

## Regulation of Research with Children: the Evolution from Exclusion to Inclusion

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# Foreword

## REGULATION OF RESEARCH WITH CHILDREN: THE EVOLUTION FROM EXCLUSION TO INCLUSION\*

DUANE ALEXANDER, M.D.\*\*

Any examination of the regulation of research involving children must be placed in some historical context; to do that, the first question to ask is when and where to begin? When, for this particular topic, is our year comparable to 1066, 1492, 1776, or 1945? Any decision like this is arbitrary, so I ask you to return with me now to the year 1973. Nineteen hundred and seventy-three was obviously not the starting point of the dynamic debate in this area, but it was clearly a watershed year in the evolution of guidelines for research involving children.

Throughout the middle of the twentieth century, research on children had been extensive in the United States, resulting in remarkable progress in understanding their normal healthy development and in our ability to treat and prevent disease. Much of this research was therapeutic and conducted on sick children, but a large portion of it was not therapeutic or individually beneficial to the subjects. However, such research produced enormous gains in knowledge and understanding. Both types of research were carried out with little controversy or public scrutiny, even when it sometimes included infants, orphans, or wards of the state.

Studies conducted on normal children formed the basis for our understanding of normal metabolism, growth, healthy development, nutritional needs, fluid and electrolyte metabolism, and intellectual development and bodily functions. It had been amply demonstrated that children were not just small adults, and in many instances attempts to extrapolate from adult studies to applications in children were folly. While particularly in Europe, nontherapeutic research involving children was generally not considered acceptable, it had proceeded in the United States with some concern, but absent formal challenge.

The guidelines that existed for research in the mid-twentieth century did not deal specifically with children. The Nuremberg Code of 1949, if literally interpreted, would not have permitted any research on children.<sup>1</sup> Its first principle, the voluntary consent

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\* This piece is taken largely from remarks made by Dr. Alexander, at the May 3, 2002, symposium: *Research With Children, The New Legal and Policy Landscape*, sponsored by the University of Maryland School of Law, Law & Health Care Program; the University of Maryland School of Medicine; and The American Society of Law, Medicine & Ethics.

\*\* Dr. Duane Alexander, a pediatrician, was named Director of the National Institute of Child Health & Human Development (NICHD) on February 5, 1986, after serving as Acting Director. Dr. Alexander had

of the human subject is absolutely essential; requiring the person involved to have the legal capacity to give consent would have been an insurmountable bar.<sup>2</sup> Conversely, those involved in writing the Code had indicated that such was not their intent. Rather, research on children was not an issue at the Nuremberg Tribunals,<sup>3</sup> so the Code never addressed that question and it was a misinterpretation to say that the code prohibited it.

The Declaration of Helsinki of the World Medical Association in 1964 also failed to directly address research on children, but it provided for what it called “non-therapeutic research on legally incompetent subjects in general” by allowing consent of the legal guardian.<sup>4</sup> Based on acceptance of the Declaration by the medical and research establishment in the United States, third party authorization for non-therapeutic research involving children became standard practice. The Institutional Guide to the Department of Health, Education and Welfare Policy on Protection of Human Subjects published by the National Institutes of Health (NIH) in 1971 required the consent of the subject or their authorized representative, without defining that term or the circumstances under which it would apply.<sup>5</sup>

By 1973, however, the existing guidelines had come under attack from a number of fronts. From the ethics community, some scholars, notably Paul Ramsey with his 1970 book, *The Patient as Person*, had launched a campaign claiming that any non-therapeutic research on children was absolutely unethical— even with parental approval.<sup>6</sup> Although this position did not receive wide support, it stimulated and stirred debate in the ethics community that brought the issue of children in research to the forefront. From the legal front, some court cases, notably *Strunk v. Strunk* in 1969,<sup>7</sup> held that parental consent alone was not sufficient for a minor child to serve as a kidney or bone marrow donor to a sibling and that court approval was required, given that the parents had a conflict of interest and that the donor did not stand to

been NICHD Deputy Director for three years and an assistant to the Director since 1978. Over the course of his career with NICHD, Dr. Alexander directed many studies, including the NICHD National Amniocentesis Study that established the safety and accuracy of amniocentesis for prenatal diagnosis, a test which is now widely used to detect numerous genetic defects. Dr. Alexander has authored numerous papers and book chapters, most relating to his research in developmental disabilities. Additionally, his work has received wide recognition, including a Meritorious Service Medal, and the Surgeon General’s Exemplary Service Medal in 1990.

1. NUREMBERG CODE, PRINCIPLE 1 (1946), available at <http://ohsr.od.nih.gov> (last visited Sept. 14, 2002). See also TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL LAW NO. 10, Vol. II, at 181-84 (U.S. Gov’t Printing Office 1948).

2. *Id.*

3. *Id.*

4. WORLD MED. ASS’N, DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MED. RES. INVOLVING HUMAN SUBJECTS (1964), available at [http://www.wma.net/e/policy/17-c\\_e.html](http://www.wma.net/e/policy/17-c_e.html) (last visited Oct. 10, 2002).

5. NIH, THE INSTITUTIONAL GUIDE TO DHEW POLICY ON PROTECTION OF HUMAN SUBJECTS (Pub. No. 72-102) (1971).

6. PAUL RAMSEY, *THE PATIENT AS PERSON* 11-19 (3d ed., Yale Univ. Press 1973).

7. 445 S.W.2d 145 (Ky. Ct. App. 1969).

benefit from the procedure. These decisions raised, for the pediatric research community, the specter of transference of this concept to the research context, and the need to obtain court approval for every individual instance of non-therapeutic research.

This legal concern was further heightened by a lawsuit filed by James Neilson in the Superior Court of the State of California in 1973, which claimed that parents and guardians had no legal authority to consent to the participation of a child or a ward in non-therapeutic research irrespective of the degree of risk.<sup>8</sup> This question had never been considered before by an American or English court and the case merits some consideration.

Neilson, an attorney, was on the faculty of the University of California at San Francisco and a member of the University's Committee on Human Experimentation that had recently been established to ensure that the University complied with the NIH requirements for review of clinical research protocols.<sup>9</sup> The committee received a proposal from Dr. Oscar Frick of the Department of Pediatrics for a study of the development of allergies and asthma in children whose families had a history of these disorders, to be funded by the National Institute of Allergy and Infectious Diseases.<sup>10</sup> The protocol involved drawing blood and administering pharmaceutical agents to children on several occasions, from several months to four years of age, to see what factors related to the development of allergies or asthma.<sup>11</sup> Normal control subjects from families without an allergic history were also to be included for comparison, and all families were to be paid \$300 per year for the child's participation.<sup>12</sup>

*Neilson* argued strongly against the study in the committee, claiming that parents had no legal right to subject their healthy children to this research, and raised the possibility that the children could later sue the committee members and the University for allowing them to participate.<sup>13</sup> However, the committee approved the study unanimously at a meeting at which *Neilson* was not present.<sup>14</sup> That was a mistake.

*Neilson* sued the committee and his own university.<sup>15</sup> His suit specifically asked the court to declare that "a parent or a guardian of a normal, healthy minor may not subject that child to experimental medical procedures not intended to benefit such child and that the approval of such conduct by the defendants is unconstitutional,

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8. *Nielsen v. Regents of the University of California et al.*, No. 665-049 Civ. 8-9 (Super. Ct. San Francisco, Cal., Aug. 23, 1973).

9. *Id.*

10. *Id.*

11. *Id.*

12. Letter from Oscar L. Frick, M.D., Professor Pediatrics, University of California, San Francisco, School of Medicine, Department of Pediatrics to The Committee of Human Experimentation, University of California, San Francisco, School of Medicine, Department of Pediatrics (on file with the Journal of Health Care Law & Policy).

13. *Id.*

14. *Id.*

15. *Id.*

invalid, and void.”<sup>16</sup> He also asked the court to enjoin the defendants from approving any studies or using any university facilities or equipment to carry out research involving invasive medical procedures or practices that would have been performed on a normal, healthy child when such procedures were not for the direct benefit of such child.<sup>17</sup> This case was never decided and is technically a legal sidelight in our history. Nevertheless, it left investigators and research regulators shivering in their boots, and the shock waves it sent through the research community and the reaction and response it engendered in terms of regulations for protecting children in research cannot be overestimated.

In addition to ethicists and the courts, Congress was a third source of attack on children in research. The issue exploded into a national debate on medical research. The hostility of some members of Congress to the *Roe v. Wade*<sup>18</sup> Supreme Court decision on abortion found an outlet and scapegoat in research on the fetus, with Congressman Angelo Roncalo, Senator James Buckley, and others railing on the floor against reports of some of the studies conducted and introducing legislation to ban all or parts of such research.<sup>19</sup>

Furthermore, revelations of the Tuskegee syphilis study<sup>20</sup> burst on the scene a year earlier, further tarnishing the image of research in general and leading to calls for increased protection of subjects against scientists. To this were added concerns about drug testing on prisoners, research on minority groups, and research involving persons with mental illness or mental retardation, especially if they resided in institutions.<sup>21</sup> In all this debate, no allegations of misconduct were raised with respect to research on children. Yet it raised similar questions of research on persons with diminished capacity to give informed consent, so research on children was part of the package when the time came for the problem to be resolved.

Under the leadership of Senator Edward Kennedy, who really has never been given adequate credit for the key role that he played, all these concerns were packaged together and handed to a national commission to resolve. This action removed concerns about research from the political arena, off the floor of Congress, and off of the national agenda for four years, allowing the debate to cool off. The commission provided a vehicle for sober reflection, consideration of the issues based on data and facts, and an opportunity to seek consensus through a public process. Creation of the National Commission for Protection of Human Subjects of Biomedical and Behavioral

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16. *Nielsen*, No. 665-048 at 13.

17. *Id.*

18. 410 U.S. 113 (1973) (rejecting state laws that ban abortions).

19. See 120 CONG. REC. H11927 (1974); 120 CONG. REC. S21,539 (1974) (statement of Sen. Buckley).

20. E.g., Jean Heller, *Syphilis Victims in U.S. Study Went Untreated for 40 Years*, N.Y. TIMES, July 26, 1972, at A1.

21. This is an original assertion, stemming from the author's personal recollections of converging events of the early 1970's.

Research<sup>22</sup> was a brilliant, if not novel, strategy and helped preserve the research enterprise in this country.

Yet, the executive branch had not been idle during this time of debate and turmoil. Spurred initially by the need for guidelines in response to applications to NIH for research on the fetus, and later expanding to cover research involving subjects with limited ability to give consent, an active process of research regulation development was under way at the NIH.

This process was initially intended as guideline development, and then regulation development, but because it was overtaken by events, it came to be the production of a draft document for public comment and to serve as a basis for discussion by the National Commission. This process was led at the NIH by Dr. Charles Lowe, Scientific Director of the NICHD; Dr. Ron Lamont-Havers, NIH Deputy Director; and Dr. Don Chalkley, who was Chief of the Institutional Relations Branch of the Division of Research Grants, the predecessor of the Office for Protection from Research Risks, now called the Office of Human Research Protection. They assembled an outside advisory group of researchers, ethicists, and lawyers who discussed the issues and provided recommendations that became draft regulations. The proposed regulations for research overall and with adults, based largely on the Institutional Guide, were published in October of 1973.<sup>23</sup> The draft regulations for research involving children, the abortus, in-vitro fertilization, prisoners, and the mentally infirm were published for comment in November of 1973.<sup>24</sup> Soon thereafter it became clear that there would be a national commission, so no further action was taken until the commission made its recommendations.

It should be noted that most of the concepts embodied in that draft were eventually incorporated in some form into the final regulations for children. Nonetheless, at the time, they stirred a storm of protest from the research community that accused the government of overreacting to concerns. They argued, that in trying to be responsive and in an effort to provide the public with reassurance those children would be protected, the government was creating a bureaucratic log jam that would stifle the very research the system was designed to preserve.

Concerns were directed principally at the requirement for children to consent to research if they were age seven or older<sup>25</sup> and at the proposed establishment of two new review committees, in addition to the newly mandated organizational review committee or Institutional Review Board (IRB) at the research institution.<sup>26</sup> First, the institution would be required to establish a protection committee for each protocol

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22. National Research Act of 1974, Pub. L. No. 93-348, § 201, 88 Stat. 342,248 (1974).

23. Protection of Human Subjects, 38 Fed. Reg. 27,882 (Oct. 9, 1973) (to be codified at 45 C.F.R. pt. 46).

24. Protection of Human Subjects: Policies and Procedures, 38 Fed. Reg. 31,738 (Nov. 16, 1973).

25. *Id.*

26. *Id.*

involving children.<sup>27</sup> The duties of the protection committee were to oversee the selection of individual subjects for research, monitor the continuing willingness of the child and parents to participate in the research, design procedures to intervene in the research if necessary to protect the subject, and evaluate the reasonableness of the parent's and subject's consent.<sup>28</sup>

In addition, the agency supporting the research, usually the NIH, would be required to appoint an ethical review board at the agency that would review all research proposals involving children, between the study section review and advisory council review.<sup>29</sup> For each protocol, this board was to advise the agency on its acceptability for funding based on societal need and ethical considerations, taking into account the adequacy of the proposed protection committee, the potential risk and benefit to the subjects, the adequacy of the scientific design, and the sufficiency of animal and adult human data to justify proceeding with this study in children.<sup>30</sup>

It is now obvious why these new layers of committees and procedures evoked such protest from the research community. The proposals provide evidence, however, of how serious the threat to continuing research on children was perceived by the government, and the trouble this research was in at the time the National Commission began its work. Pediatric research had been proceeding with considerable latitude up to that time. These draft regulations reflect the far swing of the pendulum from permissiveness to a protectionist position. But they left the Commission ample middle ground in which to work to try to achieve societal consensus on how this research should be conducted.

It was on this tide that the National Commission found itself afloat when it first met in December of 1974. I was fortunate to be a member of the staff of that Commission, with major responsibility for assisting with their reports on research on the fetus and research involving children. Under the chairmanship of Dr. Kenneth Ryan, Chief of the Department of Obstetrics and Gynecology at Harvard, the Commission agreed to make every effort to achieve consensus, correctly perceiving that a series of widely split votes and minority reports would accomplish little.<sup>31</sup> Their personal interactions and attempts to understand individual concerns and work to resolve or accommodate them as they reasoned together was in many ways responsible for the general acceptance of the Commission's recommendations by the research community, advocacy groups, and the government.

Before the issues of research on children could be addressed, the Commission had to grapple with research on the fetus as its mandated first charge which was to be accomplished in four months. They managed to do it in five. Their recommendations

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27. *Id.* at 31,741.

28. Protection of Human Subjects: Policies and Procedures, 38 Fed. Reg. at 31,741-31,742.

29. *Id.* at 31,741.

30. *Id.*

31. This is an original assertion, stemming from the author's personal recollections of events.

were turned quickly into regulations, and the congressionally imposed moratorium on fetal research was lifted.<sup>32</sup> Children took longer.

Finally, in September 1977 the Commission issued its report and recommendations on research involving children.<sup>33</sup> During nearly three years of consideration, it had extensive and valuable contributions of information and viewpoints. A survey of IRB practices in consideration of research involving children provided practical information on what was actually happening, information that was generally quite reassuring. A review of the law of informed consent for human experimentation as it applied to children was provided by George Annas, Leonard Glantz, and Barbara Katz helping to clarify these issues for the commissioners.<sup>34</sup> A number of ethicists prepared commissioned papers setting forth their views on the ethical issues involved and proposing resolutions for them.<sup>35</sup>

Additionally, The Society for Research on Child Development and a developmental psychologist provided valuable information on the ability of children of various ages to make choices about participating in research. With this information in hand, the Commission members probably had as much expertise on this topic as any group ever assembled. They went about their task conscientiously, and from initial positions that were far apart, were able to reach unanimity on every recommendation except one. Two members dissented on the issue of whether non-therapeutic research with a minor increase over minimal risk might be conducted on children with a disorder if it might help future children with the disorder.<sup>36</sup> The Commission was also able to break new ground, introduce new concepts, and affirm that children by age seven must be a part of the consent process.

Without going into detail, consider the major contributions of the Commission. First, it dealt decisively and creatively with the shibboleth of informed consent. They said it is a red herring in this process, which distracts us from the truly important issues. Of course children cannot give legally effective informed consent, but that does not mean they should have no say regarding their participation. Of course parents cannot give consent for their children in a true sense, but there is no one better or more appropriate to ask, and one surely would not proceed without their approval. So, the Commission decided to do away with the term "informed consent" in this

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32. NAT'L COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAV. RES.: RESEARCH ON THE FETUS, REPORT AND RECOMMENDATIONS at app. 20, 21 (providing the 1973 and 1974 federal regulations: Protection of Human Subjects Policies and Procedures, 30 Fed. Reg. 31,738 (Nov. 16, 1973), and Protection of Human Subjects Proposed Policy, 39 Fed. Reg. 30,618 (Aug. 23, 1974) presently codified at 45 C.F.R. 46 (2001)).

33. NAT'L COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAV. RES., REPORT AND RECOMMENDATIONS: RESEARCH INVOLVING CHILDREN (Pub No. (OS) 77-0004) (1977)) [hereinafter NAT'L COMM'N].

34. NAT'L COMM'N at app. 2-1-2-63 (NO. N01-HU-6-2120) (Chapter II of "The Law of Informed Consent to Human Experimentation," June 1, 1976).

35. *Id.*

36. NAT'L COMM'N, *supra* note 33.



process since it did nothing but create confusion and cause trouble, and instead came up with new terms that accurately conveyed what was really meant. Parents cannot give true “consent” since that is something that only a competent person can do for himself. However, they can and should be respected in their roles as parents and be asked to give authorization *for* another person who they are responsible for protecting, their child, to participate in research. Instead of calling this type of authorization “consent,” it was determined that it should be called “permission.” Likewise, because a child clearly cannot give true consent either, although that is often the case for older children only because of their *legal* status as minors rather than their lack of understanding, we must nonetheless respect their evolving personhood by asking them and getting their agreement to participate. However, instead of confusing the issue by calling it “consent,” it is deemed “assent.”

Based on expert testimony, the Commission chose age seven as the time when assent had to be formally sought and documented, although the child should be told as much as possible even at younger ages. Thus, these concepts were born. Although initially they were confusing to a research community used to dealing only with the term consent, these new terms “permission” and “assent” and the concepts they embody have proven more and more useful with the passage of time. This was the Commission’s first major contribution.

With the consent barrier breached, the Commission tackled the problem of non-therapeutic research. With the case clearly made for the value of such research on either sick *or* normal children, the Commission decided that this issue had to be faced on practical grounds based on risks rather than on theoretical grounds or ethical absolutisms. So long as children were not exposed to risks in research that were greater than those that occurred in their daily lives,<sup>37</sup> or in the course of routine physical or psychological exams when they were *healthy*,<sup>38</sup> it would be imprudent and groundless to forbid their participation in research. With this as their definition for what they called minimal risk, the Commission recommended that research with this level of risk could proceed regardless of whether the children were sick or well and irrespective of whether they benefited from it personally or not, so long as one parent gave permission and children age seven or older gave their assent. This was the Commission’s second major contribution.

This done, the Commission then placed all research involving children into one of four categories with gradation of protections, and charged IRBs with determining which category any proposed research fell into and providing the appropriate review and protection.<sup>39</sup> If research involved no more than minimal risk, it was in category one, and it was acceptable and could proceed on sick or normal children with the

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37. *Id.*

38. *Id.*

39. *See id.* at 12.

permission of one parent and the child's assent regardless of individual benefit.<sup>40</sup> If research involved greater than minimal risk, but held some potential benefit for the child that balanced or outweighed the risk, it was in category two, and would be acceptable and could proceed if one parent gave permission and the child assented (although assent was not mandatory in the treatment context).<sup>41</sup> If research involved greater than minimal risk and held *no* benefit to the individual child, it was in category three, and would be acceptable and could proceed only if the research was related to the child's condition, might benefit future children with that condition, posed only a minor increase over minimal risk, and both parents gave permission and the child assented.<sup>42</sup>

It is instructive to stop here for a minute before examining category four to consider what the Commission meant by "minimal risk" and "minor increase over minimal risk." It is very clear from their report, which reflects their discussions, that they meant minimal risk to refer to the risks of everyday life and physical exams of healthy children, not sick children.<sup>43</sup> Clearly, they did not intend this to mean that the only research procedures permitted were those encountered in daily life or routine exams, but any procedures and activities *whose risks were not greater than those risks*.

It is also clear that they did not mean minimal risk to be on a relative scale. Thus, minimal risk for a severely ill child is no different than minimal risk for a healthy child. Relativity is what the concept of "minor increase over minimal" was developed to convey; that is, that some sick children become so used to invasive medical procedures for treatment purposes that for them these and comparable procedures done for research were a minor increase over minimal risk and were, in the Commission's words, "commensurate with procedures that prospective subjects and others with the specific disorder or condition ordinarily experience" as part of their disease or treatment.<sup>44</sup> This language is used only to describe a minor increase over minimal risk and never to define minimal risk for a sick child. Thus, a sliding scale or relative standard for minimal risk would be inconsistent with the Commission's recommendations.

To return to the categories, the Commission felt a need to provide a safety valve or an escape clause to the research framework it created. Admitting that it was not totally prescient and that some important research might not fit these first three categories, the Commission provided for a special review by a national ethical advisory board to consider whether such research was so important and was designed in such an ethically acceptable manner that it could go forward. Into this fourth category would fall, for example, research on normal healthy children that was greater

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40. *See id.* at 5.

41. *Id.* at 5-6, 12, 14.

42. *Id.* at 7-8, 14.

43. *See* NAT'L COMM'N, *supra* note 33, at 7-8, 14.

44. *Id.* at 9.

than minimal risk and did not benefit them.<sup>45</sup> This categorization constitutes the Commission's third major contribution.

The Commission provided other concepts as well that are often overlooked. Special provisions were included regarding consent for emancipated minors and for when parental permission was not available or would be inappropriate.<sup>46</sup> The IRB, rather than a protection committee, was given the optional roles in exceptional circumstances of overseeing induction of individual subjects into a protocol, even to the extent of using an advocate or assent auditor in the decision-making process to assure that the child understood the research and was choosing freely to participate, and of requiring a parent to be present during the research.<sup>47</sup> Perhaps in a pang of conscience for past deeds, a special recommendation was included providing limitations and extra protection for wards of the state when involved in research.<sup>48</sup>

As provided by law, the Commission's recommendations went to the Department of Health, Education and Welfare which had to respond to them. The response to the recommendations for children was to propose regulations that essentially implemented everything the Commission recommended. Although it took until 1983 to complete the rule making process, the only substantive change was to have a committee of experts, rather than a national ethical advisory board, conduct the review required for category four research.<sup>49</sup> Having been stymied for three years by the absence of an ethical advisory board precluding consideration and funding of in-vitro fertilization research, there was no desire to repeat that experience in research involving children.

In retrospect, the Commission made many contributions to guidelines for research involving children, but probably its greatest contribution was giving a context and framework that allowed that research to proceed, while reassuring a concerned public that children would be protected in and benefit from research and not be exploited. It did not solve all of the problems, but provided a mechanism for them to be reviewed and dealt with them based on general principles. While we still struggle today with exact meanings and boundaries of minimal risk and what constitutes a minor increase over minimal, and when parental permission is not needed, we have a mechanism for dealing with all these issues and letting necessary research proceed.

One measure of success of this process is that in the ensuing 20 years, we have moved from erecting barriers to the inclusion of children and certain other classes of subjects in research because the research was perceived as a threat or a hazard, to a situation in which we demand that those barriers be torn down because they exclude those populations from the benefits of research. Specifically, this happened first with women and minorities, and then with children. It is instructive in looking at the public policy process to see how that happened.

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45. *Id.* at 10-11.

46. *Id.* at 17.

47. *Id.*

48. *Id.* at 19.

49. Additional Protections for Children Involved as Subjects in Research, 45 C.F.R. § 46.409 (1983).

In 1962, the Kefauver-Harris Amendments<sup>50</sup> regarding drug testing and approval were passed by Congress, which institutionalized the process in which drug testing was done, primarily on adults and results were extrapolated to children. As a result, 75 percent of licensed drugs were never tested on children. The dosage was just extrapolated from adult doses, effectiveness and side effects were assumed with fingers crossed, and physicians who prescribed these drugs for children did so at their own risk. Ever since that time the pediatric community has been doing what research it could in trying to change the process to include children.

The big break and change in this situation came in the early 1990s from two events made possible in part by the success of the research regulations that the department implemented based on the Commission's recommendations. First, accelerated by the AIDS epidemic, the pendulum had swung from research being viewed as a burden to be avoided, to a benefit to be sought and not denied. Second, the women's health movement built on this feeling and made exclusion of women from some highly visible clinical studies a *cause celebre*. As a consequence, Congress mandated that the NIH include women and minorities in all clinical research done with NIH support.<sup>51</sup> Guidelines to do so were implemented in 1998, with rigid review and reporting requirements.<sup>52</sup>

The pediatric community saw this as an opportunity, at last, to do something about exclusion of children from clinical research. Initially they considered asking Congress to pass similar legislation for children. That legislation probably would have passed, but instead the American Academy of Pediatrics (Academy) wrote to the NIH and asked that requirements for women and minority inclusion in research be extended to children.<sup>53</sup> The NIH considered this proposal, but recognizing that the issues with children were more complex with regard to consent, the different ages involved, different caregivers and research expertise, asked the Academy to join the NIH in convening a workshop to address these issues. The Academy agreed and this workshop was held in June of 1996.<sup>54</sup> Prior to that conference, a panel was convened to look at a large sample of NIH clinical research projects funded in the previous year to assess how frequently children might have been excluded when it would have been appropriate to include them. In the panel's judgment, this occurred 10-20 percent of the time.<sup>55</sup> This was felt to be sufficient to justify some action by the NIH, but also represented the extent to which any policy change would have an impact: it would affect only 10-20 percent of applications for clinical research.

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50. 21 U.S.C.A. § 355 (2002).

51. National Institute of Health Revitalization Act of 1997, Pub. L. No. 103-43, 107 Stat. 148 (1993).

52. NIH GUIDE FOR GRANTS AND CONTRACTS, NATIONAL INSTITUTES OF HEALTH, OFFICE OF EXTRAMURAL RESEARCH, available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html> (last visited Nov. 20, 2002).

53. Letter from the American Academy of Pediatrics to NIH (on file with author).

54. NICHD, Inclusion of Children in Clinical Research Workshop (Sept. 5, 1996) (on file with the Journal of Health Care Law & Policy).

55. NIH panel's judgment on NIH clinical research projects findings (on file with author).

The workshop participants concluded that children were not always receiving the best care because many treatments that they received had been studied only in adults.<sup>56</sup>

Participants also identified concerns about consent and protection but felt that these were outweighed by considerations of beneficence and justice in expanding research to children.<sup>57</sup> The question was how to do it. There was a general feeling that an absolute mandate should be avoided if possible, but that investigators proposing clinical studies should be on notice that they were expected to include children unless there was a good reason not to include them. Thus, the presumption would be that children would be included, and good scientific justification should be required for exclusion. NICHD's national advisory council reviewed the report from this panel at its September 1996 meeting,<sup>58</sup> and voted unanimously to ask the NIH to endorse and implement the conclusions from the workshop. This recommendation, supported by additional congressional prodding, was adopted.

The policy is really quite simple. If an applicant investigator proposes clinical research, they have to describe their plans for including children or justify the exclusion. It is a science-based policy. The investigators also need to identify what ages of children are in or out, and identify as well the expertise on their team with respect to doing research on children, and the facilities that are available for the children's participation, as part of that process.

The policy was implemented in October 1998,<sup>59</sup> and has significantly increased inclusion of children. This inclusion has been amplified by actions of Congress in 1997 and 2002 in the Better<sup>60</sup> and Best<sup>61</sup> Pharmaceuticals for Children Acts that provided patent extension incentives to drug companies that tested their products in children. Apart from that legislation, the "Pediatric Rule,"<sup>62</sup> implemented in 1998, empowered the Food and Drug Administration (FDA) to require the testing of new drugs in children, but it was struck down in a U.S. District Court of Appeals decision in October of 2002<sup>63</sup> as exceeding the FDA's statutory authority, making this a pivotal time in the history of the evolving policy governing children in research.

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56. See NICHD, *supra* note 54.

57. *Id.*

58. Minutes from NICHD's national advisory council's September 1996 meeting (on file with author).

59. NIH, NATIONAL INSTITUTES OF HEALTH, POLICY AND GUIDELINES ON THE INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS, available at <http://grants.nih.gov> (last visited Sept. 14, 2002) [hereinafter NIH POLICY].

60. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2305 (1997) [hereinafter FDAMA].

61. Best Pharmaceuticals Act for Children Act of 2002, Pub. L. No. 107-109, 115 Stat. 1408 (2002), available at <http://thomas.loc.gov> (last visited Oct. 30, 2002).

62. Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66632 (1998). See also 21 C.F.R. §§ 201, 312, 314, 601 (1998).

63. Ass'n of Am. Physicians and Surgeons, Inc., et al., v. U.S. FDA, et al., No. CIV.00-02898, 2002 WL 31323411 (D.D.C. Oct. 17, 2002).

The NIH policy on inclusion of children, as well as the policies articulated in both the Better, and Best Pharmaceuticals for Children Acts intended to bring research with children into accord with all three basic ethical principles underlying clinical research. They meet the test of beneficence by seeking to gather information that will help children just as we do for adults. They respect children as persons by allowing them to participate in research equally with adults and informing them to the extent they can understand about what the research is and what it means to them. Perhaps most relevant, they meet the test of justice by treating children equally with adults and no longer excluding them unnecessarily from research that can benefit them, or forcing them to face the risks of treatments that have been tested in adults but not in children.

As a life long advocate for children, and as someone who participated in the development of the regulations for protection of children participating in research, it is particularly satisfying to see the closing of the circle provided by this policy. By this action, we not only provide special protection when children do participate in research, but we also assure full and equal opportunity to participate in and benefit from research, bringing to children the full benefits of research enjoyed by others.