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# **Children as Experimental Subjects: A Review of Ethical and Theological Issues**

by

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The involvement of children in research raises particular ethical concerns because of their reduced autonomy and their incompetency to give informed consent. Such concerns would not be answered simply by restricting participation in research to persons who are competent to consent, for the conduct of research involving children is necessary not only to develop new treatment(s)...but also to protect children from accepted though unvalidated practices that may be harmful to them.

- *Report and Recommendations on  
Research Involving Children*

The citation above identifies the subject of this research paper—should children participate in therapeutic research even if it involves some risk to them? What special conditions must be met if therapeutic research with measurable risk is permitted? What does the government say? What does Roman Catholic theology/ethics offer on this matter

of subjecting the vulnerable to risk while trying to solve the mystery of their specific disease?

In order to attempt an answer to these questions I will 1) review the history of human experimentation in children; 2) review the development and, finally, the execution of federal legislation in the United States that address children and research, namely the National Commission's *Report and Recommendations on Research Involving Children*; 3) discuss the Roman Catholic position including the theological underpinnings regarding the use of children as research subjects. The paper will also include a discussion of some of the critical disputes during the Commission's deliberations including defining minimal risk and the wisdom of subjecting children to nontherapeutic research. Finally, I will present a case study based on the research of Duchenne Muscular Dystrophy illustrating the importance and relevance of the Commission's work in the 1970s to the regulation of research today. Special emphasis will be placed on Recommendations #2 and #4 of the Commission since these speak directly to the case to be studied.

Research is a formal investigation designed to develop or contribute to generalizable knowledge, and is generally defined by the subject. (National Commission, 1977, xx) Therapeutic research involves studies that are designed to aid subjects that have a specific disease. Nontherapeutic research is defined as research that may not help individual patients but will add to generalizable knowledge. Research conducted on normal subjects is also, for the most part, nontherapeutic.

### **Physician as Both Clinician and Researcher**

I would like to say a word about the continuing problem of unbiased researchers performing appropriate research on appropriate subjects, including vulnerable populations. Traditionally, there has been a tension between the physician as clinician and the physician as researcher, since the goals of each role differ. Research is designed primarily to generate or validate new knowledge while clinical practice is geared toward enhancing the patient's well being. For example, a clinician might want to treat a young patient with acute leukemia with an experimental chemotherapeutic agent that had great promise in

combating the loss of normal red blood cells and save the child's life. That same physician, however, as researcher, is probably focused on the results of the trial on the whole population of leukemic children when assessing a research protocol for that drug therapy. This tension was brought to national prominence in the National Surgical Adjuvant Breast Study in which data were fraudulently entered, and potential subjects were coerced to join the study by physicians who admittedly used their influence to obtain informed consent. (Mueller, 1995, 2404).

This duality of responsibility as caregiver and scientist is, in my view, a key element in any attempt to understand the origin and continuing need for vigilance within the medical community about human subjects and research. This understanding is essential so that the self-interest and likely economic gains by the scientist of any medical breakthroughs are not allowed to endanger or compromise the clinician's duties or the vulnerable patient's rights.

### **Protection of Human Subjects**

The codified history of protection for human subjects is a little over fifty years old. Since the medical atrocities in Nazi Germany during World War II, there have been progressively stringent guidelines and laws governing experimental research in the United States and throughout the world. The Nuremburg Code, the first of these guidelines, was the cornerstone for "informed, uncoerced, voluntary consent of the subject." (Grodin, 1988, 1391) However, the Nuremburg code excluded children by its "no consent-no research" language. (Kopelman, Loretta, *in* Reich, 1995, 361) Not until 1964, in the Helsinki Declaration were children recognized as acceptable subjects. The Helsinki Declaration restricted the use of children as research subjects to therapeutic research only, and required protection and surrogate decision-making if children were to be used for research. It was after this, during the 1970s, that guidelines were developed in the United States for children as research subjects.

At the level of ethical principles, guidelines developed in the United States to protect children as research subjects employed a risk/benefit approach. Michael Grodin, M.D., Director of Medical Ethics at Boston University's School of Medicine and Public Health,

characterizes the risk/benefit approach as one that allows research with children if it holds out direct benefit to them or does not place them at unwarranted risk of harm, discomfort or inconvenience. (Grodin, 1994, 31) These risk/benefit approaches balance the social utility of research with respect for and protection of children. The greater the risk of the research protocol, the more rigorous and elaborate the procedural protection for the children and consent requirements for the child and his or her parent/guardian. (Kopelman, Loretta, *in* Reich, 1995, 362)

### **History of Children and Research**

The history of children as research subjects is really a subset of the history of children in general. Children were considered chattel of their fathers until the mid-seventh century in England. In other words, they were considered property without rights. In fact, children were not considered individuals with specific needs nor were they cared for in earnest until the seventeenth century. Pediatric care at that time was considered beneath the dignity of physicians. (Grodin, 1988, 1389)

With the establishment of the American Society for the Prevention of Cruelty to Children by New York reformer Eldridge Thomas Gerry in 1874, mortality rates in children began to decrease, and pediatrics began in earnest. (Hawes and Hiner *in* Reich, 1995, 353) Hawes and Hiner summarize: "By the late 20th century virtually all advanced industrial countries...had made significant strides in reducing some of the threats to children's health and well-being." (Hawes and Hiner *in* Reich, 1995, 354) However, as children became healthier, they were used increasingly in research to try to remedy childhood illnesses with little or no regulation, control, safety studies, efficacy, or ethics.

Exposure of the now famous Willowbrook incident was, for some, the seminal event in the history of medical research on children. Willowbrook alerted physicians, ethicists, politicians, and the general public of the United States that something has to be done to protect vulnerable children from abuses by medical researchers. The Willowbrook State School on Staten Island, New York, was an institution that cared for severely mentally handicapped children. In fact, almost 80% of the children had IQs of less than 20. (Beauchamp

and Childress, 1983, 317) The population of children grew from 200 in the late 1940s to over 6,000 in 1963. These patients had serious disabilities including limited toilet training abilities. And as the population grew, so did the incidence of hepatitis.

The bacteria that causes infectious hepatitis can be found in the gastrointestinal tract, and is transmitted by contaminated hand -to-mouth contact. It was commonplace for newly admitted patients at Willowbrook to become infected with hepatitis within the first six to twelve months of their institutionalization. However, it should be noted that the strain of hepatitis contracted was described as mild when seen in children ages three to ten. (Beauchamp and Childress, 1983, 317)

In an attempt to study the disease process and develop more effective agents to abate the spread of the hepatitis, Dr. Saul Krugman and his associates conducted a number of studies beginning in the 1950s on Willowbrook patients. Some of the children in the study group of about 800 (out of 10,000 admissions to Willowbrook during that time frame) were artificially exposed to the Willowbrook strain of infectious hepatitis. The children's parents had given their consent. In fact, initially parents were either interviewed personally or by letter about the progress of their children. Wards of the state or children without parents were not included in the studies. It was considered a direct benefit of the study that the children who were exposed to hepatitis frequently developed immunity from hepatitis itself once they had contracted the mild "Willowbrook" form of the disease. The studies were reviewed and sanctioned by the regulatory agencies at the time. (Beauchamp and Childress, 1983, 318)

### **Response to Abuse of Subjects: The Belmont Report and the National Commission**

Ten years after the Beecher article, Congress passed PL 93-348, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Soon after, the Commission released the *Belmont Report* which supplied the foundational, ethical principles for all research on human subjects. These principles included respect for persons, beneficence and justice. (*Belmont Report*, 1978,4)

Respect for persons requires that the choices of autonomous individuals be respected. But some Commissioners like Robert Cooke (then President of Medical College of Pennsylvania) argued that the protection of individual autonomy via informed consent was not the vital issue in children since they are generally not autonomous until late childhood or adolescence. The real issue, he claimed, was the protection of the vulnerable – including children. (McCartney, 1978, 27) Consequently, the "dual aspect of respect for persons, that is preservation of individual autonomy, and protection of the defenseless" were both developed by the Commission in the *Belmont Report*. (McCartney, 1978, 27) That report states that respect for persons incorporates at least two basic ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. (*Belmont Report*, 1978, 4)

The National Commission discussed the issue of diminished autonomy and diminished capacity to consent – and the need to develop mechanisms to protect these vulnerable and/or nonautonomous populations like children. Cooke and Robert Turtle, a Washington, D.C. lawyer, argued for involvement of the entire family unit and the importance of parents in decision making for their children. They contended that the involvement of the whole family in the research project would provide a protective mechanism for the child-subject. Further, they argued that "only children from loving families should be allowed to participate in research." (McCartney, 1978, 27) The concerns of Cooke and Turtle were recognized by the Commission in the recommendations that require parents to be witness to specific research so that they could act on their child's behalf, if necessary. (McCartney, 1978, 27)

Commissioner Patricia King, Georgetown University Law Center, argued for a "sliding scale from nonautonomy to full autonomy". (McCartney, 1978, 27) Recognizing King's argument, the Commission required children over age seven to give their own assent to participation in research and recognized the objection of a child to participation as binding "unless the intervention holds out a prospect of direct benefit to the child and is available only in the context of research. (McCartney, 1978, 27)

The Commission was careful about the language it used to

describe informed consent. The Commissioners opted to use the word "permission" to describe parental consent because it clarified that the parents were acting as the "loving protectors and providers of their children" not as agents offering proxy consent (consent on behalf of someone else). (McCartney, 1978, 27) This step was taken to avoid difficulties that had arisen in the past when parents were viewed as proxies for their children. (McCartney, 1978, 27)

Beneficence, the second principle, requires both the provision of benefit and the avoidance of harm. This principle is applied to research in several ways. The promotion of health is a benefit of research because it improves methods to prevent or treat disease or an abnormal condition and serves to foster optimal growth and development. In addition, children can benefit from research that looks at the nature of childhood disorders, some precursors of adult disorders, and the normal physiological, psychological and social development of children. Children may benefit from this research as individuals or as a class. (National Commission, 1977, 123)

It is this ethical principle that resulted in the most difficult decision making for the Commission. Basic differences and disagreements among the Commissioners arose about the importance and scope of this principle. In particular, the difference between therapeutic (holds the prospect of directly benefitting the patient) and nontherapeutic (does not hold the prospect of directly benefitting the patient) research and its justification with children was a central issue for the Commissioners. (McCartney, 1978, 28)

The imperative for researchers to "do no harm", the other side of beneficence, is equally important in the evaluation of research on children. Avoidance of harm or nonmaleficence requires that "risk to human subjects be reduced or eliminated in the actual conduct of research". Avoidance of harm may serve as justification for research designs that evaluate the efficacy and safety of Procedures already in standard practice. (National Commission, 1977, 124) In addition, research might be justified because it avoids harm that might result from the application of inappropriate routine practices. For example, a standard medical procedure might be dangerous if not adapted for the special physiology of children and infants (i.e., oxygen levels, fluid requirements).

The third principle of the *Belmont Report* is justice or a fair



distribution of the burdens and benefits in a given population. In a research context, this principle requires that the burdens of being involved in research are fairly distributed and that the benefits produced by the research are fairly allocated.

Two dangers of injustice mentioned in the National Commission's *Report and Recommendations on Research Involving Children* are: overutilization of some groups of children because they are readily available (i.e., orphans); and the danger of using children too soon in certain studies in which animal studies, older children, or adults could be used with less risk and better allocation of that risk. (National Commission, 1977, 132)

The actual implementation of these principles procedurally included the establishment of the following: 1) evidence of informed consent or surrogate's consent prior to the onset of research protocols; 2) measurement of risk and assessment of benefit for protocols; and 3) consideration of fair procedures and outcomes in the selection of research subjects.

Peer review boards or what became known as Institutional Review Boards (IRBs) were established as an outcome of the *Belmont Report*. These bodies were charged with ensuring that research is conducted according to the principles set down by the report in each and every federally-funded research institution in the country.

Some critics consider the peer review process developed for current IRBs to be faulty because the system is built on a paternalistic rather than an autonomy model. In other words, the IRBs make decisions of risk and benefits to the subjects independent of the subjects' consent and before the research has begun. IRBs, therefore, are "frontloaded". The local board is looking at the plans for the research and the intention of the researcher which some critics consider a loophole in the process. Arthur Caplan, Ph.D., Director of Bioethics at the University of Pennsylvania, in discussing the pros and cons of the current system of regulation, notes that there might be reason to revise the process so that a procedure or protocol can be assessed while it is in progress, as its data is coming in to see what is happening and what patient outcomes are developing. Says Caplan, "Right now, IRBs don't look at corpses." (Caplan, 1995)

In any case, it is the principles developed in the *Belmont Report* that provided the essential underpinnings for ethical research practices

in children in the United States. In 1978, using the three principles developed in the Report, the National Commission issued actual regulations for children in a document entitled *Report and Recommendations: Research Involving Children*. The Commission set out to basically answer two questions: 1) under what conditions is the participation of children in research ethically acceptable? and, 2) under what conditions may such participation be authorized by the subjects and their parents? (National Commission, 1977, iii)

### **Commission Recommendations and Deliberations**

The National Commission deliberations concluded in the issuance of ten recommendations designed to protect children who might be involved in medical research (See Appendix for text of the ten recommendations.). The Commissioners spent a good deal of time determining the degree and circumstances in which children could be subjected to research protocols. The debates included focus on the principles established by the *Belmont Report*, namely 1) respect for persons, especially protection of vulnerable populations; 2) beneficence; and 3) justice. (McCartney, 1978)

Informed consent is the practical outcome or guideline designed to assure respect for persons. It is, of course, the standard for research protocols involving adults. But the doctrine of informed consent is not applicable to those who cannot decide due to their age (or diminished capacity in the case of adults). So, the protection of the vulnerable and the preservation of individual autonomy were addressed by the Commission in their insistence on parental permission prior to research participation by children *and* assent of children to the degree their age allows.

The second principle from the *Belmont Report*, beneficence, was considered the most difficult to apply to children and the most problematic to the Commission. (McCartney, 1978, 27) The words "therapeutic" and "nontherapeutic" were not used by the Commission. Rather, they used language that related to the benefit to the child – "direct" or "indirect". Requirements for conducting beneficial research included stipulations that the research risks must be justified by the anticipated benefits, the anticipated benefits relative to the risk must be

as favorable to the children as other approaches, and there must be assent of the children and permission from the parents.

### **Minimal Risk**

Minimal risk can be considered a part of the beneficence principle because this principle supports the need for a minimum standard to determine the safety of the research to the child subject. In other words, it was relatively easy for the Commissioners to decide to allow research that would help a child (therapeutic research). But it was not easy to determine how much risk to allow within the research protocol and still maintain the benefit originally intended. Benefit must outweigh risk to protect the subject. So determining minimal risk was essential.

The question of minimal risk was discussed vigorously by the Commission. The discussion ranged from Commissioners arguing for minimal risk to mean a "mere inconvenience" to those arguing for a definition that defines minimal as "that which does not involve any risks to children greater than those normally encountered in their daily lives." (McCartney, 1978, 29) Robert E. Cooke urged the use of minimal risk as the barrier to allowable research. However, he did not believe that minimal could be defined as anything "normally encountered in daily life" because it did not allow for variations in circumstances. So, for example, normal for a healthy child would be different than normal for a leukemic child. (McCartney, 1978, 29)

Cooke did not prevail, and the Commission defined minimal risk in what many critics consider a narrow manner. Minimal risk is defined by the Commission as the "probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children." (National Commission, 1977, xx) Critics claim that the Commission did not adopt a definition broad enough for peer review boards to adapt their approval to different situations but instead created confusion for IRBs. (McCartney, 1978, 30)

Research that was without benefit to the child and involved more than minimal risk was initially going to be banned by the

Commission. But the Commission was concerned that since they had such a narrow definition of minimal risk and had already adopted a national review board procedure to handle cases that did not apply to their definition, that they needed to offer some guidance so that an inordinate number of cases did not end up requiring national evaluation.

Donald Seldin, professor of internal medicine at the University of Texas, argued for a recommendation that would allow research that carried a minor increase over minimal risk even without guarantee of direct benefit to the subject. Cooke argued against Seldin's recommendation because he was concerned that some children could be harmed "for the benefit of others." (McCartney, 1978, 30) The outcome was Recommendation #5, the most controversial of all the recommendations, which offers conditions in which research can be conducted on children even without direct benefit for the subject and with a "minor increase over minimal risk." Cooke, along with Turtle, cast dissenting votes. (McCartney, 1978, 30)

The National Commission recommendations and subsequent federal regulations on minors issued in 1983 by the Department of Health and Human Services (DHHS) outlined categories of minimal risk for children to be used by the IRBs. The categories outlining minimal risk adopted by HHS were the same "sliding scale" categories offered by the National Commission. The four categories, moving from the least perilous risk to children to the most dangerous risk, include studies that 1) involve *no more than* minimum risk with the prospect of direct benefit to the child; 2) involve *more than* minimal risk with the benefit directly to the child; 3) involve *more than minimum risk with no benefit* to the child – but the possibility of generalizable knowledge; and 4) research designed to "lead to the understanding, prevention or alleviation of a serious problem." (Grodin, 1994, 123)

The risk/benefit approach that weighs risk against gain rather than precluding any research with children involving risk has spawned many critics. Key terms used by the Commission are considered vaguely defined. Interpretations vary as to the acceptability of risks that could bring harm to children and the essential elements of a benefit are debatable. (Grodin, 1994, 124) Loretta Kopelman describes the problems created as "particularly difficult with the pivotal terms 'minimal risk' and 'minor increase over minimal risk'." Problems

include: vagueness of the term minimal risk (What is the baseline for everyday hazards?); lack of guidance about the assessment of psychosocial risks such as labeling or invasion of privacy; and lack of definition of the upper limit of "minor risk over minimal" which makes it difficult for local boards (IRBs) to know what they can and cannot approve. (Kopelman *in* Reich, 1994, 362)

Clearly, this is a serious problem for IRBs, ethicists, and researchers themselves. The policies that were established for children were intended to protect them and promote their well-being. However, critics say it is difficult to determine when research involving children can be permitted. On the one hand, if research is not conducted using children, then they will not benefit from the advances science makes possible. On the other hand, if children are used as experimental subjects, vulnerable individuals, who need protection, risk possible harm. The Commission's position and, consequently, the recommendations, are considered moderate. James McCartney, Ph.D., in reviewing the recommendations, says that moderation is not by accident but reflects the intention of the Commission to "go on record as emphasizing that scientific research is important and can in most cases be performed ethically." (McCartney, 1978, 31)

The third area outlined by the *Belmont Report* is justice. When the National Commission dealt with this ethical principle, it required distributive justice. That is, the Commission required that children-subjects be selected equitably among the possible research participants. Attention to this principle ensured that administrative ease and/or the availability of a population with certain conditions or socioeconomic characteristics would not unduly burden a given group. (See Recommendation #2, Appendix) The burdens and benefits were to be shared between all groups. (McCartney, 1978, 30) In addition to a specific mention in Recommendation #2, the commission reiterated this principle in Recommendations 9 and 10, which deal with specific vulnerable populations. (See Appendix)

The principle of justice was one of the principles raised in relation to Recommendation #5, which has already been identified in this paper as the most problematic of the ten recommendations. Robert Turtle argued against the use of sick children for experiments that would require risk above the minimum. His concern is that a child "becomes accustomed to certain types of medical interventions because

of an illness, [but] it is unjust to utilize these techniques on the child in the context of research when there is little or no chance of benefitting that...child." (McCartney, 1978, 30). But the recommendation remained vague in its final form, and Turtle's objections were not heeded with specific language that might have protected sick children.

### **Roman Catholic View on Human Life and Experimentation**

The ethical principles identified by the *Belmont Report* (and the recommendations that followed) are examples of one way that public policy is developed in the United States. Morality, or the rightness or wrongness of conduct, is both distinct from and related to public policy, argues moral theologian Richard McCormick. (McCormick, 1981, 72) These two concepts are related because public policy "has an inherently moral character due to its rootage in existential human ends (goods)." He adds: "The common good of all persons cannot be unrelated to what is judged to be promotive or destructive to the individual – in other words, judged to be moral or immoral." (McCormick, 1981, 72)

While morality does not have to have religious roots, religious traditions, Christian or otherwise, have developed moral arguments based on their theological viewpoints. Roman Catholic and Reformation Protestant theological viewpoints obviously differ. It is important to consider briefly the distinction between those two views and some models of ethics in order to understand the arguments about research and children presented in this paper.

Traditional Roman Catholic moral theology is grounded in natural law. Thomas Aquinas, in his development of natural law, argues that human beings are basically good because they were created in the image and likeness of God or *Imago Dei*. (Scanlon, 1995) Because of this likeness, Aquinas argues that women and men have the ability to reason by which they can discern what God wants. This view suggests that Christians find a common ethical wisdom and knowledge not just in the scriptures or in Jesus Christ but also in human nature and human reason. Further, insistence on the goodness of the natural and the human, with its corollary that grace builds on nature and is not opposed to nature, stands as a hallmark of the Catholic theological tradition. (Curran, 1985,6) Thomas' view is considered an example of

a teleological model. That is, he views the ethical life in terms of the goal or end to be achieved. (Curran, 1985, 5) The Roman Catholic world is a moral world where persons know the difference between right and wrong by virtue of natural law.

In contrast, the characteristic Protestant view of the world and personhood is grounded traditionally in Augustinian theology. That is, persons are flawed by original sin and this permeates both the natural and the supernatural. Therefore, reform by humankind would always be suspect and should not be expected because of our seriously flawed nature. (Curran, 1995) An example of the differences in these two contrasting views in relation to children in research is presented in the next section of this paper. Paul Ramsey, Reformation Protestant, and Richard McCormick, Roman Catholic, debate the morality of using children as subjects for nontherapeutic research, that is, research that will not directly benefit them.

Ethical models provide a framework for systematic reflection, and in the case of moral theology, "the model in view of which one understands the Christian life." (Curran, 1985, 12) Traditionally, according to moral theologian Charles Curran, there have been three ethical models proposed in the literature: teleology, mentioned above in relation to Aquinas, deontology, and relationality/responsibility. Curran proposes that the relationality/responsibility model be considered the primary Catholic Christian ethical model. (Curran, 1985, 11) The relationality/responsibility ethical model "views the moral life primarily in terms of the person's multiple relationships with God, neighbor, world, and self and the subject's actions in this context." (Curran, 1985, 12)

Curran gives several reasons for the primacy of his model over teleology, based on the ends and purposes, or deontology, based on law, obligation and duty. Curran cites scripture as rationale because, he notes, new studies indicate that the primary ethical concept of the Old Testament was not the law but the covenant. The New Testament emphasizes love, and therefore, is arguably relationally focussed. Curran describes the teleological model as open to historicity, personalism, and the importance of the subject, but, he argues is not primary as a model because "one does not have as much control over one's life as this model supposes." (Curran, 1985, 13)

Curran further explains the relationality/responsibility model in

terms of its negative understanding, the problem of sin. He describes the deontological definition of sin as an act against the law of God. A teleological definition of sin views the sins as going against God. Yet, Curran claims, the scriptures describe sin, beginning with Genesis, in terms of our relationship with God, neighbor, the world, and self. So, serious (or mortal) sin is not primarily an act against the law of God (deontology) or going against the ultimate end (teleology), but a breaking of one's fourfold relationship of love with God, neighbor, world, and self.

Virtues refer to the different attitudes and dispositions that should be present and direct the way in which that person acts. (Curran, 1985, 76) The traditional virtues, faith, hope, and charity as well as others such as justice and fortitude are understood to affect the person in all of his or her multiple relationships. Deepening the relationships, claims Curran, with God, neighbor, world and self and the virtues which direct these relationships constitute the growth and continual conversion of the person. So, a person has opportunity to grow in virtue through his or her participation/relational involvement in the world.

### **Is Nontherapeutic Research on Children Acceptable? (Ramsey vs. McCormick)**

Paul Ramsey and Richard McCormick argued both sides of the ethics of children participating in research that might not help them directly – in fact, research protocols that could make them worse. McCormick defends his view using a relationality/responsibility model, while Ramsey pursues a deontological approach. McCormick, a Roman Catholic, sees the possibilities of transcendence (since humankind knows innately the right thing to do via natural law) through helping one's neighbor. Ramsey, Reformation Protestant, views men and women as fallen, and is less ready than McCormick to give people power over the vulnerable because the people are flawed.

In "Proxy Consent in the Experimental Situation", Richard McCormick, moral theologian and teacher of health care ethics, presented a view in favor of children participating in research even if the research would not directly affect them. His position was argued using the relationality/responsibility model. McCormick argued that



nontherapeutic research on children is ethically defensible if it involves minimal risk and holds the prospect of benefitting children as a group. In fact, McCormick believes that children *and* adults are capable of – and obligated to – volunteer on behalf of the community. McCormick would suggest that children would (if they could) want to do the right thing, become better by participation (more virtuous) and participate in the good of all humankind.

McCormick views parents in this case as appropriate surrogates for deciding on behalf of their children. In fact, he sees parents as capable and entitled to make a substituted judgement, and in keeping with his view of the ethical life as relational/virtue based, agreeing to have your child participate with the community (assuming minimal risk) is a good. McCormick argues that "there are basic values that define our potential as human beings that we ought to choose, support, and never directly suppress. [By these] values we can know what others would choose (up to a point) because they ought." (McCormick, 1974, 471)

In response to McCormick's view, Ramsey argued that the end never justifies the means and that the ethical principle of respect for the person always prevails. He holds that children should never be considered eligible for research that will not benefit them and that if parents or surrogates consent on the child's behalf to such nontherapeutic research, they are breaching their fiduciary duty to the child. It is on the basis of the lack of respect for the dignity of the person, self-determination, that Ramsey bases his argument not merely the exposure to possible risk that the consent might allow. (National Commission, 1977, 95)

In his article, "The Enforcement of Morals: Nontherapeutic Research on Children", Ramsey argues that the person offering the proxy consent has no right to expose a ward to any risk. He goes further, arguing that there must be "complete and informed consent for any and all nontherapeutic research." (Ramsey, 1976, 476) Since informed consent is not possible in children, protocols recruiting children for nontherapeutic research is unacceptable. Ramsey concludes by suggesting that McCormick's relational ethic can never outweigh the risk of possible harm and inherent use of children as a means to an end that they have not agreed to – and that guardians cannot presume to agree to on behalf of their ward.

## **Recommendations 2 and 4**

Recommendation #2 of the Commission sets forth general conditions applicable to all research involving children. The recommendation has five main conditions: 1) research must be scientifically sound; 2) studies must first be done on animals and adult humans, then older children before involvement of infants; 3) risks must be minimized by using the safest procedures available with a sound research design and by using procedures performed for diagnostic or treatment purposes as feasible; 4) researchers must make adequate provision to protect the privacy of children and their parents, and maintain confidentiality of information; and 5) subjects must be selected in an equitable manner. The sixth condition of the recommendation requires that all of the other recommendations' conditions within the report be satisfied. (National Commission, 1977, 3) (See Appendix.)

Recommendation #4 speaks to therapeutic research or research that promises the likelihood of direct benefit to the child-subject but has greater than minimal risk. This recommendation states that if there is more than minimal risk and direct benefit, the IRB must determine that

1) the risk is justified by the expected benefit; 2) the risk/benefit ratio is as favorable to the subjects as alternatives; 3) consent/assent of children and permission/consent by parents is provided for; and 4) conditions of recommendation #2 are met.

In the case study below, I will illustrate ways in which both of these recommendations have been violated in the case of the child-subjects whose parents have consented to their participation in the study group.

### **Case Study on Duchenne Muscular Dystrophy**

Duchenne Muscular Dystrophy (DMD) is a genetic disease affecting boys that makes them unable to produce the protein dystrophin which is a necessary component of muscle fiber function. Eventually, the repair capacity is exhausted and the muscle dies. In most cases, Duchenne forces boys into wheelchairs by the age of ten, due to muscle weakness. Since Duchenne Muscular Dystrophy is a progressive

disease, it first attacks skeletal muscles in the extremities at age two or three, then begins to affect the functioning of brain tissue, and smooth muscle like cardiac and bronchial tissue. Often, by early adulthood, death occurs as a result of heart or respiratory failure. According to the Muscular Dystrophy Association, about 30,000 boys are born with the disease annually in the United States. (Thompson, 1992, 472)

Research efforts to cure this disease that affects, and eventually kills, children have been the subject of a great deal of attention in the past five years. Neuromuscular physiologists and physicians were encouraged by the results of cell transplant, a form of gene therapy, on animals. Consequently, researchers presented protocols for human research on children with DMD to their respective IRBs.

Protocols for cell transplant or myoblast transfer vary. But basically, the process calls for placing several eraser-sized plugs or otherwise injected forms of dystrophin-containing tissue into the skeletal muscle (upper arms or upper legs) of the child under general anesthesia. The children are given immunosuppressive therapy for up to six months after the procedure so that they will not reject the transplants. In most cases, the children act as their own double blind control. That is, one arm or leg is used for actual transplant, the other is treated with a placebo control that simulates the actual transplant.

Theoretically, (and promising in some animal studies) the dystrophin from the transplanted myoblast cells will fuse with the deficient cells and eventually the amount of dystrophin will increase, causing an increase of muscle function which researchers measure by muscle strength techniques. However, the results of the published studies of myoblast transfer on children with DMD were poor. (Mendell, 1995, 832)

In response to the lack of success of the trials, a group of 25 muscle researchers called for a moratorium on the continuation of all myoblast transfer experiments in humans. The open letter, published in *Science* in the summer of 1992, asserted that the myoblast transfer failed to improve clinical status. The letter argued a classic risk/benefit rationale for the cessation of such study. Since there was no apparent benefit to the subjects, there could be no further support to risk the negative effects of general anesthesia or immunosuppression. The researchers encouraged further animal studies to work out research problems before children with DMD were again used for myoblast

transfer research. (Thompson, 1992, 738)

Since its appearance in *Science* in 1992, many ethicists and researchers have supported the moratorium letter. One of the few who disagree with the position of the letter is Peter Law, Ph.D., the researcher who has done the pioneering work with myoblast transfer and MD children. Law does not want to be confined by IRBs nor is he interested in going back to the lab to refine protocols on animal studies. (Thompson, 1992, 472)

One could argue that Dr. Law is interested in research without interference, perhaps to the detriment of his patients. Law left the University of Tennessee (where he was full professor) and started his own foundation in Memphis, the Cell Therapy Research Foundation. Law explains that "it took too long for experiments to be cleared by the university's IRB and [I] feared the 'excessive review' would unduly delay [the] next set of human studies." (Thompson, 1992, 472) Because Law's foundation is private, the IRB process is not mandatory. However, Law has a peer review board, the members of which he refuses to identify.

In addition to his interest in no external control of his studies, critics question his methodology. In fact, there are even allegations of deliberately vague or incompletely reported data. (Cho, 1995, 7) Amidst the controversy, some cell transfer researchers still plan to continue experiments including trials on even younger children using potentially toxic enzymes during the myoblast transfer process to boost efficacy data. (Cho, 1994, 13)

This case illustrates perfectly the importance of *Belmont Report* principles and subsequent recommendations. What are the ethical issues here? Are any of the recommendations violated by Dr. Law and others in this case study?

Few of the Commission standards are met according to ethicist Mildred Cho, Ph.D., University of Pennsylvania. Dr. Cho, whose background is in both cell biology and bioethics, argues that continuation of the trials is unethical for several reasons that relate to Recommendations #2 and #4 of the National Commission Recommendations. The risk/benefit ratio weighs in on the side of too much risk, violating the first condition of recommendation #4. Cho states that trials planned using younger children as well as the risk of more toxicity render currently proposed protocols unacceptable and in

violation of Recommendations #2 (second condition) and #4 (first and second conditions). In addition, Cho questions the research because children with DMD are not subjected to immunosuppression, general anesthesia or multiple injections in the course of their medical treatment for the disorder – another violation of the second condition of Recommendation #4. (Cho, 1994, 13)

There is little question among researchers about the importance of gene therapy in the cure of DMD. (Leiden, 1995, 871) However, Cho and Leiden both contend that the area of gene therapy is in its infancy and needs to be scrutinized carefully even if morbid diseases are at stake. (Cho, 1995, 7; Leiden, 1995, 871) Protocols must meet ethical research standards. Cho suggests that myoblast transfer is "too premature to be performed on humans." And further, that the research should have been done on older children and adults with the disease before the younger children were involved. (Cho, 1995, 7) This puts the research in violation of Recommendation #2.

Cho asserts that research protocol guidelines were violated at the beginning of any DMD research on children since there are adults with DMD surviving, and another population of adults with a similar disorder, Becker's muscular dystrophy, who could have been subjects for efficacy studies that can be toxic. At least adults could consent to the added risk – and are less vulnerable physiologically than children to therapies that alter major organs and therefore are less prone to toxicity. (Cho, 1994, 14) This assertion suggests that the study design was faulty from the start, and in violation of the condition of Recommendation #2 requiring scientific soundness and significance.

The answer to the questions raised about the cell therapy research of Dr. Law and others seems clear. The research is too risky for children based on the evidence that has been collected by the research studies done on children with DMD in the past five years. Some would say the original design and methodology is ethically questionable as well. The protocol is probably of little or no direct benefit based on study results to date. In fact, the research may be too risky for humans, or at least for young humans, until the toxicity issues have been resolved either in the lab or by conducting very carefully controlled human studies, possible with Becker's MD patients. Recommendations #2 and #4 have clearly been violated by this protocol. But what are the underlying principles that support no more

research? Certainly the *Belmont Report* principles: respect for vulnerable populations (persons), beneficence and justice all are key elements in this case. But the principle that is violated most clearly, it seems to the author, is beneficence (obligation to "do no harm" and minimize risk and maximize benefit). (National Commission, 1978, 6) It appears it was unnecessary to use this particular group of MD patients for the initial testing, premature to begin testing humans at all, and questionable to consider risking anesthesia and immunosuppression at this early stage of study. All of these threatened to harm the child-subjects and did not adequately seem to minimize risk to the subjects.

### Summary

This research paper began asking the wisdom of research for children if there is some risk involved in the trial, the government's role, and the theological viewpoint regarding ethical guidelines. The guidelines developed for child-subjects based on the ethical principles of the *Belmont Report* support the participation of children in research protocols – even with some risk – as long as the research is of direct benefit. Nontherapeutic research and research with more than minimal risk, as we have seen, require more protection – and specific conditions. Children are protected but parents/guardians and researchers are given important roles in deciding risk and consenting on behalf of the child. So, the adults must ultimately act in a way that will protect the vulnerable.

One could argue, I think, that a more "Catholic" view of humankind, using a framework that relied on the parents and researchers to act responsibly, undergirded some of the Commission's work. The ambiguity of definitions like minimal risk was, by the Commission's own admission, intended to put the onus on the accountability of the adults involved in the research milieu. The Commission states that the "ultimate children's right is the obligation that adults have to protect and nurture children. It is the role of adults to ensure that children are not subjected to unnecessary or excessive risks or discomfort. Such protection can only come from adults who control research with children..." (National Commission, 1977, 128) The Commission, to their credit, called on the community to "do the good."

## Appendix

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

#### Recommendation (1)

Since the Commission finds that research involving children is important for the health and well-being of all children and can be conducted in an ethical manner, the Commission recommends that such research be conducted and supported, subject to the conditions set forth in the following recommendations.

#### Recommendation (2)

Research involving children may be conducted or supported provided an Institutional Review Board has determined that (A) the research is scientifically sound and significant; (B) where appropriate, studies have been conducted first on animals and adult humans, then on older children, prior to involving infants; (C) risks are minimized by using the safest procedures consistent with sound research design and by using procedures performed for diagnostic or treatment purposes whenever feasible; (D) adequate provisions are made to protect the privacy of children and their parents, and to maintain confidentiality of data; (E) subjects will be selected in an equitable manner; and (F) the conditions of all applicable subsequent recommendations are met.

#### Recommendation (3)

Research that does not involve greater than minimal risk to children may be conducted or supported provided an Institutional Review Board has determined that : (A) the conditions of Recommendation (2) are met; and (B) adequate provisions are made for assent of the children and permission of their parents or guardians, as set forth in Recommendations (7) and (8).

#### Recommendation (4)

Research in which more than minimal risk to children is presented by

an intervention that holds out the prospect of direct benefit for the individual subjects, or by a monitoring procedure required for the well-being of the subjects, may be conducted or supported provided an Institutional Review Board has determined that:

- (A) Such risk is justified by the anticipated benefit to the subjects;
- (B) The relation of anticipated benefit to such risk is at least as favorable to the subjects as that presented by available alternative approaches;
- (C) The conditions of Recommendation (2) are met; and
- (D) Adequate provisions are made for assent of the children and permission of their parents or guardians, as set forth in Recommendations (7) and (8).

#### Recommendation (5)

Research in which more than minimal risk to children is presented by an intervention that does not hold out the prospect of direct benefit for the individual subjects, or by a monitoring procedure not required for the well-being of the subjects, may be conducted or supported provided an Institutional Review Board has determined that:

- (A) Such risk represents a minor increase over minimal risk;
- (B) Such intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, psychological or social situations, and is likely to yield generalizable knowledge about the subjects' disorder or condition;
- (C) The anticipated knowledge is of vital importance for understanding or amelioration of the subjects' disorder or condition;
- (D) The conditions of Recommendation (2) are met; and
- (E) Adequate provisions are made for assent of the children and permission of their parents or guardians, as set forth in Recommendations (7) and (8).

#### Recommendation (6)

Research that cannot be approved by an Institutional Review Board



under Recommendations (3), (4), and (5), as applicable, may be conducted or supported provided an Institutional Review Board has determined that the research presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children and, in addition, a national ethical advisory board and, following opportunity for public review and comment, the secretary of the responsible federal department (or highest official of the responsible federal agency) have determined either (A) that the research satisfies the conditions of Recommendations (3), (4), and (5), as applicable, or (B) the following:

- (I) The research presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children;
- (II) The conduct of the research would not violate the principles of respect for persons, beneficence and justice;
- (III) The conditions of Recommendation (2) are met; and
- (IV) Adequate provisions are made for assent of the children and permission of their parents or guardians, as set forth in Recommendations (7) and (8).

#### Recommendation (7)

In addition to the determinations required under the foregoing recommendations, as applicable, the Institutional Review Board should determine that adequate provisions are made for: (A) soliciting the assent of the children (when capable) and the permission of their parents or guardians; and, when appropriate, (B) monitoring the solicitation of assent and permission, and involving at least one parent or guardian in the conduct of the research. A child's objection to participation in research should be binding unless the intervention holds out a prospect of direct benefit that is important to the health or well-being of the child and is available only in the context of the research.

#### Recommendation (8)

If the Institutional Review Board determines that a research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects, it may waive such requirement provided an appropriate

mechanism for protecting the children who will participate as subjects in the research is substituted. The choice of an appropriate mechanism should depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, status and condition.

#### Recommendation (9)

Children who are wards of the state should not be included in research approved under Recommendations (5) or (6) unless such research is: (A) related to their status as orphans, abandoned children, and the like; or (B) conducted in a school or similar group setting in which the majority of children involved as subjects are not wards of the state. If such research is approved, the Institutional Review Board should require that an advocate for each child be appointed, with an opportunity to intercede that would normally be provided by parents.

#### Recommendation (10)

Children who reside in institutions for the mentally infirm or who are confined in correctional facilities should participate in research only if the conditions regarding research on the institutionalized mentally infirm or on prisoners (as applicable) are fulfilled in addition to the conditions set forth herein.

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