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ETHICS IN PEDIATRIC RESEARCH*

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Ethics, a vital component of medical practice ever since Hippocrates drafted his code almost 2500 years ago, has become a particularly crucial issue because of the great strides in medical science and technology that have been witnessed during our century – as research became an important component of our work.

In the case of adults, the consent of the patient is required whenever research is undertaken. But what makes moral dilemmas particularly difficult in the pediatric setting is the child's inability to weigh the options and risks often connected with medical matters, and to make free and informed decisions. Thus, the awesome responsibility for what are sometimes irrevocable decisions must be shifted onto others. Decisions of such magnitude are always painful, but when they must be made on someone else's behalf, they can be excruciating. Consider, for example, life-prolonging measures. An adult can decide for himself to discontinue such measures if the pain and discomfort are such that his life becomes meaningless. But how do you decide for someone else? And what about organ transplants? What happens when a child's very life depends on receiving the kidney of a sibling too young to provide "informed" consent?

İt is this issue of "informed" consent that makes research using children as subjects fraught with ethical problems. No one questions the benefits of such research on medical grounds. We are all well familiar with the immense successes of medical research – virtual eradication of smallpox in our world; elimination for all practical purposes in the industrialized countries of tetanus, diphtheria, poliomyelitis, measles, and infantile gastroenteritis, leading causes of child mortality and morbidity; the discovery of a simple and effective (though unfortunately inadequately implemented) treatment for diarrhea – still the foremost cause of death among children in the developing world.

Research has led to significant progress in treating certain forms of cancer as well as leukemia and osteosarcoma. In Wilms's tumor, the survival rate has been pushed from zero to about 90 percent over the past half century.

We also know that the use of adult subjects in research on diseases of children is inappropriate, as data obtained on adults cannot be extrapolated to children because of important pharmacologic differences in absorption, distribution, and

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metabolism, essential differences in fluid and electrolyte requirements, and because the factor of growth and development is vulnerable to toxic action. Attempts to modify adult dosages to suit children based on body weight and surface area are not always effective and have sometimes proved fatal.

But even if gains from a *medical* standpoint are indisputable, is it *ethical* to use uncomprehending young children – children incompetent to consent – in research that may conceivably put them at risk? Do parents have the right to enlist their child in an activity, no matter how praiseworthy, that may jeopardize him? Does this not constitute a *breach* of parental duty to protect? How can we reconcile the seeming contradiction of medical research's duty to vanquish disease on the one hand, with the moral imperative to protect to the utmost each individual child patient on the other? Stated differently, how can we reconcile the potential future good for many against a possible risk for a few?

Before proceeding further, let us distinguish between therapeutic reseach (undertaken in the course of treatment for the direct benefit of the subject) and non-therapeutic research (where benefits, if any, are long-term and would accrue to others). In the first case, greater risk may be justified by the potential benefit, particularly when all other treatment possibilities have been exhausted. There is broad consensus concerning the moral validity of this research, despite the absence of "informed" consent. It is the second case that raises the ethical questions, and it is this case that shall engage our attention.

It is in the nature of ethics to stretch hypothetical situations to their outer limits, to pose alternatives as starkly as possible, in order to highlight the dilemmas and the awesome dimensions of the choices. But, in fact, non-therapeutic research covers a wide range of situations – from research on children with debilitating or fatal diseases who are themselves beyond cure, to the collection of baseline data on normal, healthy children. Much of non-therapeutic research is of a decidedly prosaic nature, involving simple procedures such as physical examinations, minor changes in diet, the recording of infant weights and measurements, monitoring feeding practices, non-invasive sample collections such as urine, feces, saliva.

Invasive sample collection, including blood, cerebrospinal fluid, biopsy tissue, is of course more problematical, although it seems to me that there is little legitimate cause for objecting to taking quantities slightly larger than required in routine procedures, or to taking samples during surgery, provided the research being undertaken aims at advancing the diagnosis or treatment of childhood diseases.

The point is that in assessing the ethical validity of non-therapeutic reseach, it is very important to have a very good idea of what the risks involved may be. Thre is always at least a hypothetical risk factor in research. The goal is to assess it as realistically as possible, and to weigh it against possible gains.

In this regard, I think we can dismiss arguments of so-called purists who consider unethical all research using children as subjects on the grounds that it violates their autonomy or integrity. Such an attitude, it seems to me, is absolutely self-defeating, indirectly penalizing the very children it claims to protect. Elimination of non-therapeutic research would make it impossible to control clinical testing of new procedures and drugs, which could actually harm children, by leading to the introduction of untested substances. The thalidomide tragedy, and the blinding of infants through excessive oxygen administration, are just two examples of disasters that could have been minimized by controlled clinical research. Further, the prohibition of research using child subjects would remove all hope for overcoming cancer, leukemia, and other diseases that continue to prey upon children.

For research using children as subjects, the standard practice is to recognize the right of the parent or guardian to decide on behalf of the child. Yet there are cases of abuse, and the parents may not fully comprehend the risks involved in the research. This is why the child's consent, wherever feasible, is increasingly becoming an essential requirement. In this regard, it seems absurd to lump together into one category all those who are legally classified as "children". Many of those who are children in the eyes of the law are by no means incompetent to consent.

For research involving infants and very young children, parental consent would be acceptable only after it had been established with reasonable certainty that the parent was responsible and fully committed to the child's well-being. The project and all attendant risks would have to be fully explained in laymen's terms to the parent by the research team.

For research projects involving those children who have reached an age at which they could reasonably be expected to make decisions, informed parental consent must be supplemented by the child's own consent, with the age at which this is possible varying with the individual child. It should be emphasized that consent does not mean seeking "rubber-stamp approval. "The researchers must explain fully, in terms appropriate to the subject's age, the reason for the research, its importance, and the procedures involved, inluding all possible discomforts and risks. If the child objects, his or her decision would be absolutely final.

These are some reflections on the topic of ethics in research on children. In many cases, a well-balanced ethics committee in a hospital has to make the final decision, especially in cases where the research procedures are invasive and not directly aimed at improving the child's own health.