The University of Chicago Law School

Roundtable

A JOURNAL OF INTERDISCIPLINARY LEGAL STUDIES

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SPEED, SAFETY, AND DIGNITY: PEDIATRIC PHARMACEUTICAL DEVELOPMENT IN AN AGE OF OPTIMISM

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INTRODUCTION: BRAVE NEW WORLD FORECLOSED?

The practice of medicine will shortly experience an upheaval of historic proportions—if the therapeutic promise of recent biogenetic breakthroughs is even partially exploited. An endless supply of easily transferable organs, it is said, will be assured by mammalian cloners and pluripotent stem-cell cultivators. A cure for immune-system disorders (among many others) will be offered by gene transfers. And, as the cartographers of the human genome refine their maps, even more therapeutic possibilities—many now unimaginable—will appear to us. Though the enthusiasm of the American people is often derided as Panglossian, current expectations in this instance are not entirely unwarranted.

Although the benefits of contemplated discoveries will in all likelihood be

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enjoyed broadly, one medical sub-population—children—will be particularly benefited, if only because the number of therapeutic tools historically available to pediatricians has lagged far behind those available to other practitioners. To ensure that pediatric pharmaceuticals are developed in abundance, both the legislative and the executive branches have adopted and are currently considering a variety of research-promoting initiatives. Congress has recently committed additional funding to pediatric research and granted patent-protection extensions to companies that undertake pediatric testing of their extant products.[1] For its part, the Executive has commanded pharmaceutical companies to make pediatric research a high priority: A recent Food and Drug Administration ("FDA") rule and its companion National Institutes of Health ("NIH") guideline (collectively, the "Pediatric Rule") demand that researchers include children in their research protocols or give a compelling account for their absence.[2] Further, when administrative authority so to regulate was challenged in federal court,[3] Congress took

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1. Even as Congress has vigorously increased its commitment to funding biomedical research in general (in 2000 it resolved to increase NIH funding for biomedical research by $2.7 billion, and in 2001 by $3.4 billion; Biomedical Revitalization Resolution of 2001, HR Res 72, S Res 19, 107th Cong. (2001); HR Res 437, S Res 253, 106th Cong (2000)), it has demonstrated particular concern that incentives and other, less direct, subsidies materialize. Most significantly, Congress passed (and President Clinton signed) § 111 of the Food and Drug Administration Modernization Act, Pub L No 105-115, 111 Stat 2296 (1997), codified as amended in scattered sections of 26 USC § 351 et seq. ("FDAMA"), which grants patent-protection extension when the manufacturer promises to conduct pediatric studies of its product.

The two subsequent Congresses have been similarly concerned with pediatric testing issues. The 106th Congress considered a flurry of bills seeking to remedy this inequity, see, for example, Healthy Kids 2000 Act, HR 1085, S 592, 106th Cong (1999) (proposing additional financial support for pediatric research), and then enacted, with President Clinton's signature, the Children's Health Act of 2000, Pub L No 106-310, 114 Stat 1101, 42 USC § 201 et seq. (2000).

The 107th, for its part, has passed one bill in this genre and is now considering in committee at least three more. See Research Revitalization Act of 2002, S 3060 (Oct 4, 2002); Best Pharmaceuticals for Children Act, Pub L No 107-109, 115 Stat 1408 (Jan 4, 2002) (extending for five years the FDAMA's patent-extension regime); Better Medicine for Children Act, S 1301 (Aug 1, 2001); Orphan Drug Tax Credit Act of 2001, HR 1298 (March 29, 2001).

2. See Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed Reg 66,632, at 66,633 (Dec 2, 1998) ("FDA Pediatric Testing Initiative"); NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects (March 6, 1998) ("NIH Pediatric Guidelines"). In addition, the National Human Research Protections Advisory Committee, an advisory board within the Department of Health and Human Services, has begun urging the Food and Drug Administration to allow teenagers to enroll in studies of experimental treatments without their parents' knowledge or permission. Mary Faith Marshall, chairperson, National Human Research Protections Advisory Committee, *Comment Letter to the FDA on 45 CFR 46 Subpart D 408(c)*, Aug 13, 2001. See also Susan Okie, *FDA Urged to Broaden Study Rules*, Wash Post, July 31, 2001, at A2.

Similar initiatives, undertaken for similar reasons, have been aimed at women, minorities, and the elderly. See Memorandum for the Secretary of Health and Human Services: Increasing Participation of Medicare Beneficiaries in Clinical Trials (June 7, 2000); CDC/ATSDR Policy on the Inclusion of Women and Racial and Ethnic Minorities in Externally Awarded Research, 60 Fed Reg 47,947 (Sept 15, 1995); NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, 59 Fed Reg 14,508 (March 28, 1994).

3. See *Ass'n of Am. Physicians and Surgeons v FDA*, 2002 WL 31323411 (D DC).

up legislation specifically supporting this initiative.[4]

On their face, these initiatives appear unobjectionable, with just the right touch of political correctness to boot: Why should middle-aged white males be the only ones to enjoy one of the great blessings of contemporary technology—safe and reliable remedies for life-threatening illness? Do not our children deserve the best possible medical care?

Difficulties emerge, however, when one considers the means by which these therapeutic potentialities will be translated into pediatric remedies: experimentation on children.

The most obvious and important problem is the frankly and inevitably utilitarian justification for pediatric research. That pediatricians might have the ability—when the time comes—to cure the generations of children who are not yet ill, researchers must now ask the presently sick to suffer certain discomfort and run the risk of injury or death. The recent federal pediatric pharmaceutical development initiatives force us to ask, once again, if this calculation still comports with our moral sensibilities: Should the health and dignity of the children who currently suffer be sacrificed to the health of the many more who will later fall ill?

Less obvious, less important, but more pertinent to the present-day structuring of our institutions is the challenge that the "Pediatric Rule" poses to the federal rule that has strictly limited the nature of pediatric experimentation over the last two decades.[5] In the 1970s, largely in response to the revelation that the consulting physician to the Willowbrook School, an overcrowded state-run home for the mentally disabled, had deliberately infected healthy children with hepatitis to learn more about the disease's aetiology,[6] Congress authorized the Department of Health, Education, and Welfare ("DHEW") to regulate experimentation on children.[7] Though the final rule ("Subpart D") does not categorically prohibit pediatric experimentation, it does present itself to the research community as an attempt to limit the participation of children in clinical research trials.[8]

In light of this long-standing limitation on pediatric experimentation, the current federal research initiatives, innocuous as they seem, will likely present researchers and their institutional homes with grave legal problems, especially when corporate pharmaceutical sponsors begin to respond. Although it would

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4. See A Bill to Amend the Federal Food, Drug, and Cosmetic Act to Require Labeling Containing Information Applicable to Pediatric Patients, S 2394 (April 29, 2002); HR 4730 (May 14, 2002).

5. See Additional Protections for Children Involved as Subjects in Research, 45 CFR §§ 46.401–46.409 (2001) ("Subpart D").

6. See generally David J. Rothman & Sheila M. Rothman, *The Willowbrook Wars* 257–95 (Harper 1984).

7. See National Research Service Award Act of 1974, Pub L No 93-348 § 202(a)(2), 88 Stat 342, 349 (1976) ("National Research Act").

8. See Subpart D (cited in note 5).

be easy to assume that the "Pediatric Rule" represents the Executive's repudiation of Subpart D, it does *not* present itself as such. The current state of the law is, rather, that *both* are in force.

The impending collision between these two regimes prompts many questions. On the one hand, caregivers will want assurances that children's interests are in fact promoted: Will pediatricians acquire useful pharmacological tools in a timely manner? Will child subjects be safe? Will societal regard for the dignity of children be preserved? On the other, the research community will want to discern the boundaries of the law: How far can an aggressive researcher push the envelope? When must the institutional review board ("IRB")[9] deny authorization? What sort of protocol can government regulators cite as a violation? Finally, our legislators will want to figure out how to revise the law so as to satisfy both groups: How can we clarify boundaries for the research community *and* accommodate the speedy, safe, and dignified advance of pediatric medicine?

What follows is an attempt to discern the answer to these questions. I will first provide a brief historical background of the issues—ethical, medical, political, and legal—that inform the current debate. The subsequent discussion (Part II) will seek to define the contours of the regulations that have governed—and still claim to control—pediatric research. Part III will attempt to identify with precision the capabilities and, more strikingly, the limitations of this regime. To conclude, I will offer recommendations to remedy several of the regime's most vulnerable elements, as well as my observations concerning the direction that the next round of regulatory change might take.

I. REGULATORY WORLDS IN COLLISION

A. HISTORIC PROTECTIVE REGULATION

Since the inception of scientific medicine, the physician has had to reckon with a fundamental conflict in his art. On the one hand, he desires to heal the patient before him, the one who has come begging to be cured. On the other, the same physician wishes to expand the frontier of medical knowledge, not only to satisfy his own curiosity but also to equip himself and his fellows to address more confidently and competently the other suffering men and women who will come asking for relief.[10] The promise of the Hippocratic *Oath*, "I will abstain from all . . . harm," has been read by many generations of doctors and

9. To maintain eligibility for federal funding, an institution engaged in experimentation on humans must certify that all governmentally funded research protocols occurring under its aegis conform to the applicable regulations. In deference to the long-standing tradition of professional self-regulation, these review boards are staffed primarily by researchers from the regulated institution.

10. See generally Clark, *The Law Most Beautiful and Best* at ch 3 (cited in the biographical footnote).

patients as an attempt to resolve this dilemma for all those who would ever take up the staff of Asclepias: The sufferer at hand has priority over the sufferer yet to come.[11] As Leon Kass has summarized this ethic: "[T]he physician must produce unswervingly the virtues of loyalty and fidelity to his patient."[12] This suggests, very nearly, a fiduciary obligation—an obligation somewhat at odds with the canons of scientific research.

Indeed, the development of the inductive scientific method provided the medical fraternity with grounds for revisiting the question. Physicians learned—along with their fellow natural scientists in other fields—that by conducting medical interventions wherein as many variables as possible were controlled, repeating the process in different locations at the hand of different observers, they could systematically acquire generally applicable knowledge concerning the nature of human diseases and their treatments.[13] The process accelerated greatly in the late 19th century, after it was discovered that various charitable institutions founded for the benefit of the poor and their children—penitentiaries, hospitals, schools, reformatories, orphanages, and foundling homes—proved to be fertile fields for the spread of disease in controllable circumstances.[14] By the end of World War II, during which both Axis and Allied powers conducted extensive experimentation on humans, a new ethic was born: As long as the physician obtains his patient's "voluntary informed consent," he may legitimately experiment upon him.[15]

The next two decades witnessed the development of a research imperative. As physicians succeeded in ameliorating—even curing—a number of maladies, public appetite for other treatments grew. In 1945, Congress apportioned $700,000 to the NIH; in 1965 it granted $437 million.[16] Out of eagerness to satisfy this growing desire, American medical researchers had, it was learned in the late 1960s and early '70s, conducted experiments that violated even the permissive "informed consent" standard.[17] Most notable was the revelation that illiterate black male syphilitics in rural Alabama had been left deliberately untreated as part of an effort, commonly referred to as the "Tuskegee Study," to learn more about the natural course of the disease.[18]

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11. *The Oath*, in Hippocrates I 300–301 (W.H.S. Jones trans, Loeb Classical 1923).

12. Leon R. Kass, *Toward a More Natural Science: Biology and Human Affairs* 196 (Free Press 1985).

13. See A. McGehee Harvey, *Science at the Bedside: Clinical Research in American Medicine, 1905–1945* 368–84 (Johns Hopkins 1981).

14. See Susan E. Lederer & Michael A. Grodin, *Historical Overview: Pediatric Experimentation*, in Michael A. Grodin & Leonard H. Glantz, eds, *Children as Research Subjects: Science, Ethics, and Law* 3, 5–7 (Oxford 1994) ("*Children as Research Subjects*").

15. See The Nuremberg Code, excerpted from "Permissible Medical Experiments," Trials of War Criminals before the Nuernberg Military Tribunals under Control Council Law No. 10, Nuremberg, October 1946–1949, vol 2, 181–182 (US Govt Printing Office 1949–1953). See also Ruth R. Faden & Tom L. Beauchamp, *A History and Theory of Informed Consent* 151–56 (Oxford 1984).

16. See Henry K. Beecher, *Ethics and Clinical Research*, 274 New England J Med 1354, 1355 (1966).

17. See Faden & Beauchamp, *Informed Consent* at 161–67 (cited in note 15).

18. See generally James H. Jones, *Bad Blood: The Tuskegee Syphilis Experiment* (Free Press 1993).

In the aftermath of congressional hearings on this and other instances of investigatory overreaching, the executive and legislative branches began the process of enacting regulations to protect human research subjects. The first to act was the DHEW, which created a limited set of regulations in May 1974.[19] Congress followed shortly thereafter. In July it passed the National Research Act, which created a blue-ribbon committee, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research ("National Commission"), to formulate guidelines for future refinement and extension of the DHEW rule.[20] Several years later, in 1979, the National Commission released the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*.[21] The DHEW, now rechristened as the Department of Health and Human Services ("DHHS"), followed up with general regulations in 1981.[22] At the same time, the DHHS added to this basic rule ("Subpart A") regulations purporting to provide "additional protections" for fetuses ("Subpart B")[23] and prisoners ("Subpart C").[24] Protections for children followed in 1983 ("Subpart D"),[25] building upon the National Commission's child-specific report of 1977.[26] Many other administrative agencies followed the DHHS, each with its own set of regulations. In 1991, however, most decided to subscribe (with minor exceptions) to the DHHS rule as amended in 1983. To date, this so-called "Common Rule" governs (with minor variations) all research conducted, funded, or regulated by sixteen different federal agencies.[27]

B. CONSEQUENCES: BENIGN AND OTHERWISE

In retrospect it appears that these regulations have had the desired effect: Over the past three decades, reported incidents of child abuse in the course of biomedical investigation have been fewer and milder. It also appears, however, that this scheme might well have played a role in retarding the pace of pharma-

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19. See Protection of Human Subjects, 39 Fed Reg 18,914 (May 30, 1974).

20. See National Research Act at § 202(a)(1)(A) (cited in note 7).

21. See National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research, *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (1979) ("*Belmont Report*").

22. See Basic HHS Policy for Protection of Human Research Subjects, 45 CFR §§ 46.101-46.124 (2001) ("Subpart A").

23. See Additional Protections Pertaining to Research Development and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization, 45 CFR §§ 46.201–46.211 (2001) ("Subpart B").

24. See Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects, 45 CFR §§ 46.301–46.306 (2001) ("Subpart C").

25. See Subpart D (cited in note 5).

26. See National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research, *Report and Recommendations: Research Involving Children* (1977) (DHEW Publication No. (OS) 77-0004) ("Research Involving Children").

27. See United States Federal Policy for the Protection of Human Subjects—Notices and Rules, 45 CFR § 46, 56 Fed Reg 28,003 (June 18, 1991) ("Common Rule").

ceutical development for children, especially infants and fetuses.[28]

To see how this occurred, it is necessary to understand the basic dynamics of the pediatric pharmaceutical market.[29] Developing drugs is very costly. In addition to the expenses normally associated with any manufacturing process, a pharmaceutical company must run a potential product through three separate clinical trials before it can be marketed for public consumption: one for toxicity, the next for effectiveness, and the third for dosage. The costs of such careful testing are not trivial. At the very least, the company must make payments to the researchers, hospitals, referring doctors, and (often enough) subjects.

In light of these expenses, the company must ask itself an important question about any potential product: Will we enjoy, over the drug's period of market exclusivity, revenues that sufficiently exceed its costs? This question is often answered in the negative with regard to the pediatric market. The revenue side is generally small: Children are few in number,[30] generally healthy, and not as prone to chronic illness as, say, the elderly.[31] The cost side is quite large: In addi-

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28. See Charles J. Coté et al, *Is the "Therapeutic Orphan" about to be Adopted?*, 98 Pediatrics 118, 118–20 (1996); Committee on Drugs, American Academy of Pediatrics, *Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations*, 95 Pediatrics 286 (1995). Even if Coté and the AAP's findings of causation are mistaken, it is beyond argument that development and labeling for pediatric pharmaceuticals have declined over the past quarter century. This can be seen in data available from the early 1990s. In 1991 seventeen new molecular entities with potential for both adult *and* pediatric application were submitted to the FDA for approval. In spite of the fact that each of these drugs had the potential to benefit children, for only nine of them (56%) did the developers submit information concerning dosage for children. The situation goes downhill from there. In 1996 only 37% carried such information; in 1997 the figure was 33%, see FDA Pediatric Testing Initiative at 66,633 (cited in note 2). A similar picture can also be seen from a different angle. In 1973 the *Physician's Desk Reference* showed that, of all the medications included therein, only 22% had the information necessary for appropriate pediatric usage. By 1991 the figure had declined to 19%. Committee on Drugs (cited in this note).

This lack of information regarding the pediatric use of pharmaceuticals of general utility is even more pronounced when one takes a careful look at the quality of the labeling information provided for the drugs that comprise that 19%. While labeling for some classes of drugs does declare that they are suitable for pediatric usage, the available information relating to many other families of pharmaceuticals is generally acknowledged to be inadequate. See Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed Reg 43,900 (1997) (proposed Aug 15, 1997) ("FDA Pediatric Testing Initiative—Proposed"). The most common form that such inadequacies take is the favoring of one or more small cohorts—as, for example, boys from eight years of age to puberty—from within the general pediatric population. The cohort for which the absence of data is particularly striking is children under the age of two. FDA Pediatric Testing Initiative at 66,632 (cited in note 2).

29. For discussions of these issues, see Christopher-Paul Milne, *The Pediatric Studies Incentive: Equal Medicines For All* (Tufts Center for the Study of Drug Development 2001); *Pediatric Drug Research: Hearing Before the Committee on Health, Education, Labor, and Pensions*, 107th Cong, GAO-01-7057 (May 8, 2001) (statement of Janet Heinrich, Director, Health Care—Public Health Issues, General Accounting Office) ("Heinrich"); *Committee on Labor and Human Resources, Food and Drug Administration Modernization and Accountability Act of 1997*, S Rep No 105-43, at 51–52 (1997).

30. Persons aged fourteen years and under made up only 21.4% of the population in 2002, whereas those forty-five and over constituted 44.4%. See <http://factfinder.census.gov/> (visited Nov 8, 2002).

31. The leading cause of death for those under thirty-four years of age is unintentional injuries, which seldom require cutting-edge drugs. The causes of death, however, for those forty-five years and

tion to all of the outlays for clinical trials on adults, the pharmaceutical companies face certain additional expenses.[32] First, as the statute of limitations on tort suits is tolled until children reach majority, pharmaceutical companies must reckon with additional liability concerns.[33] While such causes of action might be rare (we really don't know, as settlements are confidential), the risk is one against which a company must nonetheless insure itself. Second, pediatric clinical trials are less revealing and more expensive than comparable trials for adults.[34] This is due, in large measure, to the "additional protections" that the pediatric regulations seek to provide for children. From the very beginning, the prohibition on risky experimentation limits the scope of the experiments that can be performed. Even after this hurdle has been passed, the researcher must incur considerable expense in satisfying a range of other burdens that regulations impose upon the execution of the trial.[35]

The practical consequences of these peculiar market dynamics are two-fold. First—and most conspicuous—companies have shied away from developing pharmaceuticals specifically tailored to the needs of pediatric patients.[36] The preferred market, not surprisingly, is the geriatric.

Second—and more interesting—has been the companies' approach to the testing and marketing of pharmaceuticals of general applicability. To obtain marketing approval, drug manufacturers were only required (prior to the 1998 FDA initiative) to test a pharmaceutical on the general adult population. Accordingly, it was often the case that they would develop agents of likely applicability to both children and adults, but would decline to perform the applicable tests on children.[37] The manufacturer was then obliged to state that the drug had not been tested for use in pediatric populations.[38]

On its face, this appears to be a deliberate decision to foreswear the benefits of the pediatric market so as to avoid the host of problems attendant on pediatric pharmaceutical development and marketing. The reality of pediatric pharmaceutical development is, however, quite different. While the labels of such drugs do carry disclaimers, everybody suspects that these drugs are likely to have the same or similar indications in pediatric populations.[39] Not the least significant of

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older are heart disease, cancer, cerebrovascular disease, and respiratory illness, all of which react to pharmacological treatment. See National Center for Health Statistics Vital Statistics System, *Deaths: Leading Causes for 1999*, 49 National Vital Statistics Reports (2001).

32. Heinrich at 2 (cited in note 29).

33. Milne, *Pediatric Studies Incentive* at 4 (cited in note 29); Heinrich at 2 (cited in note 29); S Rep No 105-43 at 51 (cited in note 29).

34. Milne, *Pediatric Studies Incentive* at 4 (cited in note 29); Heinrich at 2 (cited in note 29).

35. See S Rep No 105-43 at 51 (cited in note 29).

36. Milne, *Pediatric Studies Incentive* at 4 (cited in note 29); Heinrich at 2 (cited in note 29); S Rep No 105-43 at 51 (cited in note 29).

37. See S Rep No 105-43 at 51 (cited in note 29).

38. See Coté, 98 Pediatrics at 118 (cited in note 28).

39. See S Rep No 105-43 at 51 (cited in note 29).

those so involved are the manufacturers themselves, who can have their cake, as they say, and eat it too: On account of their calculated reluctance to pay for the testing necessary to have their products authorized for pediatric usage (absent such authorization, their tort liability to those who do employ them off-label is generally avoided), they profit from the pediatric market nonetheless.[40]

This arrangement presents practicing pediatricians with a terrible dilemma. In the face of solid evidence that a particular medication can effectively treat adults (or children in another cohort), the physician must decide whether to stick with the standard treatment (if there is one) or try to adjust the dosage of the untested drug to fit the particular child whom he is treating. Clinical data suggest that pediatricians frequently opt for the latter. Of the ten drugs most commonly prescribed to pediatric outpatients, all ten carry little or no information concerning appropriate usage for different age groups.[41]

The task, then, for the pediatrician who engages in this practice is to figure out how the standard dosage should be altered for *his* patient. The literature suggests that when physicians make their first stab at the problem they generally seek to ascertain the dosage in one of three conventional ways. The first, and most common, is to prorate the child's dosage from that of the adult on the basis of the child's body weight. Alternatively, the physician can perform a similar calculation on the basis of the area of the child's body surface. Cruder, and less frequently used, is prorationing on the basis of age.[42]

While these approaches might, in the case of certain drugs, prove to be a good first step in discerning the proper dosage, they are at best an exceedingly blunt instrument.[43] Nowhere does this become more clear than in relation to an infant. In addition to the easily discernable changes in physiology (massive increases in body weight, length, and surface area and the accompanying effusion of sensory curiosity and motor skills), the capacities of the various organ systems in the body change rapidly, remarkably, and, often enough, in a non-linear manner.[44]

Over the years, the administration of untested dosages of otherwise approved drugs led to a number of unfortunate mishaps to pediatric patients, some quite well known.[45] Thus have we gathered—largely through planned

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40. See Coté, 98 Pediatrics at 118 (cited in note 28).

41. Drugs on this list include treatments for such relatively mundane afflictions as asthma and allergies and, more frighteningly, two behavior modification drugs, Zoloft and Ritalin. See FDA Pediatric Testing Initiative—Proposed at 43,900 (cited in note 28). See also Coté, 98 Pediatrics at 118 (cited in note 28); Sheryl Gay Stolberg, *Preschool Meds*, NY Times Magazine, Nov 17, 2002, at 59.

42. See FDA Pediatric Testing Initiative—Proposed at 43,901 (cited in note 28).

43. See Ralph E. Kauffman, *Scientific Issues in Biomedical Research with Children*, in *Children as Research Subjects* 29 (volume cited in note 14).

44. See id at 29–30.

45. One of the earliest such cases of an adverse reaction to a drug's off-label usage (occurring in the late 1950s) was the development of "gray baby syndrome" in neonates following the administration of chloramphenicol, an antibiotic. Five deaths were initially reported, with another eighteen subsequently,

studies but also from the serendipity of fatal therapeutic misadventures—a substantial amount of information regarding the influence of pediatric growth and development on the toxicity and effectiveness of commonly used pharmaceuticals. Increased knowledge concerning the composition and functional capacity of organs and tissues, coupled with enhanced understanding concerning the processes of metabolism, has enabled pediatricians to discern general trends of some utility in establishing more effective dose formulation.[46]

In spite of this progress, the practicing pediatrician must still ply his trade with few and faulty tools. Not only have pharmaceutical companies declined to develop medications to address specifically pediatric ailments, even after they develop agents of potentially general applicability they deliberately choose not to conduct the tests necessary to provide pediatricians with appropriate usage data. While experience (often unfortunate) and systematic inquiry (albeit limited) have certainly enhanced the basic analytical tools these physicians can use to adjust adult dosages for pediatric applications, they still know relatively little about the complex processes of children's growth and maturation and even less about the interrelationships between their physiological development and the various medications of potential benefit now extant.[47]

C. MEDICINES FOR CHILDREN

Ever-inventive pharmaceutical research—however rewarding to drug manufacturers, satisfying to chemists and biologists, and promising to, say, geriatric specialists—brought more than a vague cause for discontent to a contemporary pediatric clinician. Pediatric patients—and their caregivers—were being left behind.

Mightily concerned—as early as the late 1970s—that the benefits of modern medicine were coming to children slowly and incompletely, the American Academy of Pediatrics ("AAP") attempted to lobby the FDA to secure more aggressive labeling requirements for drugs commonly used in pediatric medicine.[48] While it appears that they received a sympathetic hearing from the FDA, nothing was done in the 1980s to address the problem of pediatric labeling specifically.[49]

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until it was learned that a neonate's immature liver was unable to remove the drug from the body, resulting in the fatal accumulation of toxic doses. FDA Pediatric Research Initiative—Proposed, at 43,901 (cited in note 28). Other less dramatic but still serious incidents of unanticipated adverse reactions include the development of kernicterus in premature infants from the use of sulfa drugs and the staining of enamel in developing teeth from exposure to tetracycline antibiotics. Id.

46. See Kauffman, *Children as Research Subjects* at 37 (article cited in note 43).

47. See id at 39–40.

48. See Coté, 98 Pediatrics at 120–21 (cited in note 28).

49. The problems of pediatric patients were addressed at that time, rather, through more general remedies, including the Orphan Drug Act of 1982, which provided pharmaceutical companies with financial incentives to encourage the development of drugs of proven efficacy to small patient populations

As the problem became more acute in the late 1980s, the AAP returned with more vigor—and political savvy. By bringing together a number of interested parties in a series of "consensus-building" symposia, the AAP was finally able to persuade the FDA to join its cause.[50] The most immediate result was that the FDA moved aggressively to obtain—on a "voluntary" basis—more detailed pediatric information from drug manufacturers.[51] More importantly, it issued in 1994 another, more stringent, round of labeling requirements, the net effect of which was to reverse field on the relationship between testing and indication of potential pediatric usage.

Instead of requiring extensive testing before any information can be placed in the "Indications and Usage" section, the FDA's revision allowed manufacturers to place in this section a broad range of information that might support pediatric use of the drug.[52] By taking data "based on adequate and well-controlled studies in adults," and merely modifying it with pertinent pediatric information (e.g., pharmacokinetic [movement of drugs within the body], safety, and pharmacodynamic [drug strength] data), a manufacturer could make the desired dosage information available to pediatricians and also legally claim that the drug had a "pediatric indication."[53] The FDA could reasonably have thought that it was making a very attractive offer indeed.

The pharmaceutical industry's response to this invitation was not nearly as vigorous as the regulators had anticipated. In the period between the enactment of the new rule and subsequent implementation of a new style of regulation in 1998, pediatric labeling supplements were submitted for only 430 drugs and biologics, "a small fraction of the thousands of prescription drug and biological products on the market," and most of the additions were trivial.[54]

Jilted, as it were, the FDA decided in the mid-1990s to revamp the way in which labeling information for pharmaceuticals is obtained. Instead of relying

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(defined as fewer than 200,000 patients per year). Because the dearth of pediatric drugs was due, at least in part, to the relatively small size of the pediatric market, this act distinctly benefited children suffering from rare diseases, but offered no solution to the problem associated with the general need for pediatric labeling of adult drugs. Carolyn H. Asbury, *The Orphan Drug Act: The First Seven Years*, 265 J Am Med Ass'n 893 (1991). Another federal statute, the Drug Price Competition and Patent Term Restoration Act of 1984, Pub L No 98-417, 98 Stat 1585 (1984), held forth the distinct possibility that labeling information might be developed for pediatric applications. This act did not, however, result in any appreciable increase in the labeling of adult drugs for children. See Coté, 98 Pediatrics at 120–21 (cited in note 28).

50. See id at 121; Institute of Medicine, National Academy of Sciences, Drug Development and the Pediatric Population: Report of a Workshop (1991).

51. See FDA Pediatric Testing Initiative—Proposed at 43,901–02 (cited in note 28).

52. The existing rules, enacted in 1979, had required drug manufacturers to state pediatric indications and dosage information in a section titled "Indications and Usage." A statement placed in this section of the labeling required that indication and dosage be based, unless waived, on substantial evidence derived from adequate and well-controlled studies in pediatric populations. Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of the "Pediatric Use" Subsection in Labeling, 59 Fed Reg 64,240 (1994).

53. Id at 62,421.

54. FDA Pediatric Testing Initiative at 66,632 (cited in note 2).

on voluntarily provided information, the FDA decided to require manufacturers to evaluate their products for safety and effectiveness in pediatric patients if the product is likely to be used in a substantial number of cases *or* if the product would provide a meaningful benefit over existing treatments.[55] A draft version was issued in August 1997, the final rule in December 1998.[56]

Hoping to support the change in FDA policy, the NIH also changed its stance regarding the inclusion of children in the research it funds.[57] In guidelines released in March 1998 ("Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects"), the NIH states its ambitions: "The goal of this policy is to increase the participation of children in research so that adequate data will be developed to support the treatment modalities for disorders and conditions that affect adults and may also affect children."[58] Reversing its own long-standing policy that the use of children in NIH-sponsored research must be limited, the NIH declared that "[i]t is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, [sic] conducted or supported by the NIH, unless there

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55. See id at 66,634.

56. The FDA's vigor can be discerned from its reaction to enactment in November 1997 of the Food and Drug Administration Modernization Act, which established economic incentives for drug companies to conduct more pediatric studies. See FDAMA (cited in note 1). Under the FDAMA, the manufacturer of a drug protectable under either the Drug Price Competition and Patent Term Restoration Act, see Pub L No 98-417, 98 Stat 1585, or the Orphan Drug Act, Pub L No 97-414, 96 Stat 2049 (Jan 4, 1983), could obtain a six-month extension of monopoly privileges if it provided the FDA with adequate pediatric labeling for the agent. While pleased that Congress saw fit to enact this legislation (a similar proposal by Sen. Nancy Kassebaum had died in committee, see Better Pharmaceuticals for Children Act of 1994, S 2010, 103d Cong (1994)), the drafters of the FDA regulations did not think that these provisions of the FDAMA were sufficiently aggressive to achieve the vast changes in pediatric drug labeling that the FDA desired. See FDA Pediatric Testing Initiative at 66,633 (cited in note 2). According to these regulators, Congress had failed, in enacting the FDAMA, to consider several issues that the FDA had wrestled with over the past decade.

Most disconcerting to the regulators was Congress' dependence on voluntary response programs. See id. The FDA had long ago concluded that voluntary programs such as the one enacted by these provisions of the FDAMA did not work. Id. It believed, simply put, that few penny-pinching drug-mongers would go to the significant expense of testing their products on several pediatric cohorts in order to gain the slight and relatively short-term benefit of selling their wares for a mere six months more. Compare Sheryl Gay Stolberg, *Children Test New Medicines Despite Doubts*, NY Times, Feb 11, 2001, at A1.

Torn between its own good judgment and Congress' more cautious mandate, the FDA issued a unilateral compromise. In deference to the Congressional desire expressed in the FDAMA, the FDA decided to allow the manufacturers of drugs covered by this act to submit labeling information on a voluntary basis and receive, as authorized by the FDAMA, patent-protection extensions. However, should the FDA consider the study results inadequate, it reserved the right to order further testing. Additionally, the manufacturers of products not covered by the FDAMA would have to abide by the FDA's mandatory guidelines. See FDA Pediatric Testing Initiative at 66,633 (cited in note 2).

Congress reaffirmed its preference for a voluntary testing regime in December 2001, when it extended the FDAMA's patent incentive program for five years. See Best Pharmaceuticals for Children Act (cited in note 1). See also Alice Dembner, *Pediatric Testing Program Extended: Drugmakers Keep Patent Incentive*, Boston Globe, Dec 20, 2001, at A8.

57. See NIH Pediatric Guidelines at § II (cited in note 2).

58. Id at § I.

are scientific and ethical reasons not to include them."[59]

This regulatory change was not, however, undertaken without opposition. In October 2001 the Association of American Physicians and Surgeons, the Competitive Enterprise Institute, and Consumer Alert brought suit in the federal District Court for the District of Columbia, arguing that the FDA had no authority to propound the "Pediatric Rule."[60] On March 18, 2002, in sympathetic reaction, the FDA—now controlled by Bush appointees—announced that it would suspend enforcement of the "Pediatric Rule" for two years (beginning May 10, 2002).[61] In making its announcement, the FDA argued that its coercion was unnecessary in light of congressional authorization—and reauthorization—of FDAMA's voluntary patent-extension regime.[62] This decision was immediately attacked and the FDA quickly backed down.[63] One month later, Tommy G. Thompson, DHHS Secretary, announced that he would "enforce and improve the FDA's pediatric rule."[64] The Secretary's capitulation was premature. In October 2002 the District Court held that the FDA had indeed overstepped its bounds.[65]

Judge Kennedy's word is unlikely to be the last. Anticipating the possibility of just such a ruling, supporters of the "Pediatric Rule" had already introduced legislation in both houses of Congress, in April and May 2002, that would unequivocally grant such authority to the FDA.[66] To much fanfare (if *New York Times* editorials count as such), the Senate bill was voted out of committee and placed on the legislative calendar on August 1, 2002.[67] In its haste to return to the campaign trail, however, the Senate was unable to vote before adjournment (which took place, incidentally, on the very day of Judge Kennedy's ruling). In light of the strong support this bill obtained in committee (the vote was unanimous), the ardor of its supporters, and the lack of any organized opposition, the "Pediatric Rule" will likely return, this time with unassailable statutory force.[68]

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59. Id at § III.

60. See *Ass'n of Am. Physicians and Surgeons v FDA*, 2002 WL 31323411. See also *Why Give Kids Drugs Without Pediatric Testing?*, USA Today, April 8, 2002, at A12; Sam Kazman, *FDA Overreaches*, USA Today, April 8, 2002, at A12 (op-ed); Comment, *Pediatric Testing of Prescription Drugs: The Food and Drug Administration's Carrot and Stick for the Pharmaceutical Industry*, 49 Am U L Rev 739, 744 (2000) (arguing that FDA lacks authority to impose mandatory pediatric testing).

61. See Ceci Connolly, *FDA to Suspend a Rule on Child Drug Testing*, Wash Post, March 19, 2002, at A10; Marilyn Elias, *Plan to End Pediatric Drug Trials Draws Fire*, USA Today, April 3, 2002, at D9.

62. See Connolly, *FDA to Suspend a Rule on Child Drug Testing* (cited in note 61).

63. See Elias, *Plan to End Pediatric Drug Trials Draws Fire* (cited in note 61).

64. Marc Kaufman and Ceci Connolly, *U.S. Backs Pediatric Tests in Reversal on Drug Safety*, Wash Post, April 20, 2002, at A3.

65. See *Ass'n of Am. Physicians and Surgeons v FDA*, 2002 WL 31323411.

66. S 2394 (April 29, 2002); HR 4730 (May 14, 2002) (cited in note 4).

67. *The Need for Pediatric Drug Tests*, NY Times, Oct 14, 2002, at A18 ("Any senator who tries to block its progress should be held accountable for endangering the health of children.").

68. See Marc Kaufman, *Court Strikes Down FDA Rule*, Wash Post, Oct 18, 2002, at A9; Robert Pear, *Judge Voids Rules on Pharmaceutical Tests*, NY Times, Oct 19, 2002, at A9.

II. EXEGESIS: HOW DOES 45 CFR § 46 MEAN TO PROTECT CHILDREN?

In 1998 the FDA and NIH appeared to change course on the long-standing inhibition of pediatric drug testing implicit in Subpart D. Appearances deceive. Subpart D has not been replaced; the "additional protections" accorded to children since 1983 remain intact. The current state of the law is that *both* Subpart D and the newer rules are in force: The older regime made exclusion of children the default rule, the newer demands inclusion. Vigorous testing must extend to the specially protected classes, but children must still be specially protected.

For many of the participants in this enterprise, this conflict appeared only faintly on their radar screens, if at all. The FDA acknowledged the potential for problems when it announced its new requirements, but declared (perhaps disingenuously) that children would continue to be safeguarded by the existing regulations.[69] Many within the executive branch have noted that testing will accelerate, but have phrased their concern in terms of the "safety" of children—not at all in terms of the "dignity" interests emphatically protected by the preexisting regulatory regime.[70]

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69. See id at § IV.B.2; FDA Pediatric Testing Initiative at 43,906 (cited in note 2).

70. That the foremost concern is safety is understandable in light of recent events. With the death on September 17, 1999, of Jesse Gelsinger, an eighteen-year-old subject in a gene transfer therapy experiment, many of the parties actively promoting human biomedical research came to recognize that one of the costs of this research agenda is risk to the subject, often a risk of more-than-trivial magnitude. The response was rapid. In October, President Clinton asked the National Bioethics Advisory Commission to conduct a study to reexamine the system of protections for subjects of biomedical research. Neal F. Lane, Assistant to the President for Science and Technology, Remarks at the 35th Meeting of the National Bioethics Advisory Commission (Oct 22, 1999). In November the NIH imposed additional reporting requirements on gene therapy researchers, to which even more were added in March 2000. And in December, Rep. John L. Mica (R-Fla.) held the first congressional hearing on the matter. House Committee on Government Reform, Subcommittee on Criminal Justice, Drug Policy and Human Resources, "Do Current Federal Regulations Adequately Protect People Who Participate in Research?" (Dec 9, 1999). Since then at least three additional hearings have been held. See Senate Committee on Health, Education, Labor, and Pensions, Subcommittee on Public Health, "Gene Therapy: What is the Federal Response for Patient Safety?" (May 25, 2000) and "Gene Therapy: Is there Oversight for Patient Safety?" (Feb 2, 2000); House Committee on Government Reform, Subcommittee on Criminal Justice, Drug Policy and Human Resources, "Human Subject Research Protection" (May 3, 2000).

This initial response has been followed by a number of executive actions. In May 2000 President Clinton & DHHS Secretary Shalala proposed changes to the rules governing the manner in which human experimentation is conducted, including (1) the direct observation of the consent process, (2) the renewal of "informed consent" after adverse incidents, (3) conducting a public review of "informed consent" requirements, (4) increasing training requirements for researchers, (5) expanding IRB capacity to monitor ongoing trials, (6) conducting public hearings on financial conflicts of interest, and (7) imposing civil financial penalties for non-compliance with federal regulations. White House Press Office, "President Clinton Announces Strong New Steps to Protect the Safety of Patients Participating in Clinical Trials" (May 23, 2000) ("Clinton Safety Proposal"). On June 18, the DHHS removed the Office for Protection from Research Risks ("OPRR") from the NIH to the direct control of the Secretary and re-christened it the Office for Human Research Protections ("OHRP"). 65 Fed Reg 37,136 (June 13, 2000). The Office of the Inspector General, DHHS, has issued a number of reports advocating extensive revamping of the system. See Office of Inspector General, Department of Health and Human Services, *Recruiting Human Subjects: Pressures*

It is Congress that appears to appreciate that more is at stake here than the physical safety of child subjects. In late 2000, Congress passed, and President Clinton signed into law, the Children's Health Act, which commands the Secretary of the DHHS to review the adequacy of Subpart D.[71] The most salient aspect of this demand is the unique focus of its questions. While the statute manifests some congressional concern that increased safety might result from improvements in the institutional mechanisms of safety review,[72] its primary focus is on the ethical integrity of the definitions and formulations of Subpart D.[73]

The congressional diktat is, if I read this statute correctly, quite a bold one. It orders the executive to ask a very hard question: Does a regulatory regime grounded in the ethic of "voluntary informed consent" have the capacity to protect child research subjects from assaults, not on their health alone, but on their dignity also?

Unfortunately, the DHHS has not risen to the occasion. Instead of under-

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in Industry-Sponsored Clinical Research, OEI-01-97-00195 (June 2000); *Protecting Human Research Subjects: Status of Recommendations*, OEI-01-97-00197 (April 2000); *Institutional Review Boards: A Time for Reform*, OEI-01-97-00193 (June 1998). See also *Medical Research on People*, Wash Post, May 5, 2000 at A26.

71. See Children's Health Act of 2000, Pub L No 106-310 § 1003 (Oct 17, 2000).

72.

> (d) Consideration of Additional Provisions.—In conducting the review under subsection (a), the Secretary of Health and Human Services shall consider and, not later than 6 months after the date of the enactment of this Act, report to Congress concerning—
>
> (1) whether the Secretary should establish data and safety monitoring boards or other mechanisms to review adverse events associated with research involving children; and
>
> (2) whether the institutional review board oversight of clinical trials involving children is adequate to protect children.

Id at § 1003(d).

73.

> (b) Areas of Review.—In conducting the review under subsection (a), the Secretary of Health and Human Services shall consider—
>
> (1) the appropriateness of the regulations for children of differing ages and maturity levels, including legal status;
>
> (2) the definition of "minimal risk" for a healthy child or for a child with an illness;
>
> (3) the definitions of "assent" and "permission" for child clinical research participants and their parents or guardians and of "adequate provisions" for soliciting assent or permission in research as such definitions relate to the process of obtaining the agreement of children participating in research and the parents or guardians of such children;
>
> (4) the definitions of "direct benefit to the individual subjects" and "generalizable knowledge about the subject's disorder or condition";
>
> (5) whether payment (financial or otherwise) may be provided to a child or his or her parent or guardian for the participation of the child in research, and if so, the amount and type given;
>
> (6) the expectations of child research participants and their parent or guardian for the direct benefits of the child's research involvement;
>
> (7) safeguards for research involving children conducted in emergency situations with a waiver of informed assent;
>
> (8) parent and child notification in instances in which the regulations have not been complied with;
>
> (9) compliance with the regulations in effect on the date of the enactment of this Act, the monitoring of such compliance, and enforcement actions for violations of such regulations; and
>
> (10) the appropriateness of current practices for recruiting children for participation in research.

Id at § 1003(b).

taking the searching examination that Congress ordered, it has (by way of the Office for Human Research Protections and the National Human Research Protections Advisory Committee) established a "Children's Workgroup," which met only once within the statutorily imposed six-month period,[74] and then drafted a ten-page report, in which it summarily asserted that "the regulations for the protection of children as research subjects . . . are sound, have worked in the past and appear to be working now."[75] In lieu of a revision, the workgroup recommended only that "a series of explanatory memoranda be developed and promulgated" for the "clarification of several aspects of the regulations."[76] Prior to the expiration of the Advisory Committee's charter in July 2002, only one such memorandum was drafted.[77]

This decision is quite unfortunate. As I will demonstrate in the pages that follow, the regulations that govern the practice of pediatric biomedical research are more seriously flawed than this DHHS draft report suggests. A quarter century ago, Congress created a blue-ribbon commission to help regulators contrive a human experimentation regime that could adequately deal with the fundamental problem presented by researchers' desire to experiment on children: Can the otherwise normative principle of "voluntary informed consent" be transformed so as to adequately govern researcher interactions with subjects commonly thought incapable of granting such consent? It is my belief that the subsequently enacted regulations failed to do this.

In the hope that Congress might pause before granting statutory status to the DHHS's "Pediatric Rule," or, failing that, demand a more earnest revision of Subpart D, I offer the following analysis.

A. THE BELMONT REPORT: PROTECTIONS FOR ALL RESEARCH SUBJECTS

The intellectual foundation of the regulatory scheme that emerged in the early 1980s can be found in two committee documents written in the late 1970s. In 1974, shortly after the DHEW had hastily drafted a rule,[78] Congress created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to think more carefully about the issues at stake and to formulate a report to guide the construction of a more finely wrought apparatus.[79]

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74. National Human Research Protections Advisory Committee, *Children's Workgroup Report* 1 (April 5, 2001).

75. Id at 10.

76. Id.

77. See Alan Fleischman, *Minimal Risk, Minor Increment over Minimal Risk, and Disorder/Condition*, Presentation to the National Human Research Protections Advisory Committee, Washington, D.C. (April 30, 2002) <http://ohrp.osophs.dhhs.gov/nhrpac/mtgs.htm> (visited Nov 8, 2002).

78. See Protection of Human Subjects: Policies and Procedures, 38 Fed Reg 31,738 (1973).

79. See National Research Act at § 201-202 (cited in note 7). The National Commission's founda-

In crafting its reports, the National Commission was presented with a unique challenge. Instead of being charged with the task of merely extending and refining the DHEW rules, the Commission was asked to formulate general guidelines that would assist the regulators in their upcoming drafting duties *and*, quite exceptionally, to give the regulation's interpreters (lawyers and laymen alike) philosophical rules of thumb illuminating their application.[80] Although the document is easily derided as logically self-contradictory, the National Commission succeeded in performing its dual function: It enunciated a widely shared and easily comprehensible set of principles that were reflected in the final regulations. Since that time the Belmont Report has also guided public discussion relating to the regulation of biomedical research.[81]

1. Philosophic Principles

True to its dual mandate, the National Commission's Belmont Report first spelled out three basic ethical principles and then demonstrated how they might manifest themselves in the actual practice of human-subject research.

Respect for Persons: The first of these, "respect for persons," is the pronunciation, with an important twist, of the patently Kantian doctrine that serves as a pillar of modern liberal thought: "[I]ndividuals should be treated as autonomous agents."[82] The twist—a very important one—is this: Those who are *not* "autonomous agents" are entitled to special protection from invitations to join research protocols. The practical manifestation of this principle is twofold, depending upon the faculties of the subject:

Potential research subjects considered "autonomous agents" may be freely enrolled in research provided that (1) the investigator adequately reveals the nature of the project, (2) the presentation is comprehensible to the potential subject, and (3) the subject is not the victim of unjustifiable pressure to enroll in the study.

With respect to those persons deemed to have "diminished autonomy," participation in research should take place under the most limited and carefully scrutinized circumstances, if at all. Specifically mentioned as in this category are infants, young children, the mentally disabled, and prisoners.

The second and third principles of the Belmont Report invoke a more utilitarian doctrine by asking researchers to pay careful attention to the conse-

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tional document was the *Belmont Report* (cited in note 21). The chronologically prior work, *Report and Recommendations: Research Involving Children* (cited in note 26), applied the principles soon to be released in the *Belmont Report* to research involving children.

80. See National Research Act at § 202(a)(1)(A)(ii) (cited in note 7).

81. See, for example, National Bioethics Advisory Commission, *Ethical and Policy Issues in Research Involving Human Participation: Summary* 2 (Aug 2001); Albert R. Jonsen, *The Birth of Bioethics* 103–106 (Oxford 1998).

82. *Belmont Report* at § B.1 (cited in note 21).

quences of their work, both positive and negative.

Beneficence: The second principle, "beneficence," addresses the issue of effects at the individual level.[83] Its two components are, first, to "do no harm" and, second, to "maximize possible benefits and minimize possible harms." The first of these, the authors declare, is a simple restatement of the long-standing Hippocratic maxim. Though this second component of "beneficence" could easily be read as a Benthamite (i.e., utilitarian) equivocation upon the Hippocratic/Kantian first component, the National Commission, it appears, intends it to function as a complementary principle. Regardless of the incoherence of this formulation, the authors' intention—made manifest in their subsequent application of the principle—is that all decisions regarding the design and implementation of a research protocol should seek to balance benefits against risks. The researcher should, of course, attempt to minimize, even eliminate, any risk to the individual subjects. If the researcher is unable to eliminate the risk (as is usually the case), he should then not invite patients to become research subjects unless the benefit clearly outweighs the risks.

Justice: The third principle, "justice," asks researchers to pay attention to the allocation of risks and benefits at the societal level.[84] Recognizing that it is typically the case that one class (the poor and disenfranchised) bears the burdens of scientific research while another (the wealthy and powerful) derives the benefits, the authors of this report argue that "just" research would ensure that members of a class unlikely to reap the subsequent practical benefits of a study not be asked to participate in such research. In practical terms, they suggest that implementing this principle might require a reversal in the natural order of things: First the rich and mighty, only later the poor and weak, ought to serve as guinea pigs.

2. Practical Implementation

Given the utopian note on which the Belmont Report ends, it is remarkable how strongly it influenced the subsequent formulation of the DHHS regulations. The least surprising manifestation of the Belmont principles is that "autonomy," the first part of the principle of "respect for persons," is addressed most prominently. Under the banner of "voluntary informed consent," these rules first demand that the researcher obtain documentation of consent from the subject or his legally authorized representative; they then articulate a further demand, spelling out in meticulous detail the informational elements that must be found in the paper that the patient eventually signs.[85]

These exceedingly elaborate requirements demanding "voluntary informed

83. Id at § B.2.
84. Id at § B.3.
85. See Subpart A at § 46.116–17 (cited in note 22).

consent" are moderated at both extremes, however, by rules derived from the second principle ("beneficence"), the concern that research protocols effectively minimize, if not eliminate, the risks to which the individual research subjects will be exposed.[86] Accordingly, the regulations seek to constrain the adventuresome and empower the cautious.

To constrain: Even if the subject were willing and eager to consent, there are certain sorts of investigations to which the researcher may not invite him. He may not be invited to participate in a protocol in which the procedures are not "consistent with sound research design and which . . . unnecessarily expose subjects to risk."[87] If, however, the risk exposure is necessary, the risks to the subjects must be "reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result."[88]

To empower: In a number of narrowly defined cases where the process of obtaining "informed consent" will, for all intents and purposes, prevent the research from being carried out, the researcher may omit or modify aspects of the "consent" documentation or, in more extreme cases, forgo the "consent" process altogether,[89] provided, *inter alia*, that the "research involves no more than minimal risk to the subjects."[90]

In translation, the Belmont principle that suffered the greatest distortion was the third: "justice." The DHHS regulations do command, as did the Belmont Report, that in formulating a protocol the researcher should ensure that the "[s]election of subjects is equitable,"[91] and then goes on to note that these researchers should be "particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons."[92] Other than this vacuous admonition, the general regulations have nothing more to say about vulnerable populations as such. The National Commission's appeal to an egalitarian redistribution of the benefits and burdens of the medical research agenda does not seem to have commanded the respect of the actual regulators.

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86. Id at § 46.111(1). The requirement of "informed consent" can be either a blessing or a curse to a researcher, depending on the refinement of his moral sensibilities and the nature of his inquiries. To the unscrupulous, it is a blessing in that his duly acquired receipt of the subject's "informed consent" can easily serve as the justification for research in which the subject runs risks entirely out of proportion to the protocol's anticipated benefits (either for the patient or the medical community). To the scrupulous, it is a curse in that he must, for every inquiry, inflict these papyrian procedures on his subjects, even if their interposition would practically destroy his experiment.

87. Id at § 46.111(1)(i).

88. Id at § 46.111(2).

89. See id at § 46.116(c)–(d).

90. Id at § 46.116(d)(1).

91. Id at § 46.111(3).

92. Id.

B. SUBPART D: "ADDITIONAL PROTECTIONS" FOR CHILDREN

The regulators' refusal to provide more specific guidance concerning research on children and other "vulnerable populations" should not lead us to conclude that the DHHS ignored the third Belmont principle altogether. The scandals and concerns motivating the National Commission to propose the principle of "justice" do dominate the DHHS regulations, but in a manner that avoids invoking that principle *per se*.

The locus of these rules, Title 45, Part 46, of the Code of Federal Regulations, is divided into four subparts: A, B, C, and D. The first and longest of these, titled "Federal Policy for the Protection of Human Subjects," sets forth the basic standards for consent and subject-level risk/benefit analysis that govern all research under the DHHS umbrella. It is in the subsequent three subparts where the influence of the "justice" principle can be discerned. Each of these—Subparts B, C, and D—delineates the *additional* protections that should be accorded, respectively, to pregnant women on behalf of their fetuses, prisoners, and children: three discrete and vulnerable populations specifically mentioned in the National Commission's discussion of "justice."

The most distinctive feature of these three populations is not that they are losers in some equitable calculus, namely, that research performed on them yields therapies for other groups.[93] It seems, rather, that the regulators extended additional protection to these groups on account of their limited ability to consent to (or decline) participation. In the words of the first section of the Belmont Report, these are people deserving of protection on account of their "diminished autonomy."[94]

Whether these additional protections for fetuses, prisoners, and children found their way into the federal regulations under the influence of the first Belmont principle or the third, it is clear that all parties who had a hand in drafting them—including legislators, blue-ribbon commissions, and the regulators themselves—considered these protections to be an important part of this regulatory scheme.

Like the basic DHHS regulations, the objective of the regulations touching on children—Subpart D—is to balance our *communal* desire that research subjects be protected from invitations to participate in inordinately risky experiments against the *personal* desire of patients and their representatives to have and exercise some discretion regarding the nature and scope of the bodily incursions and risks to which child research subjects will be exposed.

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93. This is, nonetheless, a prominent feature of research on prisoners.

94. National Commission, *Belmont Report* at § B.1 (cited in note 21).

1. Risk Minimization

In the realm of ordinary medical research this drama of conflicting desires plays itself out between *consenting adults*—where both maturity and consent are significant—in the course of the screening that occurs before a patient is ever invited to become the subject of a study. The regulations require the principal investigator and the institutional review board to minimize the risk that the protocol entails; if a significant risk remains, the researchers must certify that it is counterbalanced by a corresponding benefit, either to the subject or to the larger community.[95]

This risk/benefit dynamic is even more pronounced in the *pediatric* regulations.[96] In formulating and approving experiments on children, the principal investigator and the IRB are required to be significantly more cautious in their evaluation of the risks to which subjects will be exposed. In research involving adults, all that the research community must do is minimize and balance: Very dangerous protocols can be approved if the potential benefit is correspondingly significant. Under these rules, it is conceivable that somewhat milder versions of the experiments conducted by Dr. Karl Brandt and his fellow concentration-camp "physicians"—add consent, subtract foreordained fatality—could pass muster. The goal of the pediatric regulations, on the other hand, is to narrow the breadth of these parameters. The basic risk-level rule dictated by the pediatric regulations is that the research protocol must present the child with "no greater than minimal risk."[97]

But "greater than minimal risk" is allowed under three circumstances.[98] The most permissive standard is applied to research protocols that "[hold] out the prospect of direct benefit for the individual subject."[99] In these circumstances (commonly, if somewhat euphemistically, referred to as "therapeutic research"), the protocol may subject the child to "more than minimal risk."[100] While this exception is quite permissive (both in theory and in practice), the regulations do seek to constrain it by requiring that the "risk [be] justified by the anticipated benefit to the subjects"[101] and that the "relation of the anticipated benefit to the risk [be] at least as favorable to the subjects as that presented by available alternative approaches,"[102] a situation commonly referred to as "clinical equipoise."[103]

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95. See Subpart A at § 46.111(2) (cited in note 22).
96. I would refer the reader at this point to the Appendix.
97. Subpart D at § 46.404 (cited in note 5). See also Appendix, Category I.
98. Subpart D at § 46.405. See also Appendix, Categories II, III & IV.
99. Subpart D. See also Appendix, Category II.
100. Subpart D at § 46.405 (cited in note 5).
101. Id at § 46.405(a).
102. Id at § 46.405(b).
103. See generally Loretta M. Kopelman, *Research Methodology: Controlled Clinical Trials*, in Warren Thomas Reich, ed, *Encyclopedia of Bioethics* 2278 (MacMillan, 2d ed 1995); Don Marquis, *An Argument that All*

The researcher may also subject the child to procedures involving "more than minimal risk"[104] if the research is "likely to yield generalizable knowledge about the subjects' disorder or condition."[105] This standard (also quite permissive) is constrained, nonetheless, by the requirement that the increased risk represent no more than a "minor increase over minimal risk"[106] and that the procedure "[present] experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations."[107]

Risky research that cannot be shoehorned into either of these two frameworks may also be performed if the researcher can make a showing that the "research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children."[108] Approval for such an experiment can be obtained upon petition to the Secretary of the DHHS, but only after a panel report and public comment.[109]

2. Consent

The general research regulations seek to ensure the adult subject's autonomy by allowing him ample discretion regarding the protocols in which he will choose to participate *after* the IRB has screened out those projects exhibiting minimal scientific merit and unfavorable risk/benefit balances. Like the general research regulations, the pediatric rules also seek to provide the potential research subject and his legal guardians with a certain degree of freedom to make decisions regarding his participation.

This impulse at the core of the regulatory movement of the 1970s—to restore autonomy to the subjects of biomedical research—faces, of course, a fundamental, even ineluctable, problem in the realm of pediatric research, *viz.*, that a child simply cannot give legally binding "voluntary informed consent." To work around this problem, the regulators contrived a scheme of proxy consent. The child cannot legally speak for himself, yet he might well (and often does) have distinct and volubly articulated apprehensions regarding the specific assaults on his body to which his guardian has consented. Accordingly, this scheme seeks to accommodate both the wishes of the parent(s) and the con-

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Prerandomized Clinical Trials are Unethical, in Edward Erwin et al, eds, *Ethical Issues in Scientific Research: An Anthology* 159 (Garland 1994); Eugene Passamani, *Clinical Trials—Are They Ethical?*, 324 New Eng J Med 1589 (1991); Benjamin Freedman, *Equipoise and the Ethics of Clinical Research*, 317 New Eng J Med 141–45 (1987).

104. Subpart D at § 46.406 (cited in note 5).

105. Id at § 46.406(c). See also Appendix, Category III.

106. Subpart D at § 46.406(a) (cited in note 5).

107. Id at § 46.406(b).

108. Id at § 46.407(b)(2)(i). See also Appendix, Category IV.

109. Subpart D at § 46.407(b)(2)(i) (cited in note 5). Because of the extraordinary nature of the approval process, it is not surprising that only seven research projects have been authorized in this manner.

cerns of the child.

To strike this balance, the pediatric regulations seek to modulate the consent that must be obtained from each party on the basis, once again, of (1) the magnitude of the risks and (2) the relationship between these risks and the benefit that the child might derive from participation. As the risk increases and the potential personal benefit declines, the more formal must be the manifestation of the *parents'* reflection on their grant of permission to proceed.[110]

As regards the *child's* personal willingness to participate in experimentation, however, the element of risk—the factor that plays such a crucial role in determining the nature of required parental "permission"—becomes utterly irrelevant. In determining whether the "assent" of the child must be obtained, the pediatric regulations look, rather, to two other criteria: the presence of a potential benefit for the child and the child's maturity. The basic rule, as set forth in § 46.408(a), declares that the child's "assent" is a "necessary condition for proceeding with the research." There are, however, three rather significant exceptions to this rule. The most strikingly powerful one mirrors the parental "permission" requirements: If "the research holds out a prospect of direct benefit that is important to the health or well-being of the child and that benefit is available only in the context of the research, the 'assent' of the child is not a necessary condition for proceeding with the research."[111] Child-subject "assent," in sum, is given no high priority.

But the most significant exception is Subpart D's tremendous deference to the discretion of the IRB that screens the protocol. In determining a child's capability to "assent," the IRB must reckon with no strict formulations regarding risk, chronological cohort, etc. The regulations merely declare that "the IRB shall take into account the ages, maturity, and psychological state of the children involved."[112] Even after establishing a general rule regarding "assent" for a particular protocol, the IRB may waive the "assent" requirement if it determines that "the capability of some or all of the children is so limited that they cannot reasonably be consulted."[113] Finally, the IRB may "waive the assent requirement," even where it has "determine[d] that the subjects are capable of assenting," in those circumstances where obtaining the "assent" would jeopardize the successful completion of the protocol. On account of the several substantial exceptions to the "assent" requirement, it is hard to see how, precisely, this ad-

110. In the two low-risk research classifications, the IRB may allow research in which only *one* of the child's parents (or guardians) grants "permission." Subpart D at § 46.408(b) (cited in note 5). See also Appendix, Categories I & II. In the other two, where the research is more dangerous and less beneficial, the researcher must obtain "permission" from both parents, unless one is "deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care" of the child. Subpart D at § 46.408(b) (cited in note 5). See also Appendix, Categories III & IV.

111. Subpart D at § 46.408(a) (cited in note 5). See also Appendix, Category II.

112. Subpart D at § 46.408(a) (cited in note 5).

113. Id.

ditional requirement is supposed to provide "additional protection" for those children whom physicians, researchers, and parents have chosen to enroll in biomedical research.

C. SUMMARY

In the translation of popular rage into administrative rules (by way of congressional hearings and blue-ribbon committees), it is to be expected that differences in emphasis and degree will emerge. Surprising indeed would be a perfect fit between the final rules and their demotic genesis. The case of Subpart D is no exception. The impulse was the sense (growing since the 1940s but crystallized in the early 1970s) that medical researchers were insufficiently respectful of the dignity that all—even the powerless and abandoned—do finally possess. This concern remained relatively strong through Sen. Kennedy's Tuskegee hearings and the reports of the newly minted National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The National Commission expected the autonomous to protect their own dignity through the processes of "informed consent"; it expected the state, however, to protect the dignity of the vulnerable by shielding them from such invitations. In so doing, it leaned heavily upon the concept of "justice": Researchers should not use a vulnerable population group (e.g., poor blacks or mentally disabled wards of the state) to benefit another (e.g., urban debaucheés or the United States Marines).

A noteworthy transformation occurred, however, when these reports were redacted into Subpart D. Instead of protecting vulnerable populations by way of research bans—either categorical or qualified—the regulations sought to protect them by way of the "informed consent" process. This conflict is not insuperable in the case of the illiterate sharecropper. The integrity of his consent can in fact be assured if the researcher truly takes pains to be honest, clear, and patient. The case of the child cannot, unfortunately, be so easily resolved in that manner. No child, no matter how well he understands the import of the procedure, can give legally binding "voluntary informed consent." In spite of this legal factum, the drafters of Subpart D worked hard to craft a replacement: The parent(s) give their "permission" and the child gives his "assent." Can such a procedure be an adequate substitute?

III. CRITIQUE: CAN A CHILD GIVE "VOLUNTARY INFORMED CONSENT"?

A. OBTAINING "PERMISSION" FROM PARENTS

Concerning one issue the pediatric regulations are clear: Except under ex-

traordinary circumstances, the permission of at least one parent is necessary if a child is to participate in any experiment. It makes sense that this, at the very least, is to be a minimum requirement for enrollment. It is a long-standing tradition in the Western world that parents have tremendous discretion to make decisions for their children regarding a whole range of very important matters. It is parents, after all, who make or facilitate decisions concerning a child's education, religion, habits, sexual initiation, etc.[114]

This is perhaps even more true in the context of medical treatment. The law generally acknowledges that parents are in the best position to determine what sort of treatment is best for the child and the family and, not trivially, that parents must significantly bear the untoward consequences of a failed therapeutic attempt. A previous generation focused on the financial loss: A medical misadventure resulting in a handicapped child imposes significant burdens on the family and deprives it of the child's subsequent services.[115] We now speak of the loss in terms of forgone companionship.

But the issue at hand—the requirement that a child's participation in research cannot occur without parental permission—is considerably more complex than that. The most obvious complication is, of course, that parental dominion over children is not unlimited. The state limits corporal punishment, requires a certain form of education for a specified term of years, restricts the type of labor that children may perform, prohibits incest, and, not insignificantly, requires parents to emancipate their children at the age of eighteen.

The same complexity can be found in the medical context. In a previous generation, courts were generally willing to respect parental decisions to withhold treatment for a variety of significant medical procedures (e.g., repair of a hare-lip and cleft palate and treatment of non-fatal spinal degeneration) but almost invariably intervened when parents refused to consent to life-saving treatment of proven effectiveness and trivial risk (e.g., Jehovah's Witnesses whose children are dying from blood loss).[116] This presumption has noticeably waned over the years, especially since 1972, when the New York Court of Appeals ordered a fifteen-year-old boy who suffered from neurofibromatosis (the "elephant man disease") to undergo extensive plastic surgery, in spite of his mother's religiously based objections.[117] Courts are now willing, at the very least, to entertain the possibility that in extreme circumstances a parentally chosen medical intervention can be trumped by the state's own choice of therapy.[118]

The pediatric regulations reflect this trend. Even though parents have broad

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114. See, for example, *Pierce v Society of Sisters*, 268 US 510 (1925).

115. See *Lacey v Laird*, 166 Ohio 12, 139 NE2d 25 (1956).

116. See, for example, *In re Seiferth*, 309 NY 80, 127 NE2d 820 (1955); *In re Green*, 448 Pa 338, 292 A2d 387 (1972). See generally Leonard H. Glantz, *The Law of Human Experimentation with Children*, in *Children as Research Subjects* 103, 104–106 (volume cited in note 14).

117. See *In re Sampson*, 29 NY2d 900, 278 NE2d 918 (1972).

118. See, for example, *In re Hofbauer*, 47 NY2d 648, 393 NE2d 1009 (1979).

authority to make decisions regarding their children's participation in biomedical research, these choices can be and are limited by the state. Because, however, much medical research on children occurs in a therapeutic context and is specifically intended to provide some medical *benefit* to the child, the federal regulations governing pediatric research are, in this regard, still relatively permissive. In the tradition of deference to parental decisions, the regulations allow parents to enroll children in risky research protocols so long as the intervention holds out the prospect of some benefit for the child.

1. The Problem of Proxy Consent

The vexing complication arises, however, from the fact that plenty of medical research occurs which does *not* hold out the prospect of direct and personal medical benefit. The question that then arises is a terribly challenging one: May parents, those people peculiarly entrusted with the responsibility of protecting their child from the buffetings of the world, consent that he be subjected to potentially harmful procedures from which he will receive no benefit whatsoever? Does the duty to guide and protect preclude this sort of consent? Some parents might be interested in sacrificing their child's health and comfort for the greater good of medicine, but why would the child—utterly unwilling to share his toys—be willing to make repeated and painful donations of his spinal fluid? But the fact remains that the child has no legal voice and, barring unusual circumstances, it is the parent who must speak for him. To what sort of standard should this proxy be held?

Traditional standards for proxy consent in other realms of medical research and care provide some limited guidance.[119] When an adult becomes incompetent, surrogate decisions are often made in accordance with three hierarchically ordered principles. The first, and preferred, option is that the patient's treatment conform to the directives he laid out before the onset of his debilitation. Because the sound—in body and mind—are rarely inclined to imagine the multitude of ways they might become debilitated and thus to lay out adequate guidance, their caregivers must turn to other, less prescriptive methods of guiding the physician. Preferable is the exercise of substituted judgment: What would he want were he now capable of speaking? Least favored is the task of determining what course of treatment is in the "best interests" of the afflicted. Translated into legal jargon, the proxy must here act as a fiduciary.

But when we try to apply each of these standards to the question at hand we see how unique the conundrum is. The first rule is clearly inapplicable, given that a child, prior to finding himself in this situation, has never had legal authority to declare his will. That the second offers a certain appeal—and debilities—is

119. See generally Dan W. Brock, *Ethical Issues in Exposing Children to Risks in Research*, in *Children as Research Subjects* 81, 84–85 (volume cited in note 14).

suggested by the debate started in the 1970s between two theologians, Richard McCormick and Paul Ramsey.[120] The basic argument advanced by McCormick for the exercise of substituted judgment holds that parents are indeed capable of assuming, with a certain knowledge of their child's fundamental goodwill, that he would be more than willing—absent the fright of the moment—to act altruistically: "[H]e would choose this were he capable of choice because he 'ought' to do so."[121] The riposte articulated by Ramsey is far more libertarian: "No child or adult incompetent can choose to become a participating member of medical undertakings, and no one else on earth should decide to subject these people to investigations having no relation to their own treatment."[122]

The most illuminating, however, is the third approach, that the proxy must act in the "best interests" of the child. This standard has a certain visceral attraction: Most parents would instinctively say that they *always* act in the best interests of their children. Not necessarily. Parental dedication to the child's "best interests" is assumed, but this is neither legally nor logically self-evident: The Supreme Court has indicated that a child's interest can be perceived as separable from his parents' estimation thereof.[123]

Careful examination of asserted parental dedication to a child's "best interests" reveals that this parental assertion can be subject to various interpretations, especially in the context of biomedical research. On the one hand, it can be argued that this standard, when interpreted as a "fiduciary duty," is far too exacting for any parent, save the pathologically overbearing. In the day-to-day familial struggle to satisfy adequately the needs of a variety of constituencies—including but not limited to employers, spouses, friends, community, and, not to be forgotten, other children—every parent inevitably falls far short of acting in the "best interests" of any given child. Kids are dragged on shopping trips, sit in pediatricians' waiting rooms with their siblings, get dumped early in the morning into for-profit day-care centers, are left in the evening with channel-surfing baby-sitters, and are ignored by their father at the end of the day as he unwinds in front of the tube with a can of cold beer cradled in his limp hands. Undivided

120. See Paul Ramsey, *The Patient as Person: Explorations in Medical Ethics* 11–58 (Yale 1970); Richard A. McCormick, *Proxy Consent in the Experimentation Situation*, 18 Persp Biology & Med 2 (1974); Paul Ramsey, *A Reply to Richard McCormick: The Enforcement of Morals: Nontherapeutic Research on Children*, Hastings Ctr Rpt, Aug 1976, at 21; Richard A. McCormick, *Experimentation in Children: Sharing in Sociality*, Hastings Ctr Rpt, Dec 1976, at 41; Paul Ramsey, *Children as Research Subjects: A Reply*, Hastings Ctr Rpt, Apr 1977, at 40. See generally Lainie Friedman Ross, *Children as Research Subjects: A Proposal to Revise the Current Federal Regulations Using a Moral Framework*, 8 Stan L & Pol'y Rev 159, 160 (1997).

121. McCormick, 18 Persp Biology & Med at 9 (cited in note 120). A stronger version of this argument, invoking a pedestrian form of Aristotelian teleology, posits that parents, because they play a fundamental role in developing the child's persona, can reasonably presume that the child, upon reaching maturity, will share his parents' social goals: Because it is I, the father, who will determine what sort of person my son will become, I am most uniquely situated to divine the will of that man-to-be!

122. Ramsey, *The Patient as Person* at 14 (cited in note 120).

123. See generally *Parham v R.*, 442 US 584, 603 (1979) (considering a teen-age girl's claim that her parents' decision to institutionalize her was appropriately contestable).

attention, such as a "fiduciary" must give, to the identifiable interests of his *cestui que trust* is not the standard by which parents normally act. This standard would, if its implications were teased out, categorically exclude any research on children that does not hold out at least the prospect of some direct benefit for the child in question.

Interpreted slightly more generously, however, "best interests" is a quite capacious standard. While a child's intellectual development might well be *best* secured by spending his mornings at the local Montessori school rather than being stunted by trips to the store to procure food and clothing, bored by too many hours in doctors' waiting rooms, angered when left with sitters, and saddened by an unfocused father, the aim of each of these things—protection from starvation, exposure, and untreated disease at home, not to mention the preservation of parental sanity—contributes, each in its own way, to the child's long-term "best interests."

Many have argued that a child's participation in medical experimentation is one way in which his "best interests" can be promoted, even if—or perhaps especially if—the intervention holds out no prospect of direct medical benefit for that child.[124] Parents regularly ask their children to give up something they treasure—a favorite toy, the good graces of an exclusive school-yard clique, or their playtime—to provide a more bountiful Christmas to kids on the other side of the tracks, to befriend ostracized classmates, or to cheer up the denizens of the local nursing home. While much of this is requested in the genuine belief that the child's actions might actually make the world a better place, this sort of parental initiative likely aims rather more at the positive psychological development of their own child. As a number of observers of the biomedical research enterprise have noted, it is surely possible that the same instinct can motivate parents to enroll their children in biomedical experiments: This is yet another context in which children might develop the charitable instincts that parents want them to possess.

At least one parent is on record as declaring as much. Upon being told by a researcher that his son's refusal to donate a small sample of blood for research purposes—in spite of the father's clearly articulated desire to the contrary—would be respected as binding, the father angrily exclaimed: "This is my child. I was less concerned with the research involved than with the kind of boy that I was raising. I'll be damned if I was going to allow my child, because of some idiotic concept of children's rights, to assume that he was entitled to be a selfish, narcissistic little bastard."[125]

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124. See William G. Bartholome, *Parents, Children, and the Moral Benefits of Research*, Hastings Ctr Rpt, Dec 1976, at 44; Henry K. Beecher, *Research and the Individual* 63 (Little 1970); Terrence F. Ackerman, *Fooling Ourselves with Child Autonomy and Assent in Nontherapeutic Clinical Research*, 27 Clinical Res 345 (1979). See generally Lois A. Weithorn & David G. Scherer, *Children's Involvement in Research Participation Decisions: Psychological Considerations*, in *Children as Research Subjects* 133 (volume cited in note 14).

125. Brock, *Children as Research Subjects* at 89 (article cited in note 119).

2. Research Promotion Strategies

That being said, what standard of proxy consent do the regulations present to investigators (and their institutions' lawyers) who wish to maximize the participation of children in their studies? The answer, I think, is that the regulations allow the designers of ambitious research protocols to make one of two moves: to characterize the research as beneficial to the child at hand, or, if that is not possible, beneficial to the practice of pediatric medicine or the development of pediatric bioscience.

a. "Direct Benefit"

The first, most easily justified strategy, is to find some way of representing the research as actually being of "direct benefit" to the child. This can, as suggested above, proceed on two levels.

(1) Therapeutic

First, and most easily, the protocol can be classified as being of potential medical benefit to the child. Under such a rubric, almost any research protocol can be legally defended if the prospect of a "therapeutic" effect can be identified. While such an intervention is subject to two constraints—that (1) the benefits outweigh the risks and that (2) its therapeutic potential be at least as great as customary treatment—these provide little protection in many practical circumstances. Pediatric oncological testing provides a good illustration. Even the most preliminary of chemotherapeutic trials—a test to determine how much of a drug it takes to kill a patient—can plausibly be represented as being of "direct benefit" to the child dying of cancer: We have tried everything else; this might work. Besides, the possibility of extended life dwarfs several months of discomfort.

(2) Psychological

On the second level, a researcher can seek to define the "benefits" to the subject as psychological in character. Even though this would require a more permissive interpretation of the fiduciary-beneficiary relationship, there is good reason to believe that this could pass muster. First, the pediatric regulations speak only in terms of "the subject's well-being" and "direct benefit,"[126] *not* in terms limited to corporeal health. The pediatric regulations put few additional restrictions on any research that "holds out the prospect of direct benefit for the individual subject."[127] So long as the risk is "justified" by the "anticipated bene-

126. Subpart D at § 46.405–406 (cited in note 5).
127. Id at § 46.405.

fit" to the subject, almost anything goes.[128] Second, one could seriously argue, as have Terrence Ackerman *et al.*, that the psychological benefit accruing to the child presents a powerful case for the inclusion of those children of sufficient maturity to understand the import of their actions. Third, the case law might well sustain such a recategorization.[129]

b. Utility

The second move a researcher can make is to resort to a broad-based utilitarian justification for experimenting on children. Even if the intervention cannot provide a benefit—corporeal or psychological—to the child at hand, a utilitarian calculation (one that includes the benefits which might accrue to those future children whose condition might be alleviated by the increase in biomedical knowledge obtained by way of the experiment) can be invoked to justify pediatric research.

Given a choice, this is not the argument to which a researcher should have to resort in order to justify his protocol. Not only is it disfavored among the ethicists[130] (the regulatory impulse that led to the Belmont Report was, after all, largely Kantian in sentiment, celebrating personal dignity rather than Benthamite utilitarianism), both of the courts that have examined the issue were also not terribly impressed. As Judge David Ross of New York declared: "[A] parent or guardian . . . may not consent to have a child submit to painful and/or potentially life-threatening research procedures that hold no prospect of benefit for the child and that may have the same result as a denial of necessary medical treatment."[131]

This utilitarianism is not, however, foreign to the Code of Federal Regulations.[132]

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128. Id at § 46.405(a).

129. This phenomenon is interestingly demonstrated by the law that has emerged to govern kidney "donations" from the physically healthy but mentally retarded to their dying siblings. In each of these cases, the healthy sibling had *no* prospect of *any* physical benefit from the transfer; if anything, he ran rather considerable risks. The families largely succeeded, however, in convincing the courts to allow the donation (the surgeons had refused to do so without obtaining judicial approval) by pointing to the psychological benefit that the retarded children would derive from the survival of their siblings. See, for example, *Little v Little*, 576 SW2d 493 (Tex 1979); *Strunk v Strunk*, 445 SW2d 145 (Ky 1969). See generally Glantz, *Children as Research Subjects* at 106–10 (article cited in note 116).

130. See Ross, 8 Stan L & Pol'y Rev at 166 (cited in note 120). See also Brock, *Children as Research Subjects* at 90 (article cited in note 119).

131. *T.D. v New York State Office of Mental Health*, 228 AD2d 95, 124, 650 NYS2d 173, 192 (NY App Div 1996). See also *Grimes v Kennedy Krieger Institute*, 366 Md 29, 131, 782 A2d 807, 858 (2001) ("a parent, appropriate relative, or other applicable surrogate, cannot consent to the participation of a child or other person under legal disability in nontherapeutic research or studies in which there is any risk of injury or damage to the health of the subject").

132. Two of the four risk categories are explicitly justified in Subpart D by utilitarian arguments. See Appendix, Categories III & IV. The first permits the research if it is "likely to yield generalizable knowledge about the subjects' disorder or condition." Subpart D at § 46.406(c) (cited in note 5). The second

3. Summary

When we consider what practical consequences will result when the current research-expansion initiatives eventually confront the DHHS pediatric regulations, it will be important to keep in mind these rather considerable weaknesses. In spite of the drafters' clear desire to protect children from investigatory overreaching by requiring parental consent, there is a tension in this mechanism that will simply not go away. A parent's job, before all others, is to look out for his child's interests. Though not evident at first glance, circumstances may arise in which this can be done only with difficulty if the parent, as Judge Ross described the situation, has no authority to subject a child to non-therapeutic but painful research protocols.[133]

One can, of course, try to slide by this tension in one of two ways. Most baldly, one can ignore the problem and turn to the utilitarian justifications found in Subpart D. With greater promise, one could work to redefine "benefit" to encompass the pedagogic within the pediatric. The sure way of addressing the problem, however, has been to discern "therapeutic" potential in any intervention.

A frightening illustration of the unfortunate consequences of the regulation's "therapeutic" exception can be found in the case of Dr. Leonard Bailey's unsuccessful transplantation of a baboon's heart into "Baby Fae" in 1984.[134] With no intervention from his IRB, Dr. Bailey performed an exceedingly risky procedure that possessed, nonetheless, the possibility of conveying a great therapeutic benefit: life. While one can question the propriety of this experiment on the basis of its many legal and ethical lapses, not the least of which was Dr. Bailey's failure to search for a newborn's heart for transplantation (one *was* available at the time), it is not at all clear that his risk/benefit calculation was erroneous. At bottom, so long as the researcher's experiment can clear this hurdle he is home free.

B. OBTAINING "ASSENT" FROM CHILDREN

In addition to the requirement that a researcher obtain "permission" from the parent(s) or guardian of a minor before enrolling him in a medical experiment, the DHHS rules also require that a researcher obtain the child's "assent" to the intervention. While this requirement, as discussed above, can be qualified or waived in a rather significant number of circumstances, the default rule is that

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permits research if "the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children." Id at § 46.407(a). And one sort of research, that involving not "greater than minimal risk," requires no justification whatsoever. Id at § 46.404.

133. See *T.D.*, 228 AD2d at 124, 650 NYS2d at 192 (cited in note 131).

134. See generally Glantz, *Children as Research Subjects* 126–27 (article cited in note 116).

without this "assent," an investigatory intervention may not proceed. This requirement poses many interesting and practical questions: Do minors have a legal right to consent, assent, or refuse to participate in experimentation? Is it appropriate that we endow them with a power to do such? Does this right provide the child with any "additional protection" against investigatory overreaching?

A useful way to understand the "Common Rule" is to view it as an attempt to balance the autonomy of the potential research subject (to assess the nature of the risks he is willing to run) against our communal desire (to constrain the scope of this individual choice to interventions that have a favorable benefit-risk ratio) and then, but only then, allow the potential subject to assess and assume the risks. The unusual nature of pediatric experimentation makes this already complex balancing act even more problematic: The decision-making unit is not one, but two or three. We have explored the complexities of this situation from one point of view, the parent's ability to give "permission" for his child's involvement; let us now address it from the other, the child's ability to "assent" to such.

The basic requirement of the pediatric regulations regarding the child's "assent" is that the researcher must obtain it before the child can participate in an experiment. Subpart D provides, as discussed above, many circumstances under which the IRB may waive this requirement, but fails—at least in the code itself—to provide these committees with firm guidance concerning the ages at which the request for such a waiver might be regarded as suspect. The report prepared by the National Commission does, however, seek to confront this question more forthrightly.[135] The authors of this report recommended that an IRB should consider the "assent" of a child over the age of seven to be mandatory, unless the "intervention holds out a prospect of direct benefit that is important to the health or well-being of the child at hand and is available only in the context of the research."[136] Infants need not "assent," nor should "assent" be sought from incapacitated children of any age.[137]

The Commission's observations place even more discretion in the hands of the child. "The objection of a child of any age," the report declares, "to participation in research should be binding."[138] It allows, however, that objections of small children may be overridden if the interventions are ones "from which the subjects might derive significant benefit to their health or welfare" and enjoins the researchers to take seriously the objections of school-aged children, recommending third-party dispute resolution should the child and parents be in disagreement.[139] As the Commission concludes, "[a]lthough parents may legally

135. See National Commission, *Research Involving Children* at 12–17 (cited in note 26).
136. Id at 12–13.
137. Id at 16.
138. Id.
139. Id.

override the objections of school-age children in such cases, the burden of that decision becomes heavier in relation to the maturity of the particular child."[140]

1. What Does the Law Have to Say?

The National Commission's observation that "parents may legally override the objections of school-age children" begs the question as to what the law actually *does* have to say regarding the dispositive character of a child's wishes. The initial answer to this question suggests that, whatever the National Commission might wish, the actual regulators said that the question is to be decided according to the laws of the jurisdiction in which the researcher and patient happen to find themselves. As the regulations declare: "'Children' are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted."[141]

The legal question can profitably be phrased in two complementary ways. First, if the parents want their child to participate but the child does not, can the parents force his participation? Second, if the child wants to participate, but the parents do not want him to enroll, can they prevent such from occurring? The answers to these two questions suggest that Subpart D's assent requirements (as the National Commission suggested that they should be interpreted) are a bit more indulgent toward the wishes of children than courts might be.

Helpful guidance concerning these questions can be found in the common-law development, over the past four decades, of the rules governing the ability of minors to obtain medical treatment without parental consent.[142] As we have discussed at length above, parents have traditionally enjoyed the right to make most decisions concerning the medical care of their minor child, even over the child's objections.[143] In the 1960s and early '70s many practicing physicians were presented with a unique moral and legal challenge. With the advent of easy access to recreational drugs and contraception, teenagers suffering from the various physical consequences of the psychedelic and sexual revolutions frequently asked physicians—on their own initiative—to treat their maladies. Because physicians who treat under-age patients expose themselves to civil battery suits, doctors were forced to choose between their Hippocratic obligation to heal and their legal duty to obtain parental consent before administering treatment. Many potential patients were understandably loath to request parental authorization.

The consequence was the further development of several exceptions to the

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140. Id.

141. Subpart D at § 46.402(a) (cited in note 5).

142. See generally Walter Wadlington, *Consent to Medical Care for Minors: The Legal Framework*, in Gary B. Melton et al, eds, *Children's Competence to Consent* 57 (Plenum 1983).

143. See, for example, Robert W. Bennett, *Allocation of Child Care Decisionmaking Authority: A Suggested Interest Analysis*, 62 Va L Rev 285 (1976).

general rule of parental control over medical decisions regarding their children. One of these, the simplest, and least relevant for our purposes, was the general lowering of the age of consent.[144] Another was the "emancipated minor" rule. By engaging in certain "adult" activities—including marriage, motherhood, military service, and self-support—a minor acquired the right to consent to medical treatment.[145] Exceptions were also crafted for the treatment of specific conditions, such as sexually transmitted diseases, drug addiction, and prenatal care.[146] Yet another was the further development of the "mature minor rule." Under the strict patriarchal rule, a child—even a teenager days away from majority—was legally incompetent. The "mature minor rule" changed this categorical exclusion into a rebuttable presumption: Upon a showing of sufficient cognitive and emotional maturity, a minor could obtain the right to consent to medical treatment.[147] The most permissive response to this sort of problem is the development of the "rule of sevens." This rule holds that between birth and the age of seven, a child cannot consent; from seven to fourteen a child was rebuttably incapable of consenting; and from the age of fourteen until majority the presumption was one of capacity.[148]

This doctrinal evolution suggests that, while the law is still hesitant to grant any purchase to the desires of a child under the age of seven, it is occasionally willing to entertain those of children between seven and fourteen, and eager to let those over fourteen act independently from their parents. On this reading, in both of the strained situations described above—the child refusing to participate and the child wanting to participate—the law would not be willing to sustain the very young child's desires, but would be increasingly receptive as he matures. Viewed from this perspective, the regulations' general desire to grant children a decisive role receives some sustenance: The regulations push the envelope a bit with respect to the seven-to-fourteen cohort (granting more autonomy than the common law might), but are certainly within the purview of the "rule of sevens"

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144. See, for example, Wadlington, *Children's Competence to Consent* 57 (cited in note 142).

145. See, for example, Minn Stat Ann §§ 144.341–342 (2001).

146. See Wadlington, *Children's Competence to Consent* at 61–62 (cited in note 142) ("Such 'condition specific' consent provisions seem to reflect a policy of expedience on the part of legislatures that have adopted them. . . . The statutes are directed toward problems that legislatures acknowledge as presenting serious medical difficulties among minors; they abrogate the historical legal incapacity of minors to consent to treatment for fear that if parental consent were required in the specifically enumerated instances many adolescents would refrain from or delay treatment, to the detriment of themselves and their community.")

147. See *Younts v St. Francis Hosp.*, 205 Kan 292, 301, 469 P2d 330, 338 (1970) (holding that a seventeen-year-old girl "was mature enough to understand the nature of the consequences and to knowingly consent to the beneficial surgical procedure").

148. See, for example, *Cardwell v Bechtol*, 724 SW2d 739, 749 (Tenn 1987) ("[I]t would rarely, if ever, be reasonable, absent an applicable statutory exception, for a physician to treat a minor under seven years, and . . . between the ages of seven and fourteen, the rebuttable presumption is that a minor would not have the capacity to consent; moreover, while between the ages of fourteen and eighteen, a presumption of capacity does arise, that presumption may be rebutted by evidence of incapacity, thereby exposing a physician or care provider to an action for battery.")

with regard to those over the age of fourteen.

The various cases that have skirted about the issue of children's consent to medical interventions suggest that, even as courts are willing to let minors make many decisions concerning medical care, there exist important limitations on this authority. First the base-line: It appears that the courts might well be comfortable with a child's participation in research not personally beneficial if it is clear that both the parents and the child have given their consent. In this respect, the pediatric regulations' emphasis on dual consent would appear to be on firm ground. It also appears that courts might consider parental consent to be necessary, notwithstanding the child's expressed willingness to participate.[149] Once again, the pediatric regulations appear to comport well with the decided cases. It does not appear, however, that courts would be so willing to treat the child's objections as dispositive. A court might be willing to acknowledge the refusal of a fifteen-year-old; it is not so obvious that it would treat an eight-year-old's refusal in the same way. The law appears to be willing to afford a great deal of weight to the volition of a high-school student, but considerably less to that of the schoolboy.

2. Does this Provision Provide "Additional Protections"?

Apart from the question concerning the extent to which the courts might respect the system of dual consent found in the pediatric regulations, we should certainly ask whether it is appropriate that a code purporting to provide a child with "additional protections" give him the right to veto his parents' decision. The answers provided by the ethicists can be found all over the map. William Bartholome sets the standard quite low, arguing only that the child must consent to the research performed on him; William Curran and Henry Beecher raise the bar a bit, declaring that the child must be at least four years old before his assent (or refusal) could be dispositive; and Terrence Ackerman sets it highest, arguing that parents alone should decide, as the system of dual consent makes a mockery of the parental duty to children.[150]

One's response to this question likely turns upon an answer to two other questions, one interpretive, the other empirical. First: Does this veto exist to provide the child with "additional protections" or to provide him with a genuine opportunity to make an autonomous moral decision? Second: Does the dual-consent regime actually provide the child with substantially greater protection than he would enjoy under a more patriarchal approach?

As discussed already, the entire regulatory scheme can best be understood

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149. See Wadlington, *Children's Competence to Consent* at 69 (cited in note 142).

150. See Bartholome, *Parents, Children, and the Moral Benefits of Research* 44–45 (cited in note 124); William J. Curran & Henry K. Beecher, *Experimentation in Children: A Reexamination of Legal Ethical Principles*, 210 J Am Med Assn 77, 77–83 (1969); Ackerman, 27 Clinical Res (cited in note 124). See generally Ross, 8 Stan L & Pol'y Rev at 160 (cited in note 120).

as an attempt to balance our communal desire, on the one hand, to police the researcher-subject relationship and our concern, on the other, that potential subjects enjoy as much autonomy as possible. To ensure that the balance is appropriate, the regulations set up a series of relatively strong barriers followed by an ultimate decisional firewall.

In the case of the rules governing research on autonomous adults, the intermediate barriers are rather weak and control over the firewall is granted to the subject: Before the invitation makes its way to the subject, the principal investigator and the IRB need only screen out unnecessary risks and provide him with detailed information concerning the nature and scope of the experiment. But it is the research subject who must make the final decision regarding the proffered request.

Ascertaining the location of the firewall in the pediatric regulations is a bit more difficult. In research involving children, Subpart D places an additional burden on the investigator and the IRB: The risk-minimization criteria are far more stringent than those found in the general regulations. But the system of dual consent makes it difficult to figure out where the firewall is: Do the parents (in providing their "permission") serve this function or is it the child himself (in granting "assent") who is meant to man the firewall?

This is not a trivial hermeneutical question, given that the moral legitimacy of the "assent" provision turns on it. If we read the regulations as placing the firewall with the parents, Subpart D escapes the opprobrium that one might otherwise heap upon it. This reading proceeds thus: The code grants to parents the right to make final critical decisions regarding medical experimentation with the expectation that they will exercise this authority with something approaching the exacting discretion we expect fiduciaries to exercise. The code's requirement that researchers obtain the child's affirmative "assent" and its grant to the child of the right to object should *not* be seen as another (even if supererogatory) firewall, but, rather, as an indulgence dispensed to children to enable them to exercise their moral agency freely and thereby mature into autonomous *and* charitable adults. This argument is not textually implausible, as Subpart D very rarely allows the IRB to waive parental "permission" requirements but makes it quite easy for the IRB to waive the "assent" provision.

If, however, we read the "assent" requirements as placing the decisional firewall in the child's control, it becomes considerably more doubtful that the drafters of this code successfully executed Congress' mandate to provide child subjects with additional protections.[151] The problem here should be readily apparent. These regulations were enacted because it was clear that children, who are still developing their cognitive and moral faculties, are poorly situated to resist invitations from either parents or doctors—those whom they have been taught to trust—to participate in medical experimentation. Even if one were to

151. See National Research Act at § 202(a)(2) (cited in note 7).

conclude that Subpart D generally succeeds in its goal of protecting children by preventing researchers from inviting them to participate in frivolous and/or dangerous research, it fails to protect them to the extent that it actually endows children with substantive decision-making authority.

On the assumption—shared by parents and child—that it is the child who is manning the firewall, the parent, by the simple act of "allowing the child to decide for himself," has strongly influenced the child's decision, one way or other.[152] Even teenagers (though they are loath to admit it) do look to their parents for guidance. If, on the other hand, the child does not know who is manning the firewall (or cannot possibly comprehend what it might mean to take that decision-making burden on his own shoulders) a parent's well-intentioned

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"Well, you were the one who said we shouldn't force religion on them—that they'd find it for themselves." Ed Fisher, *Ed Fisher's First Folio* 86 (MacMillan 1955).

buck-passing, seemingly encouraged by Subpart D, constitutes nothing short of abandonment or betrayal.

One could argue, of course, in defense of Subpart D, that this dual consent formulation does provide children with additional protection in that it sets up, in addition to the base-line firewall (parental "permission"), yet another protection in the form of the "assent" requirement: Even after parents guard against investigatory overreaching as diligently as they can, the "assent" requirement allows children to narrow the range of acceptable experimentation even further. While I do not doubt that this is a logical possibility, this dual consent regime also comes with all the vices attendant on any system of governance that relies on checks and balances, most notably the willingness to shrink from making difficult decisions in the hope that the other branch will make the right choice.[153]

One can hope, nonetheless, that those parents who wish to enroll their children in biomedical research experiments will view the "assent" requirement as pedagogic rather than decisive and thus be willing to scrutinize research protocols with the highest degree of care. We ought to be concerned, however, that the presence of this "assent" requirement in Subpart D will enable—even invite—the parents of a prospective research subject to pass the buck on to their children.

The "assent" feature of the pediatric regulations is a classic case of the double-edged sword. By giving children the right to "assent" and the power to "object," one of its blades surely cuts through the paternal power that has long characterized the triangular relationship between researchers, children, and parents. This is no inconsiderable gain, particularly for children of mature age and faculties. Cutting in the other direction, however, is the burden that this provision moves from parents to their children. While one might hope that parents will diligently exercise the prerogatives of their remaining power to withhold "permission," these regulations, as they stand, present the distinct possibility—both in theory and in practice—that children must serve as the ultimate gatekeepers for regulations intended, first and foremost, to offer them protections they have rarely enjoyed.

IV. SUMMARY AND RECOMMENDATIONS

A. SUMMARY

We can only conclude that the pediatric regulations fail to give affirmative answers to the two questions we posed.

153. See Charles L. Black, *Structure and Relationship in Constitutional Law* 70–71 (LSU 1969).

1. The "Therapeutic Research" Exception

The distinction between "therapeutic research" and "non-therapeutic research" does *not* sufficiently protect child subjects. As the threshold question for determining both the permissible level of risk ("Can the intervention entail a risk that is 'greater than minimal'"?) and the magnitude of parental deliberation ("Do both parents need to agree?"), this is a very important question indeed. It fails in two ways. First, it is silent as to the nature of the required "benefit," opening up the distinct possibility that a researcher could defend investigatory overreaching with the invocation of the psychological benefit accruing to his subjects. Second, such an intervention can transgress the otherwise applicable "minimal risk" limitation with great ease. To enroll a child in a highly risky experiment, all the researcher need argue is (1) that its therapeutic potential is at least as favorable as the customary treatment and (2) that its potential benefit outweighs its risks. Surely the possibility (even if remote) of one more year of life is worth six months of nausea!

2. Proxy Consent

The proxy consent process does *not* serve as an adequate substitute for the otherwise obligatory "voluntary informed consent." First, we have no settled standard of judgment by which parent(s) can be guided and to which they should be held. On the one hand, the use of "substituted judgment" allows parents perhaps too much discretion, as it is an empty vessel into which their self-congratulatory expectations can be poured. On the other hand, the use of a "best interests" standard—if such be taken to impose a fiduciary obligation—might well categorically prevent almost all pediatric testing. When a fiduciary acts, he must do so for the exclusive benefit of his *cestui que trust*. More capacious interpretations have been proffered, namely, in the best interests of the family and the psychological development of the child, but these can suffer from abuse similar to that suffered by the "substituted judgment" standard.

Second, it is entirely unclear how the child-"assent" requirement endows a child subject with "additional protection." This provision is unproblematic if one views the opportunity to decline to participate as an indulgence we dispense to children to enable them to exercise their moral agency freely and thereby mature into autonomous *and* charitable adults. One might then inquire, however, why this requirement can be so easily waived. If, on the other hand, one views the "assent" provision as placing the decisional firewall in the child's control, it becomes quite dubious that child subjects have thereby been granted "additional protection." This can be seen from two points of reference. As previously noted, there are far too many situations in which the IRB may allow the researcher to "waive" the "assent" requirement. Also, we place in the hands of children—whose moral faculties are still developing well into their teen-age

years—responsibility for a decision that only mature and responsible adults can reasonably make.

B. RECOMMENDATIONS

1. Definitional Clarity for Subpart D

Many of the problems I have identified in this Article could be ameliorated by enhancing the definitional clarity of Subpart D.

To minimize abuse of the provision that allows "therapeutic" experiments to present risks that are "greater than minimal," the regulations could be amended in two ways. First, the standard demanding that the experiment "[hold] out the prospect of direct benefit for the individual subject"[154] could be revised to mandate that the probability of such benefit be "more likely than not," or some such formulation. Second, the regulations could be revised to exclude categorically any experiments that propose—apropos the benefits accruing to the research subject—to enhance *only* the psychological "well-being" of the child.[155]

To give greater integrity to the current system of proxy consent, two changes might be made: The first is easily effected; the other presents special complexities. First, the "assent" provision should either be strengthened or eliminated. I believe that the "assent" provision represents our abdication of adult responsibility and ought accordingly be eliminated. Should an opposite view prevail, Subpart D might properly be amended so as to give IRBs a considerably more limited discretion to "waive" the requirement that the child "assent." Second, a standard for parental "permission" could be established. What do we rightly expect of parents? Should they exercise "substituted judgment," act in their children's "best interests," or act as "fiduciaries"? Narrowing the list of options is easy enough: Allowing the imputation of substituted judgment imposes no constraint; expecting fiduciary behavior forecloses experimentation altogether. Lighting upon a more conventional "best-interests" standard does little, however, to resolve the problem. Even if Subpart D were to declare explicitly that this standard ought to govern, it is hard to see what practical effect that might have, as few of the other parties to this enterprise are ultimately interested in second-guessing parental decisions to proceed.

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154. Subpart D at § 46.405 (cited in note 5).
155. Id.

2. Protecting the Dignity of Child Research Subjects—Coping with a Failure of "Informed Consent"

When Congress demanded in the early 1970s that "additional protections" for children be included in the general regulations, the paramount concern was that "vulnerable populations" were not adequately protected from over-eager researchers. It was in those terms that it phrased this concern and in those terms that the authors of the Belmont Report endeavored to guide the regulators at the DHHS. When, however, the regulators finished their work, this paternalistic concern had been significantly transmogrified. Instead of describing how children *qua* "vulnerable population" could be protected, it created an elaborate system of proxy consent to compensate for the fact that children simply cannot give legally binding consent for any sort of biomedical research.

Should Congress decide that it is interested in protecting children involved in biomedical research—not just from the inevitable safety risks but also from the equally inevitable assaults on human dignity—it should be willing to approach this problem in a slightly more radical way. Rather than look to "informed consent" or any of its offspring as a tool to protect the dignity of children, it ought to conjure up the spirit that inspired these regulations and seek to heed its warning: The dignity of all people, adults and children alike, cannot be protected by resort to "voluntary informed consent" alone. Any researcher who proposes to experiment on children should be particularly aware of this fact and do everything possible—from design to administration—to avoid perpetration of an assault on human dignity. It wouldn't hurt if the law also reminded him of that obligation.

CONCLUSION: ELUSIVE VALUES—SPEED, SAFETY, AND DIGNITY

The choice that Congress and the Executive will have to make—whether it be to enforce the existing code more strictly, tighten up its definitions, eschew proxy consent as a means for protecting children, or retreat from prior commitment to the "Pediatric Rule"—should not be easy. This is not because our representatives will be tugged in several directions by diverse interest groups (as they certainly will be), but, rather, because the fundamental interests at stake simply are so patently divergent. On one hand is the interest that the presently sick child (and society at large) has in the preservation of that child's dignity. On the other is the health of the many children, similarly suffering, who have yet to come. As Plato would say, these two interests are "incommensurable,"[156] or, as we would have it, "them's apples 'n' oranges."

It would certainly be easy to suggest that the answer be dictated by philosophical taste: Kant sides with the former, Bentham with the latter. *de gustibus non*

156. Plato, *Theaetetus* 147d–148b (N.H. Fowler ed & trans, Loeb Classical 1923).

disputanda. I wish to suggest, however, that the problem cannot be dismissed as a matter of personal predilection. Choices will certainly be made—to respect scrupulously societal notions of personal dignity, to seek the greatest good for the greatest number, or (as is most likely) to strike a balance between the two. But each of these choices comes at a price. The more we seek to protect the dignity of a few currently suffering children, the less will we be able to treat many more such children in the future. And vice-versa. A communal refusal to subject children suffering from cancer to the many unpleasantries of chemotherapeutic trials necessarily retards the pace of development of therapies for other such children.

Consider NASA's insistence that, in preparing for a landing of robot lunar explorers in 1999, it could work—and was working—"faster, better, cheaper." Sober reflection, after a series of disastrous failures, elicited the wry comment that one could have any two of these good things at the same time, but not all three. Is it perhaps so with the triad of pediatric research goals also: speed, safety, and dignity? Surely, not all good things can be had simultaneously.

The euphoria occasioned by the remarkable biomedical discoveries of the last several years is difficult to resist.[157] Many thoughtful people, including the former Vice-President, have been caught up in it. In August 2000, Albert Gore, Jr., committed himself to deliver the therapeutic benefits thereof to the American people: "Within the next few years, scientists will identify the genes that cause every type of cancer. . . . We will find new medicines and new cures, not just for cancer, but for everything from diabetes to H.I.V./AIDS [sic]."[158]

No considerate observer wants to be the skunk at the garden party, but in any case in which widely held moral sensibilities are or might be offended, and surely in any case in which human life and dignity is placed at risk, one must

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157. This enthusiasm is not limited to human health, as the following text from a pet food advertisement suggests:

> "I wish my dog didn't scratch so much."
> "I wish my cat didn't shed so much."
> "I wish my dog would live until my kids are grown."
> "I wish my older cat was more playful."
> If You Ever Wished it for Your Pet, Purina Scientists Are Working on it Today. Over 70 years ago, when we began our study of pet nutrition, who would've dreamed our simple mission would evolve into the study of nutritional genetics? Back then, no one knew it would become possible to micro-design pet food based on our knowledge of genetics. Who would have thought an adjustment to a pet food formula could minimize the risk of certain health problems just by the way the nutrients interact with the genes? We now know, as we continue our enthusiastic research into the mysteries of DNA, that the possibilities are virtually unlimited. The knowledge we've gained so far is already at work in Purina pet foods. Everything we ever wished for our pets, we're working to make a reality, through the science of Purina.
> PURINA. Redefining *the* Possible.

National Geographic, Oct 1998, at the last page of the unpaginated front matter, directly opposite the message *From the Editor* at 1.

158. Albert Gore, Jr., Acceptance speech at Democratic National Convention, Los Angeles, Aug 2000.

ask—as a matter of societal claims and aspirations: What price progress?

In times and circumstances such as ours, it is easy to forget a lesson we all know: Choices have consequences, many of which are unwanted. A powerful reminder of this fact was beautifully articulated by Hans Jonas in 1969, on the eve of this regulatory revolution. Possessed of a subtle understanding of the practical consequences of German idealism, Jonas reminded us of the tangible cost that future generations would have to pay for his generation's solicitude toward the dignity interests of the patient at hand:

> Let us not forget that progress is an optional goal, not an unconditional commitment, and that its tempo in particular, compulsive as it may become, has nothing sacred about it. Let us also remember that a slower progress in the conquest of disease would not threaten society, grievous as it is to those who have to deplore that their particular disease be not yet conquered, but that society would indeed be threatened by the erosion of those moral values whose loss, possibly caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having.[159]

Whatever we mean to accomplish with the next generation of medical research, we should not ignore the fact that the benefits desired do not come without a price.

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159. Hans Jonas, *Philosophical Reflections on Experimenting with Human Subjects*, 98 Daedalus 219, 245 (1969).

APPENDIX

Category	*Authority*	*Tolerable Risk Level*	*Ancillary Description of Tolerable Risk*	*Required Benefit Level*	*Required Permission for Involvement*
I	§ 46.404	• no greater than minimal	• undefined	• none	• one parent
II	§ 46.405	• greater than minimal (including, occasionally, very severe risk)	• undefined	• some prospect of direct benefit to subject	• one parent
				• sufficient to justify the risk	
				• must be at least as favorable as customary treatment	
III	§ 46.406	• minor increase over minimal	• must be commensurate with experiences in subject's daily life	• no prospect of direct benefit to subject	• both parents
				• knowledge gained must be generalizable and of vital importance for understanding or ameliorating subject's condition	
IV	§ 46.407	• unlimited	• determined by Secretary of DHHS on a case-by-case basis	• research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children	• both parents