have mental impairments. Living conditions in most of these institutions (including Fernald and Wrentham) have improved considerably in recent years, and sensitivity toward people with cognitive impairments has likewise increased. As Fred Boyce, a subject in one of these experiments has put it, "Fernald is a much better place today, and in no way does it operate like it did then. That's very important to know that."⁸⁸

The Massachusetts Task Force describes conditions in state-operated facilities like Fernald, particularly as they bear on human experimentation, as follows:

Until the 1970s, the buildings were dirty and in disrepair, staff shortages were constant, brutality was often accepted, and programs were inadequate or nonexistent. There were no human rights committees or institutional review boards. If the Superintendent (in those days required to be a medical doctor) "cooperated" in an experiment and allowed residents to be subjects, few knew and no one protested. If nothing concerning the experiments appeared in the residents' medical records, if "request for consent" letters were less than forthright, or if no consent was obtained there was no one in a position of authority to halt or challenge such procedures.⁸⁹

Although public attitudes toward people who are institutionalized are admittedly different today than they were fifty years ago, it is likely that this state of affairs would have been troubling to most Americans even then. Historian Susan Lederer has revealed several episodes of experimentation with institutionalized children

in America that caused considerable public outcry even before 1940, presaging the concern generated by Willowbrook when this research became a public issue in the 1960s.⁹⁰

The LMRI staff reported in the early 1960s that the pediatric researchers whom they had gathered agreed in principle that the convenience of conducting research on institutionalized children did not outweigh the moral problems associated with this practice:

Several investigators spoke about the practical advantages of using institutionalized children who are already assembled in one location and living within a standard, controlled environment. But the conferees agreed that there should be no differential recruitment of ward patients rather than private patients, of institutionalized children rather than children living in private homes, or of handicapped rather than healthy children.⁹¹

A particularly poignant dimension of the unfairness of using institutionalized children as subjects of research is that it permits investigators to secure cooperation by offering as special treats what other, noninstitutionalized children would find far less exceptional. The extra attention of a "science club," a quart of milk, and an occasional outing were for the boys at Fernald extraordinary opportunities. As Mr. Boyce put it:

I won't tell you now about the severe physical and mental abuse, but I can assure you, it was no Boys' Town. The idea of getting consent for experiments under these conditions was not only cruel but hypocritical. They bribed us by offering us special privileges, knowing that we had so little that we would do practically anything for attention; and to say, I quote, "This is their debt to society," end quote, as if we were worth no more than laboratory mice, is unforgivable.⁹²

Even when a child was able to resist the offers of special attention and refused to participate in the experiment, the investigators seem to have been unwilling to respect the child's decision. One MIT researcher, Robert S. Harris, explicitly noted that "it seemed to [him] that the three subjects who objected to being included in the study [could] be induced to change their minds."⁹³ Harris believed that the recalcitrant children could be "induced" to join in the study by emphasizing "the Fernald Science Club angle of our work."⁹⁴

From the perspective of the science, it was considered important to conduct the research in an environment in which the diet of the children-subjects could be easily controlled. From this standpoint, the institutional setting of Fernald was ideal. The institutional settings of the boarding schools in the Boston area, however, would have offered much the same opportunity. Although the risks were small, the "children of the elite" were rarely if ever selected for such research. It is not likely that these children would have been willing to submit to blood tests for extra milk or the chance to go to the beach.

The question of what is ethical in the context of unfair background conditions is always difficult. Perhaps the investigators, who were not responsible for the poor conditions at Fernald, believed that the opportunities provided to the members of the Science Club brightened the lives of these children, if only briefly. Reasoning of this sort, however, can all too easily lead to unjustifiable disregard of the equal worth of all people and to unfair treatment.

Today, fifty years after the Fernald experiments, there are still no federal regulations protecting institutionalized children from unfair treatment in research involving human subjects.⁹⁵ The Committee strongly urges the federal government to fill this policy void by providing additional protections for institutionalized children.⁹⁶

CONCLUSION

If an ethical evaluation of human experiments depended solely upon an assessment of the risks to subjects as they could reasonably be anticipated at the time, the radiation experiments conducted on children reviewed in this chapter would be relatively unproblematic.⁹⁷ During this time, the association between radiation exposure and the subsequent development of cancer was not well understood, and in particular, little was known about iodine 131 and the risk of thyroid cancer. Both researchers and policymakers appear to have been alert to considerations of harm and concerned about exposing children to an unacceptable level of risk.

At the same time, however, the scientific community's experience with radionuclides in

humans was limited, and this approach to medical investigation was new. Although the available data about human risk were encouraging and the biological susceptibility of children to the effects of radiation was not appreciated, we are left with the lingering question of whether investigators and agency officials were *sufficiently* cautious as they began their work with children. This is a difficult judgment to make at any point in the development of a field of human research; it is particularly difficult to make at forty or fifty years' remove. Investigators and officials had to make decisions under conditions of considerable uncertainty; this is commonplace in science and in medicine. Although the biological susceptibility of children was not then known, investigators and officials held the view that children should be accorded extra protection in the conduct of human research, and they made what they thought were appropriate adjustments when using children as subjects. If human research never proceeded in the face of uncertainty, there would be no such experiments. How little uncertainty is acceptable in research involving children is a question that remains unresolved. Today, we continue to debate what constitutes minimal risk to children, in radiation and in other areas of research. The regulations governing research on children offer little in the way of guidance, either with respect to conditions of uncertainty about risk or when risks are known.

As best as we can determine, in eleven of the twenty-one experiments we reviewed, the risks were in a range that would today likely be considered as more than minimal, and thus as unacceptable in nontherapeutic research with children according to current federal regulations. It is possible, however, that four of the eleven might be considered acceptable by the "minor increase over minimal risk" standard.⁹⁸ In these four experiments, the average risk estimates were between one and two per thousand, the studies were directed at the subjects' medical conditions,

and they may well have had the potential to obtain information of "vital importance."

Physical risk to subjects is not the only ethically relevant consideration in evaluating human experiments. With the exception of the studies at Fernald, we know almost nothing about whether or how parental authorization for the remaining nineteen experiments we reviewed was obtained. And with the exception of the Fernald studies and the experiment at Wrentham, we know very little about the children who were selected to be the subjects of this research. Therefore, we cannot comment on the general ethics of these other experiments.

The experiments at Fernald and at the Wrentham School unfairly burdened children who were already disadvantaged, children whose interests were less well protected than those children living with their parents or children who were socially privileged. At the Fernald School, where more is known, there was some attempt to solicit the permission of parents, but the information provided was incomplete and misleading. The investigators successfully secured the cooperation of the children with offers of extra milk and an occasional outing—incentives that would not likely have induced children who were less starved for attention to willingly submit to repeated blood tests.

One researcher speaking almost thirty-five years ago set out the fundamental moral issue with particular frankness and clarity:

... we are talking here about first and second class citizens. This is a concept none of our consciences will allow us to live with. ... The thing we must all avoid is two types of citizenry.⁹⁹

It might have been common for researchers to take advantage of the convenience of experimenting on institutionalized children, but the Committee does not believe that convenience offsets the moral problems associated with employing these vulnerable children as research subjects—now or decades ago.

THE VANDERBILT STUDY

In an exceptionally large study^a at Vanderbilt University in the 1940s, approximately 820 poor, pregnant Caucasian women were ad-

ministered tracer doses of radioactive iron. Vanderbilt worked with the Tennessee State Department of Health, and the research was

partly funded by the Public Health Service.^b Today, most women take iron supplements during pregnancy. This experiment provided the scientific data needed to determine the nutritional requirements for iron during pregnancy.

The radioiron portion of the nutrition study, directed by Dr. Paul Hahn, was designed to study iron absorption during pregnancy.^c The women, who were anywhere from less than ten weeks to more than thirty-five weeks pregnant, were administered a single oral dose of radioactive iron, Fe-59, during their second prenatal visit, before receiving their routine dose of therapeutic iron.^d On their third prenatal visit, blood was drawn and tests performed to determine the percentage of iron absorbed by the mother. The infants' blood was then examined at birth to determine the percentage of radio-

iron absorbed by the fetus. The doses to the women were estimated in the study article, using crude dose-estimation methods available at the time, to be from 200,000 to 1,000,000 countable counts per minute.^e Although the investigators did not estimate doses to the fetuses in the original study, Dr. Hahn later estimated fetal doses to be between 5 and 15 rad. This estimate, however, has been questioned.^f

There is at least some indication that the women neither gave their consent nor were aware they were participating in an experiment. Vanderbilt study subjects, expressing bitterness at the way they believed they had been treated, testified at an Advisory Committee meeting that the proffered drink, called a "cocktail" by the investigators, was offered with no mention of its contents. "I remember taking a cocktail," one woman said simply. "I don't remember what it was, and I was not told what it was."^g Although it is not clear what, if anything, the subjects were told, information about the Vanderbilt experiment was available to the general public. In late 1946 news reports appeared in the Nashville press.^h

a. Most of the other tracer studies involving pregnant women and offering no prospect of benefit that were reviewed by the Committee involved fewer than twenty women as subjects.

b. William J. Darby, Director of the Tennessee-Vanderbilt Project et al., *Summary Report, Section B, Tennessee-Vanderbilt Nutrition Project, July 1, 1946 to December 31, 1946* (ACHRE No. CORP-020395-A), 97-110. This nutrition study summary report notes, "Considerable expansion of the program of study of maternal and infant nutrition has been made possible by a grant of \$9,000 per year which was made by the U.S. Public Health Service. These funds were available beginning November 1, 1946." *Ibid.*, 99. The summary observes that the grant was to be used for additional personnel, including the appointment of Dr. Richard Cannon, an obstetrics resident, to the staff of the Division of Nutrition beginning 1 January 1947. Dr. Cannon's name subsequently appears as an investigator in the medical report discussing the radioiron portion of the study, along with Dr. Paul Hahn's and others.

c. P. Hahn et al., "Iron Metabolism in Human Pregnancy as Studied with the Radioactive Isotope, Fe-59," *American Journal of Obstetrics and Gynecology* 61 (March 1951): 477-486. The exact years of the radioiron portion of the nutrition study are uncertain. Minutes from a meeting of the nutrition study investigators indicate the study was to begin in September 1945. Tennessee-Vanderbilt Nutrition Project, Nutrition in Pregnancy Study, "Minutes of Meeting for Discussion of Nutrition in Pregnancy Study, August 17, 1945" (ACHRE No. CORP-020395-A), 17A-C.

The radioiron study probably began at approximately that time and appears to have continued until sometime in 1947, based on a review of periodic study summaries.

d. The Advisory Committee has not been able to determine whether Dr. Hahn got the radioactive iron used in the study from a private or government source, or both.

e. Counts per minute is a measure of the radioactivity detected by a specific counting instrument. The sensitivities of counting instruments vary; a specific instrument may not "see" and count all the radiation coming from a particular substance. Thus, the total amount of radiation emitted by a substance may be calculated by considering the sensitivity of the counter.

f. Contemporary estimates of the fetal doses by the Committee and others suggest that the fetal effective dose was a few hundred millirems.

g. Wilton McClure, transcript of audio testimony before the Advisory Committee on Human Radiation Experiments, Small Panel Meeting, Knoxville, Tennessee, 2 March 1995, 182.

h. "Iron Doses with Radioactive Isotopes Aid to Pregnancy, Experiment Shows," *Nashville Banner*, 13

The actual risk to the fetuses in the Vanderbilt experiment has long been a matter of study. In 1963-1964, a group of researchers at Vanderbilt found no significant differences in malignancy rates between the exposed and nonexposed mothers.¹ However, they did identify a higher number of malignancies among the exposed offspring (four cases in the exposed group: acute lymphatic leukemia, synovial sarcoma, lymphosarcoma, and primary liver carcinoma, which was discounted as a rare, familial form of cancer). No cases were found in a control group of similar size, and approximately 0.65 cases would have been expected on Tennessee state rates, compared to which the three observed cases is a marginally significant excess. This led the researchers to conclude that the data suggested a causal relationship between the prenatal exposure to Fe-59 and the cancer. The investigators also concluded that Dr. Hahn's estimate of fetal exposure was an underestimation of the fetal-absorbed dose.

A 1969 study, funded by the AEC and conducted by one of the investigators from the 1963-1964 study, attempted to reconstruct the doses of Fe-59 to the fetuses in the original Vanderbilt study.² The investi-

gators observed that the one case of leukemia might have been due to radiation damage, but that the doses in the other two cases were low; therefore, the relationship between the radiation exposure and the cancer in those cases might not have been causal. However, the researchers also noted that due to incomplete data, they could not estimate the dose absorbed by the fetus with confidence and that no definitive conclusions could be drawn from this study as to whether these exposures resulted in damage to the fetus.³

The Vanderbilt study raises many of the same ethical issues as the experiments reviewed in this chapter. Like these experiments, the Vanderbilt study offered no prospect of medical benefit to the pregnant women or their offspring, raising the question of the conditions under which it is acceptable to put children at risk for the benefit of others, whether before or after birth. What could the investigators reasonably have been expected to know about the risks to which they put their subjects? Did they exercise appropriate caution in exposing fetuses to radiation? What were the pregnant women told, if anything, and was their permission sought? Who were these women, and how were they positioned relative to pregnant women, generally?

The Committee did not have the resources to pursue these questions in both research in which children were the subjects and research in which children were exposed as fetuses. We did establish that the Vanderbilt study was not the only experiment during this period to expose fetuses in research that offered no prospect of medical benefit to them or their mothers. While the Committee did not conduct an exhaustive review of the scientific literature, we did find twenty-seven human radiation

December 1946: "VU to Report on Isotopes." *The Nashville Tennessean*, 14 December 1946 (ACHRE No. CORP-020395-A).

i. The investigators identified the hospital records of 751 exposed mothers and 771 unexposed controls, as well as 719 exposed offspring and 734 unexposed offspring, and mailed them questionnaires. Of the exposed mothers, 90.4 percent responded, as did 91.45 percent of the unexposed mothers, 88.2 percent of the exposed offspring, and 89.2 percent of the unexposed. Ruth M. Hagstrom et al., "Long Term Effects of Radioactive Iron Administered During Human Pregnancy," *American Journal of Epidemiology* 90 (1969): 1-8.

j. Norman C. Dyer and A. Bertrand Brill, "Fetal Radiation Dose from Maternally Administered Fe-59 and I-131," in *Radiation Biology of the Fetal and Juvenile Mammal: Proceedings of the Ninth Annual Hanford Biology Symposium at Richland, Washington, May 5-8, 1969*, eds. Melvin R. Sikov and D. Dennis Mahlum (Washington, D.C.: GPO, December 1969),

78-88. This study was reviewed in detail by the Committee. The study also investigated fetal absorption of radioiodine because that isotope was and is commonly used in diagnosis and therapy, including in pregnant women.

k. *Ibid.*, 85.

studies that included pregnant or nursing women as subjects between 1944 and 1974.¹ Of these studies, eight were considered therapeutic, and nineteen offered no prospect of benefit to the subject. Most of the nineteen were tracer experiments.

These studies were performed in order to examine human physiology during preg-

nancy or to study the uptake of radioactive substances by fetuses or nursing infants.^m They generally addressed valid scientific questions that could not be investigated in other populations. Knowledge of fetal exposure to radioiodine, for example, was relevant to issues such as potential harm to the fetus from maternal uptake of radioiodine in diagnostic tests or to estimate the potential effects of environmental exposure to radioiodine on the human fetus. In other studies, radioactive iron was administered to better understand the physiology of maternal and fetal intake of iron during pregnancy.

l. All of the nineteen studies reviewed in detail by the Committee were conducted or at least partially funded by the federal government or were supplied with radioisotopes by the AEC. For the earlier years, the Committee relied on the ACHRE experiments database, AEC isotope distribution lists provided by DOE, and relevant biographies. The Committee also consulted relevant medical indexes and computer databases; the isotope distribution lists provided by DOE did not cover these years. While the computer search would have located nontherapeutic tracer experiments for this period as well, very few were identified.

m. Of the nineteen tracer experiments (funded by the government) involving pregnant or nursing women identified by the Committee, only three administered tracer doses to nursing women that offered no prospect of benefit; in at least one of the studies the infants were exposed. In one case, six nursing women

were given radioiodine to determine excretion in breast milk, the infants were not given the exposed milk. In another case, two infants were intentionally exposed to the breast milk of their mothers, who were given I-131. An I-131 tracer study on the general population, incidentally included two nursing women. The report indicates that both had been nursing their children, and since there is no indication that the mothers were warned to avoid breastfeeding after the exposure, it is quite probable that the infants were exposed.

NASOPHARYNGEAL IRRADIATION

Nasopharyngeal irradiation,^a introduced by S. J. Crowe and J. W. Baylor of the Otolological Research Laboratory at the Johns Hopkins University, was employed from 1924 on as a means of shrinking lymphoid tissue at the entrance to the eustachian

tubes to treat middle ear obstructions, infections, and deafness. For this treatment, intranasal radium applicators (sealed ampules containing radium salt) were inserted (at least three insertions per treatment cycle) into the nasopharyngeal area for twelve-

a. Nasopharyngeal irradiation was studied in adults as well as children. In the early 1940s, 732 submariners were subjects of a controlled experiment designed to test whether nasopharyngeal radium treatments could be used to shrink lymphoid tissue surrounding the eustachian tubes, thereby preventing and treating aerotitis media in submariners by equalizing external and middle ear pressure. This treatment was successful in 90 percent of the cases. H. L. Haines and J. D. Harris, "Aerotitis Media in Submariners," *Annals of Otolaryngology, Rhinology, and Laryngology* 55 (1946): 347-371. In a 1945 journal article, it was noted that a controlled study was considered by the Army Air Forces, but rejected

because of the urgent need to treat fliers immediately and keep them flying. However, the published report describes differences between various dose groups, implying an uncontrolled experimental comparison was made. Captain John E. Hendricks et al., "The Use of Radium in the Aerotitis Control Program of the Army Air Forces: A Combined Report by the Officers Participating," *Annals of Otolaryngology, Rhinology, and Laryngology* 54 (1945): 650-724. Tens of thousands of servicemen were subsequently given this nasopharyngeal radium treatment.

Relying on the risk estimate developed in the Sandler study, Stewart Farber, a radiation-monitoring specialist with a background in public health, has projected

minute periods.^b The therapeutic effect of the treatments resulted from the penetrating radiation emitted from the radium source (gamma and beta rays), not from the internal deposition of radium itself. Crowe and his colleagues reported that "under this treatment, the lymphoid tissue around the tubal orifices gradually disappeared, marked improvement or complete return of the hear-

ing followed, and in many the bluish discoloration of the tympanic membrane also disappeared."^c This method was used for more than a quarter century as a prophylaxis against deafness, for relieving children with recurrent adenoid tissue following tonsillectomy and adenoidectomy, and for children with chronic ear infections. Asthmatic children with frequent upper respiratory infections were also often considered for this type of irradiation.

51.4 excess brain cancers over a fifty-year period in the 7,613 servicemen irradiated in the Navy and Army Air Forces studies noted above. Stewart Farber, Consulting Scientist of the Public Health Sciences, to Stephen Klaidman, ACHRE Staff, 8 March 1995 ("Nasopharyngeal Radium Irradiation-Initial Radiation Experiments Performed by DOD on 7,613 Navy and Army Air Force Military Personnel during 1944-45"), Alan Ducatman, M.D., of the University of West Virginia School of Medicine, who coauthored a letter with Farber to the *New England Journal of Medicine* regarding the radium exposure of military personnel, wrote that he found "no convincing evidence of excess cancer in the exposed population." He added, however, "there is also no good evidence for the null hypothesis." Alan Ducatman, West Virginia University School of Medicine, to Duncan Thomas, Member of the Advisory Committee on Human Radiation Experiments, 22 February 1995 ("I'm sorry I could not respond . . .") (ACHRE No. WVU-021795-A).

Han K. Kang, with the Environmental Epidemiology Service of the Veterans Health Administration, is currently conducting a study to assess the feasibility of an epidemiologic study of Navy veterans who received radium treatments. Han K. Kang, Environmental Epidemiology Service, Veterans Health Administration, "Feasibility of an Epidemiologic Study of a Cohort of Submariners Who Received Radium Irradiation Treatment," 23 August 1994. It is not clear, however, that sufficient numbers of treatment-documented personnel can be identified, as a group representing submariners has apparently been able to identify only six former Navy personnel from a pool of twenty-seven whose records indicate they received radium treatment. (It is not clear whether the data being collected by the VFW with the support of Senator Joseph Lieberman of Connecticut will be from a representative sample of respondents. If, in fact, these data are from a highly nonrepresentative sample, the study may not be considered scientifically valid.) However, the Veterans of Foreign Wars organization apparently is now processing hundreds of surveys filled out by veterans who say they underwent nasopharyngeal radium treatment. Once this task is completed, Senator Lieberman plans to present the data to the Department of Veterans Affairs with a recommendation that an epidemiologic study be conducted.

An average of 150 patients a month, mostly children, were given the treatment at the Johns Hopkins clinic over a period of several years.^d Many children received the treatment more than once as recurrent lymphoid tissue was considered an indication for treatment.

Crowe and his colleagues reported that the results following irradiation of the nasopharynx alone were not only as good as, but often better than, those following removal of tonsils and adenoids.^e In review articles, they noted that approximately 85 percent of treated patients responded with decreased numbers of infections and/or improved hearing when treated at young ages. They also concluded that "it is effective, safe, painless, inexpensive and has proved particularly valuable for prevention of certain ear, sinus and bronchial condition in children."^f

Although early articles by Crowe and colleagues indicate that nasopharyngeal radium treatments were accepted as standard procedure for the prevention of childhood deafness, these treatments, like most standard interventions in medicine, had not been subjected to formal scientific evaluation. A controlled study was conducted from 1948

b. Samuel J. Crowe, "Irradiation of the Nasopharynx," *Annals of Otolary, Rhinology and Laryngology* 55 (1946): 31.

c. *Ibid.*, 30.

d. *Ibid.*, 33.; Dale P. Sandler et al., "Neoplasms Following Childhood Radium Irradiation of the Nasopharynx," *Journal of the National Cancer Institute* 68 (1982): 3-8.

e. *Ibid.*, 33.

f. *Ibid.*

to 1953 by Crowe and his colleagues to determine "the feasibility of irradiation of the nasopharynx as a method for controlling hearing impairment in large groups of children associated with lymphoid hyperplasia in the nasopharynx; to draw conclusions concerning the per capita cost of such an undertaking as a public health measure."^g Crowe et al. wrote in an NIH "Notice of Research" that "the procedure of treatment is not new, as an individual measure; this is the first adequately controlled experiment of sufficient size for accurate statistical analysis."^h

This work was funded by NIH for the entire period of study. As recorded in an NIH grant application, the study involved approximately 7,000 children screened for hearing impairment.ⁱ Of those screened, approximately 50 percent were selected for further study based on the chosen criteria for hearing loss. Half of this study group was irradiated with radium, while the other half served as a control group. Crowe and colleagues reportedly concluded from this study (published in 1955) that the radium treatments did shrink swelling of lymphoid tissue and improve hearing.^j This type of therapy was ultimately discontinued because of newly available antibiotics and the use of transtympanic drainage tubes, as well as awareness of the potential risks of radiation treatment.

In addition to the targeted lymphoid tissue, the brain and other tissues in the head and neck region, including the paranasal sinuses, salivary glands, thyroid, and parathyroid glands are also exposed to significant doses of radiation during the radium treat-

ments, prompting concern that these treated individuals might have been placed at increased risk for radiation-induced cancers at these sites. Dale P. Sandler et al., in their 1982 study of the effects of nasopharyngeal irradiation on excess cancer risk for children treated at the Johns Hopkins clinic, found "a statistically significant overall excess of malignant neoplasms of the head and neck among exposed subjects," based however on only four cases in comparison with 0.57 expected.^k This excess was accounted for mainly by three brain tumors that occurred in the irradiation subjects. One other malignant tumor, a cancer of the soft palate, was also reported. The Department of Epidemiology at the Johns Hopkins University has undertaken a further follow-up study of the Crowe et al. cohort of children irradiated there, previously studied by Sandler et al.^l Verduijn et al., in their 1989 study of cancer mortality risk for those individuals (mostly children) treated by nasopharyngeal irradiation with radium 226 in the Netherlands, reported that "the present study has found no excess of cancer mortality at any site associated with radium exposure by the Crowe and Baylor therapy. Specifically, the finding of Sandler et al. of an excess of head and neck cancer was not found in this study group."^m

Among the Japanese atomic bomb survivors, no excess of brain tumors was found. However, several studies have noted an increased risk of both benign and malignant brain tumors following therapeutic doses of radiation to the head and neck region during childhood.ⁿ From the Com-

g. S. J. Crowe et al., The Johns Hopkins University School of Medicine and School of Hygiene and Public Health, to Federal Security Agency, Public Health Service, National Institutes of Health, July 1948 ("The Efficiency of Nasopharyngeal Irradiation In the Prevention Of Deafness in Children, Notice of Research Project, Grant No. B-19") (ACHRE No. HHS No. 092694-A).

h. Ibid.

i. Ibid.

j. Ibid.

k. For the combination of benign and malignant neoplasms, there were 23 cases, for a relative risk of 2.08 with a 95 percent confidence interval of 1.12 to 3.91. Sandler, "Neoplasms Following Childhood Radium Irradiation," 5.

l. Jessica Yeh and Genevieve Matanowski, fax to Anna Mastroianni (ACHRE), 7 July 1995 ("Nasopharyngeal Power Analysis"), 1-3.

m. Verduijn et al., "Mortality after Nasopharyngeal Irradiation," *Annals of Otolaryngology, Rhinology, and Laryngology* 98 (1989): 843.

n. S. Jablon and H. Kato, "Childhood Cancer in Relation to Prenatal Exposure to Atomic-Bomb Radiation,"

mittee's own limited risk analysis of these experiments, we concluded that the brain and surrounding head and neck tissues would be put at highest risk and estimated the lifetime risk at approximately 4.35 per 1,000 and an increased relative risk of 62 percent.^o

The Hopkins nasopharyngeal study raises different ethical issues than those posed by the other experiments reviewed in this chapter, all of which offered no prospect of medical benefit to the children who served as subjects. By contrast, the nasopharyngeal irradiation experiment was designed to determine whether children at risk for hearing loss would be better off receiving radiation treatments or not receiving such treatments.

The Lancet, ii (1970): 1000-1003.; M. Colman, M. Kirsch, and M. Creditor, "Radiation Induced Tumors," in *Late Biological Effects of Ionizing Radiation, Vol. 1* (Vienna: International Atomic Energy Agency, 1978), 167-180; R. E. Shore, R. E. Albert, and B. S. Pasternak, "Follow-up Study of Patients Treated by X ray Epilation for Tinea Capitis: Resurvey of Post-Treatment Illness and Mortality Experience," *Archives of Environmental Health* 31 (1976): 17-24; and C. E. Land, "Carcinogenic Effects of Radiation on the Human Digestive Tract and Other Organs," in *Radiation Carcinogenesis*, eds. A. C. Upton et al. (New York: Elsevier, 1986), 347-378.

^o. The radiation dose estimate to the head and neck region was calculated according to the following assumptions: (1) Source description: 50 mg of radium, active length 1.5 cm, filtered by 0.3 mm of Monel metal. (2) Average treatment: 60 mg/hrs; based on three 12-minute treatments (radium applicators inserted through both nostrils) = $(12 \times 3 \times 50 \times 2) / 60$ mins per hour = 60 mg-hrs. (3) Dose rate at points in a central orthogonal plane surrounding the source: for distances up to 5 centimeters dose estimated using published data (Quimby Tables, Otto Glasser et al., *Physical Foundations of Radiology*, 3d ed. [New York: Paul Hoeber, Inc., 1961]) for linear radium sources with dose increased by 50% to allow for the reduced filtration provided by the applicator wall and converting roentgen to rad by a multiplication factor of 0.93. For distances greater than 5 centimeters, the dose rate is reduced in accordance with the inverse square

A central issue here was whether it was permissible to withhold this intervention from "at risk" children. The application of radium was at this point a common, but scientifically unproven, treatment for children at risk of hearing loss; the risks of the treatment were not well characterized. If it was really unknown which was better for children—receiving radium or no intervention—then the medical interests of the children were best served by being subjects in the research because, as a consequence, they would have a 50 percent chance of receiving the better approach. The nasopharyngeal experiment thus belongs to a class of research the Committee did not investigate—therapeutic research with children.

law, with a proportionality constant of 690 rad-cm². There was no dose correction for attenuation of the gamma rays by tissue absorption, which has been calculated to be about 2%/cm (yielding a dose reduction of about 20% at 10 cm).

The local gamma dose to the head and neck region was assumed to be distributed according to an inverse square law $d(r) = 690/r^2$ rad. The Committee approximated the exposed region of the body by a sphere with radius 10 centimeters. This was felt to be a conservative assumption, because although the dose does not go to zero at the base of the neck, a 10-centimeter sphere would also extend outside the skull. Averaging this dose distribution over the exposed sphere, the average dose to the head was found to be 20.7 rad. The exposed volume is about 4189 cm³, or 29 percent of the total body, so the average whole body dose is about 6.0 rad. Multiplying this by the BEIR V risk coefficient for children exposed at age five, 1.4/1,000 person-rad, produces a lifetime risk of about 8.4/1,000. This calculation assumes that the brain and other head tissues have average radiosensitivity. BEIR V also gives absolute-risk coefficients for brain cancer ranging from 1 to 9 per million person-year-rad, with 3 being a reasonable average. Applying this figure to an average head dose of 20.7 rad, the Committee estimates a lifetime risk of about 4.35/1,000. The corresponding relative risk coefficients average about 3 percent per rad, so this dose would correspond to an excess relative risk of 62 percent.

Table 2. Summary and Risk Analysis for Studies Examined by the Advisory Committee

Primary Author	Date of Publ.	Title of Study	Isotope	Number of Children	Cancer Risk	Risk Estimate (%) Incidence*
K. M. Saxena	1965	Thyroid Function in Mongolism	I-131	104	Thyroid	0.03 (0.1)
McDougall	1964	Estimation of Fat Absorption from Random Stool Specimens	I-131		Thyroid	0.06
M. A. Van Dilla	1963	Thyroid Metabolism in Children and Adults Using Very Small (Nanocurie) Doses of Iodine-125 and Iodine-131	I-131	8	Thyroid	0.001
R. T. Morrison	1963	Radioiodine Uptake Studies in Newborn Infants	I-131	25	Thyroid	0.15 (0.2)
K. M. Saxena	1962	Minimal Dosage of Iodine Required to Suppress Uptake of Iodine 131 by Normal Thyroid	I-131	63	Thyroid	0.10 (.18)
R. E. Ogborn	1960	Radioactive-iodine Concentration in Thyroid Glands of Newborn Infants	I-131	28	Thyroid	0.25 (0.49)
S. Kurland	1957	Radioisotope Study of Thyroid Function in 21 Mongoloid Subjects, Including Observations in 7 Parents	I-131	24 (17 children)	Thyroid	0.15 (1.0)
L. Oliner	1957	Thyroid Function Studies in Children: Normal Values for Thyroidal I-131 Uptake and PBI-131 Levels up to the Age of 18	I-131	83	Thyroid	0.34 (2.3)
E. E. Martmer	1956	A Study of the Uptake of Iodine (Iodine-131) by the Thyroid of Premature Infants	I-131	70	Thyroid	0.7 (2.2)
F. Bonner	1956	Studies in Calcium Metabolism: Effect of Phytates on 45-Ca Uptake in Boys on a Moderate Calcium Breakfast	Ca-45	57	Total	0.001
A. Friedman	1955	Radioiodine Uptake in Children with Mongolism	I-131	129	Thyroid	0.12 (0.82)
C. E. Benda	1954	Studies of Thyroid Function in Myotonia Dystrophica	I-131	6	Thyroid	0.02
L. V. Middlesworth	1954	Radioactive Iodine Uptake of Normal Newborn Infants	I-131		Thyroid	0.20 (0.27)
S. H. Silverman	1953	Radioiodine Uptake in the Study of Different Types of Hypothyroidism in Childhood	I-131	34	Thyroid	0.13 (0.6)
P. S. Lavik	1952	Use of Iodine-131 Labeled Protein in the Study of Protein Digestion and Absorption in Children with and without Cystic Fibrosis of the Pancreas	I-131	15	Total	0.05

H. W. Scott	1951	Blood Volume in Congenital Cyanotic Heart Disease: Simultaneous Measurements with Evans Blue and Radioactive Phosphorus	P-32	20	Total	0.08
L. M. Sharpe	1950	The Effect of Phytates and Other Food Factors on Iron Absorption	Fe-55 Fe-59	17	Total	0.03
W. A. Reilly	1950	Carrier-Free Radioactive Iodine-131 Thyroid Uptake and Urinary Excretion in Normal and Hypothyroid Children	I-131	16	Thyroid	0.04 (0.3)
V. C. Kelley	1950	Labeled Methionine as an Indicator of Protein Formation in Children with Lipoid Nephrosis	S-35	4	Total	0.02
G. H. Lowrey	1949	Radioiodine Uptake Curve in Humans: II. Studies in Children	I-131	26	Thyroid	0.2 (1.0)
E. H. Quimby	1947	Uptake of Radioactive Iodine by the Normal and Disordered Thyroid Gland in Children	I-131	54	Thyroid	0.16 (2.2)

*Risk estimates are reported as average values for each experiment; maximum values () are reported when available.

NOTES

1. As noted in the report of the Massachusetts Task Force, "many of the people who became residents of the Walter E. Fernald School . . . were not admitted with a diagnosis of mental retardation. Societal and cultural norms of the day permitted persons to be admitted to state-operated institutions for a number of reasons. All were labeled mentally retarded just by virtue of having lived within the facility." Task Force on Human Subject Research, to Philip Campbell, Commissioner, Commonwealth of Massachusetts Executive Office of Health and Human Services, Department of Mental Retardation, April 1994, "A Report on the Use of Radioactive Materials in Human Subject Research that Involved Residents of State-Operated Facilities within the Commonwealth of Massachusetts from 1943 to 1973" (ACHRE No. MASS-072194-A), 1.

2. Task Force on Human Subject Research, April 1994 ("A Report on the Use of Radioactive Materials in Human Subject Research that Involved Residents of State-Operated Facilities within the Commonwealth of Massachusetts from 1943 to 1973"); and the Working Group on Human Subject Research to Philip Campbell, June 1994 ("The Thyroid Studies: A Follow-up Report on the Use of Radioactive Materials in Human Subject Research that Involved Residents of State-Operated Facilities within the Commonwealth of Massachusetts from 1943 through 1973") (ACHRE No. MASS-072194-B).

3. Unfortunately, the published reports of the twenty-one research projects we review in this chapter often provide little or no information that could be used to identify the individual children. Many published reports provide information only about the child's age, weight, and diagnosis. Other reports provide only the child's initials and diagnosis. In either case, it would be difficult or impossible to identify specific individuals from this limited information. An existing chart may or may not confirm a child's involvement in a research project. If the investigators maintained records, those could serve as a key to identify the individuals. Even if the hospital records do exist, however, records for a period of several years prior to publication of the research would have to be reviewed in order to match a set of initials with a diagnosis. However, it is unlikely that research records have been maintained for many of these projects for the past three to five decades. Finally, the identification of an individual would be only the first step in tracking him to his current location.

Many of the children at the Wrentham and Fernald Schools have been located through extensive local efforts. The existence of the research records, as well as the records of these long-term residential institutions, have made these identifications possible.

4. There are a few exceptions to the usual involvement of parents in decisions concerning their minor children. Children who are considered either "eman-

ipated minors" or "mature minors" are generally able to receive routine medical care without any need for parental involvement. Emancipated minors are minor children who have taken on adult responsibilities, such as maintaining financial independence and/or living away from the parents' home. A mature minor, on the other hand, is considered to be decisionally capable under special circumstances because he or she has demonstrated the maturity and ability to decide treatment decisions for himself or herself. Adolescents can be considered emancipated or mature minors and are thereby exempted from parental consent. In addition, if a minor is close to the age of majority (at least fifteen), the treatment clearly benefits the minor and is medically necessary, there is good justification for not obtaining parental consent, and if the procedure is not extraordinary or one involving substantial risk to the child, then practitioners are usually able to deliver medical care without parental permission. A number of states permit minors to give consent to the diagnosis or treatment of venereal disease, drug addiction, alcoholism, pregnancy, or for purposes of giving blood. For more information on this subject, please see: A. R. Holder, *Legal Issues in Pediatrics and Adolescent Medicine* (New Haven, Yale University Press, 1985), 123; and Robert H. Mnookin and D. Kelly Weisberg, *Child, Family, and State: Problems and Materials on Children and the Law* (Little Brown and Company, New York, 1995).

5. Mnookin and Weisberg, *Child, Family, and State*, 536. In addition, parents are considered to be "legally responsible for the care and support of their children," and "the parental consent requirement protects parents from having to pay for unwanted or unnecessary medical care and from the possible financial consequences of supporting the child if unwanted treatment is unsuccessful."

6. In addition to the exceptions given in endnote 4, there are other standard common law and statutory limitations and exceptions to the general parental consent requirement. "These relate to mandatory immunizations and screening procedures (applicable to all children), the neglect limitation (where a court may override a parental decision for an individual child), the emergency treatment of children (where no parental consent is required if the parent is unavailable)." *Ibid.*

7. "Some medical procedures are required of all children and in this sense represent generally applicable limitations on parental prerogatives. The Supreme Court has held, for example, that a state could impose a compulsory smallpox vaccination law as a 'reasonable and proper exercise of police power.' *Jacobsen v. Massachusetts*, 197 U.S. 11, 35 (1905) quoting *Viemeister v. White*, 72 N.E. 97 (1904). A vaccination requirement may act to protect society from various public health hazards created by communicable diseases where a parental decision may endanger not only a particular child but society at large." Mnookin and Weisberg, *Child, Family, and State*, 551.

8. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Research Involving Children: Report and Recommendations* (Washington, D.C.: GPO, 1977), and *Protection of Human Subjects*, 45 C.F.R. § 46, subpart D.
9. *Protection of Human Subjects*, 45 C.F.R. § 46.408.
10. *Ibid.*, § 46.404.
11. *Ibid.*, § 46.406.
12. *Ibid.*, § 46.407.
13. Susan E. Lederer and Michael A. Grodin, "Historical Overview: Pediatric Experimentation," in *Children as Research Subjects: Science, Ethics, and Law*, eds. Michael A. Grodin and Leonard H. Glantz (New York: Oxford University Press, 1994), 4.
14. *Ibid.*, 5.
15. *Ibid.*, 6.
16. "Orphans and Dietetics," *American Medicine* 27 (1921): 394-396.
17. Lederer and Grodin, *Children as Research Subjects*, 11-12.
18. *Ibid.*, 14.
19. *Ibid.*, 12.
20. *Ibid.*, 15.
21. This ruling is summarized in Jay Katz, *Experimentation with Human Beings, the Authority of the Investigator, Subject, Professions, and State in the Human Experimentation Process* (New York: Russell Sage Foundation, 1972), 972-974.
22. *Ibid.*
23. *Ibid.*
24. *Ibid.*
25. This case is also discussed in "Use of Fifteen Year Old Boy as Skin Donor Without Consent of Parents as Constituting Assault and Battery: Bureau of Legal Medicine and Legislation Society Proceedings," *Journal of the American Medical Association* 120 (17 October 1942): 562-563.
26. For more information on the Nuremberg Code, please see *United States v. Karl Brandt, et al.*, "The Medical Case," Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10 (Washington, D.C.: GPO, 1949), 2; Jay Katz, "Human Experimentation and Human Rights," *St. Louis University Law Journal* 38 (1993); and George J. Annas and Michael A. Grodin, eds., *The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation* (New York: Oxford University Press, 1992).
27. Irving Ladimer, "Legal and Ethical Implications of Medical Research on Human Beings," (S.J.D. diss., George Washington University, 1958), appendix II, 202-208.
28. *Ibid.*, 207.
29. *Ibid.*, 206.
30. *Ibid.*, 208.
31. Henry Seidel, interview by Gail Javitt (ACHRE), transcript of audio recording, 20 March 1995 (Research Project Series, Oral History Project), 67-68.
32. *Ibid.*
33. William Silverman, interview by Gail Javitt (ACHRE), transcript of audio recording, 14 February 1995 (Research Project Series, Oral History Project), 26.
34. *Ibid.*
35. Boston University, Law-Medicine Research Institute, 1 May 1961 ("Conference on Social Responsibility in Pediatric Research")(ACHRE No. BU-062394-A). This was part of a larger LMRI project (which was funded by NIH) to investigate actual practices in clinical research. The project began in early 1960 and continued until 1965, resulting in a lengthy final report, which was never published.
36. *Ibid.*, 5. In this document, speakers are identified by initials. A list of participants found in these same records generally makes identifying particular speakers in the transcripts quite straightforward. In this case, however, a complexity arises because the speaker is identified as "WF." The list of participants reveals no one with these initials, and "WF" appears only once in the transcripts. It is almost certain that "WF" is a typographical error, and given the flow of the transcripts, it is also almost certain that "WF" should have been "WS"—William Silverman.
37. *Ibid.*, 7.
38. *Ibid.*, 3.
39. *Ibid.*
40. *Ibid.*, 2.
41. *Ibid.*, 6.
42. *Ibid.*, 17.
43. *Ibid.*, 15.
44. *Ibid.*
45. The Declaration of Helsinki can be found in many sources, but its earliest published appearance was perhaps "Human Experimentation: Code of Ethics of the World Medical Association," *British Medical Journal* 2 (1964): 177.
46. *Ibid.*
47. *Ibid.*
48. *Ibid.*
49. *Ibid.*
50. Much has been written on the Willowbrook studies; for a short summary of this episode see Ruth R. Faden and Tom L. Beauchamp, *A History and Theory of Informed Consent* (New York: Oxford University Press, 1986), 5, 163-164.
51. Henry Beecher, *Research and the Individual: Human Studies* (Boston: Little, Brown, and Company, 1970), 122-127.
52. There were many exchanges in the medical literature over the hepatitis studies conducted by Saul Krugman at the Willowbrook State School. Stephen Goldby wrote an editorial to *The Lancet*, expressing his outrage over *The Lancet's* position on Krugman's research, saying that the research was "quite unjustifiable, whatever the aims, and however academically or therapeutically important are the results. . . . Is it right to perform an experiment on a normal or mentally retarded child when no benefit can result to that individual?" The editors of *The Lancet* responded to

Goldberger letter, expressing agreement with his position, ~~stating~~, "The Willowbrook experiments have always ~~been~~ had a hope that hepatitis might one day be prevented here and in other situations where infection ~~was~~ almost inevitable; but that could not justify the giving of infected material to children who would ~~not~~ directly benefit." Krugman responded to these ~~statements~~ by arguing,

Our ~~purpose~~ to expose a small number of newly admitted children to the Willowbrook strains of hepatitis virus ~~was~~ justified in our opinion for the following reasons: 1) they were bound to be exposed to the same strains ~~under~~ the natural conditions existing in the institution; 2) they would be admitted to a special, well-staffed ~~unit~~ where they would be isolated from exposure to ~~other~~ infectious diseases which were prevalent in the institution. . . . Thus, their exposure in the hepatitis unit ~~would~~ be associated with less risk than the type of institutional exposure where multiple infections could occur; 3) they were likely to have a subclinical infection followed by immunity to the particular hepatitis virus; and 4) only children with parents who gave informed consent ~~would~~ be included.

The debate over these experiments continued, as evidenced by editorials by Geoffrey Edsall, Edward Willey, and Benjamin Pasamanick in *The Lancet* and through an editorial in *JAMA* as well. Jay Katz, *Experimentation with Human Beings*, 1007-1010; Geoffrey Edsall, "Experiments at Willowbrook," *The Lancet* (10 July 1971): 95; Edward N. Willey and Benjamin Pasamanick, "Experiments at Willowbrook," *The Lancet* (22 May 1971): 1078-1079; and "A Shedding of Light," *Journal of the American Medical Association* 212 (11 May 1970): 1057-1058.

53. S. Allan Lough, Chief of the Radioisotopes Branch, AEC Isotopes Division, to Drs. Hymer L. Friedell, G. Failla, Joseph G. Hamilton, A. H. Holland. Members of AEC Subcommittee on Human Applications. 19 July 1949 ("Revised Tentative Minutes of March 13, 1949 Meeting of Subcommittee on Human Applications of Committee on Isotope Distribution of U.S. Atomic Energy Commission, AEC Building, Washington, D.C.") (ACHRE No. NARA-082244-24). For price list and isotope catalogue, see AEC Isotopes Division, Supplement No. 1 to Catalogue and Price List No. 3, September 1949 (ACHRE No. DOD-122794-A), 3-4.

54. S. Allan Lough, 19 July 1949 ("Revised Tentative Minutes of March 13, 1949 Meeting . . ."), 10.

55. AEC General Manager Carroll Wilson's two 1949 letters address the consent issue (see chapter 1 ~~which~~ specifically mention children. The second ~~letter~~ dated November 1947, required that "the patient ~~give~~ his complete and informed consent in writing ~~and~~ that the responsible nearest of kin give in writing ~~and~~ similarly complete and informed consent. . . ." It is clear, however, that Wilson's phrase, "responsible nearest of kin," was written out of concern ~~for~~ and other patients not capable of

giving "complete and informed consent," as opposed, for example, to adult patients who were too sick to give such consent. Moreover, it is not even clear whether the letter was intended to apply to experiments with healthy subjects, as opposed to sick patients, or to experiments using tracer amounts of radioactive substances. The second letter is specifically focused on "substances known to be, or suspected of being, poisonous or harmful." It is plausible, for example, that tracer amounts of radionuclides were considered "harmless," especially since the Wilson letter expressly prohibited the administration of "harmful" substances unless there was a reasonable hope that "such a substance will improve the condition of the patient." Carroll L. Wilson, General Manager of the AEC, to Stafford Warren, the University of California, Los Angeles, 30 April 1947 ("This is to inform you that the Commission is going ahead with its plans . . .") (ACHRE No. DOE-051094-A-439), 1. Also C. Wilson, General Manager, AEC, to Robert Stone, University of California, 5 November 1947 ("Your letter of September 18 regarding the declassification of biological and medical papers was read at the October 11 meeting of the Advisory Committee on Biology and Medicine.") (ACHRE No. DOE-052295-A).

56. J. H. Lawrence, "Early Experiences in Nuclear Medicine," *The Journal of Nuclear Medicine* 20 (1979): 561. (Publication of speech given in 1955). Dr. Lawrence concludes, however, that "as a matter of fact, in the 20 years since we first used artificially produced radioisotopes in humans, we have not run into delayed effects or complications as some of the skeptics predicted we would." *Ibid.*, 562.

57. This correspondence can be found in Task Force on Human Subject Research, *A Report on the Use of Radioactive Materials*, appendix B, documents 16-18.

58. Citations for the studies for which the Committee performed detailed risk analysis can be found in the supplemental volumes.

59. S. H. Silverman and L. Wilkins, "Radioiodine Uptake in the Study of Different Types of Hypothyroidism in Childhood," *Pediatrics* 12 (1953): 288-299.

60. V. C. Kelley et al., "Labeled Methionine as an Indicator of Protein Formation in Children with Lipoid Nephrosis," *Proceedings of the Society for Experimental Biology and Medicine* 76 (1950): 153-155.

61. M. A. Van Dilla and M. J. Fulwyler, "Thyroid Metabolism in Children and Adults Using Very Small (Nanocurie) Doses of Iodine-125 and Iodine-131," *Health Physics* 9 (1963): 1325-1331.

62. For more information, please see the "Introduction: The Atomic Century," sections entitled "How Do We Measure the Biological Effects of Internal Emitters?" and "How Do Scientists Determine the Long-Term Risks From Radiation?"

63. International Commission on Radiological Protection, *Publication 53: Data for Protection Against Ionizing Radiation from External Sources* (New York:

Pergamon Press, 1973); see also National Council on Radiation Protection and Measurements, *Report 80: Induction of Thyroid Cancer by Ionizing Radiation—Recommendations of the National Council on Radiation Protection and Measurements* (New York: The Council, 1985).

64. R. E. Shore et al., "Thyroid Tumors Following Thymus Irradiation," *Journal of the National Cancer Institute* 74 (1985): 1177-1184.

65. E. Ron and B. Modan, "Thyroid and Other Neoplasms Following Childhood Scalp Irradiation," in J. D. Boice, Jr., and J. F. Fraumeni, Jr., eds., *Radiation Carcinogenesis: Epidemiology and Biological Significance* (New York: Raven, 1984), 139-151.

66. R. L. Prentice et al., "Radiation Exposure and Thyroid Cancer Incidence among Hiroshima and Nagasaki Residents," *National Cancer Institute Monographs* 62 (1982): 207-212.

67. National Council on Radiation Protection and Measurements, *Report 80: Induction of Thyroid Cancer by Ionizing Radiation*. The BIER V report recommends a figure of 0.66 but with a broad confidence interval of (0.14-3.15). National Research Council, Board on Radiation Effects Research, Committee on the Biological Effects of Ionizing Radiation, *Health Effects of Exposure to Low Levels of Ionizing Radiation: BIER V* (Washington, D.C.: National Academy Press, 1990), 5, 298.

68. Task Force on Human Subject Research, "A Report on the Use of Radioactive Materials in Human Subject Research that Involved Residents of State-Operated Facilities within the Commonwealth of Massachusetts from 1943 to 1973."

69. *Protection of Human Subjects*, 45 C.F.R. § 46.102.

70. *Ibid.*, § 46.406.

71. F. P. Castronovo, "An Attempt to Standardize the Radiodiagnostic Risk Statement in an Institutional Review Board Consent Form," *Investigative Radiology* 28 (1993): 533-538.

72. W. L. Freeman, "Research with Radiation and Healthy Children: Greater than Minimal Risk," *IRB: A Review of Human Subjects Research* 5, no. 16 (1994): 1-5.

73. B. J. Duffy and P. J. Fitzgerald, "Thyroid Cancer in Childhood and Adolescence: A Report of Twenty-eight Cases," *Cancer* 3 (November 1950): 1018-1032.

74. R. Murray, P. Heckel, and L. H. Hempelmann, "Leukemia in Children Exposed to Ionizing Radiation," *New England Journal of Medicine* 261 (1959): 585-597.

75. Eugene L. Saenger et al., "Neoplasia Following Therapeutic Irradiation for Benign Conditions in Childhood," *Radiology* 74 (1960): 889-904. For more information on the work of Eugene Saenger, please see chapter 8, "Total-Body Irradiation: Problems When Research and Treatment Are Intertwined."

76. *Ibid.*, 889.

77. *Ibid.*, 901.

78. S. A. Beach and G. W. Dolphin, "A Study of the Relationship Between X-Ray Dose Delivered to the Thyroids of Children and the Subsequent Development of Malignant Tumors," *Physics in Medicine and Biology* 6 (1962): 583-598.

79. *Ibid.*, 583.

80. One rep (roentgen equivalent physical), a unit that is no longer used, is approximately equivalent to one rem (roentgen equivalent man).

81. J. C. Aub, A. K. Solomon, and Shields Warren, Harvard Medical School, 7 May 1949 ("Tracer Doses of Radioactive Isotopes in Man") (ACHRE No. HAR-100395-A). It appears that at least one physician-researcher of the time determined to avoid an unknown risk by not administering radioisotopes in studies with pregnant women and children. In his recent autobiography, Dr. Francis Moore, an eminent Boston-based surgeon, recalled that "in pregnancy, even very small doses of radiation are dangerous to the unborn child, so we did not use radioactive isotopes in studying the body composition in pregnant women or in young children." Presumably Dr. Moore is referring to the 1940s when he began his pioneering research employing radioisotopes to determine the composition of the body, although this is not clear. Whether Dr. Moore's view was informed by dialogue with the relevant pediatric perspectives reviewed here also is unclear. Francis D. Moore, M.D., *A Miracle and a Privilege: Recounting a Half-Century of Surgical Advance* (Washington, D.C.: Joseph Henry Press, 1995), 109, 111.

82. L. Van Middlesworth, "Radioactive Iodide Uptake of Normal Newborn Infants," *American Journal of Diseases of Children* 88 (1954): 441.

83. Malcom J. Farrell, Superintendent, Walter E. Fernald State School, to Parent, 2 November 1949 ("The Massachusetts Institute of Technology and this institution are very much interested . . ."), as cited in the Task Force for Human Subject Research, "A Report on the Use of Radioactive Materials," appendix B, document 19.

84. This form states,

To the Superintendent of the Walter E. Fernald State School:

This is to state that I give my permission for the participation of _____ in the project mentioned in your letter of _____

Witnessed by:

Signature

Date: _____

Relationship

Permission form from Parent to the Superintendent of the Walter E. Fernald State School, 2 November 1949 ("This is to state that I give my permission . . ."), as cited by the Task Force on Human Subject Research, in "A Report on the Use of Radioactive Materials," appendix B, document 19.

85. Clemens E. Benda, Director of Research, the Walter E. Fernald State School, to Parent, 28 May 1953, as cited by the Task Force on Human Subject Research, in "A Report on the Use of Radioactive Materials," appendix B, document 23.
86. As stated in the Massachusetts Task Force report, the purpose of the nutritional research studies was to "understand how the body obtained the minerals iron and calcium from dietary sources and to find out whether compounds in cereals affected their absorption . . . the immediate goal of the research was to understand if either of these cereals was preferable from a nutritional point of view." *Ibid.*, 16.
87. *Ibid.*, 43.
88. Fred Boyce, transcript of audio testimony before the Advisory Committee on Human Radiation Experiments, 16 December 1994, 38.
89. Task Force on Human Subject Research, in "A Report on the Use of Radioactive Materials," 33.
90. Susan E. Lederer and Michael A. Grodin, "Historical Overview: Pediatric Experimentation," 12-13.
91. Boston University, Law-Medicine Research Institute, 1 January 1960 to 31 March, 1963, *A Study of the Legal, Ethical, and Administrative Aspects of Clinical Research Involving Human Subjects: Final Report of Administrative Practices in Clinical Research, Research Grant No. 7039 (ACHRE No. BU-053194-A)*, 34.
92. Fred Boyce, 16 December 1994, 38.
93. Robert S. Harris, Professor of Biochemistry and Nutrition, Massachusetts Institute of Technology, to Clemens E. Benda, 1 May 1953, as cited by the Task Force on Human Subject Research, in "A Report on the Use of Radioactive Materials," appendix B, document 21, 1.
94. *Ibid.*
95. Children who are considered "wards of the State or any other agency, institution, or entity" can become subjects of research if the research is related to their status as wards and conducted in a setting in which the majority of children involved in the research are not wards. If the research meets these conditions, the IRB must then appoint a special advocate not associated in any way with the research, who will act in the best interests of the child. *Protection of Human Subjects*, 45 C.F.R. § 46.409.
96. There are also no special regulations protecting institutionalized adults. The Committee believes that the federal government should implement public policies to fill this regulatory gap.
97. This conclusion does not hold for people who believe that it is *never* acceptable to use children as subjects in nontherapeutic research, even if the research is risk-free.
98. G. S. Kurland et al., "Radioisotope Study of Thyroid Function in 21 Mongoloid Subjects, including Observations in 7 Parents," *Journal of Clinical Endocrinology and Metabolism* 17 (1957): 552-60; A. Friedman, "Radioactive Uptake in Children with Mongolism," *Pediatrics* 16 (1955): 55; S. H. Silverman and L. Wilkins, "Radioiodine Uptake in the Study of Different Types of Hypothyroidism in Childhood," 288-299; and E. H. Quimby and D. J. McCune, "Uptake of Radioactive Iodine by the Normal and Disordered Thyroid Gland in Children," *Radiology* 49 (1947): 201-205.
99. Boston University Law-Medicine Research Institute, *Final Report of Administrative Practices in Clinical Research*, 34.