Clinical Investigation in Children

Presidential Address to The Society for Pediatric Research^[8]

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The purposes of the Society for Pediatric Research are clearly and simply stated in the constitution and by-laws: 'To foster pediatric investigation and to provide an opportunity for younger men to present their work.'

As President of the Society it is my duty to comment upon and raise for discussion events and issues which may affect the realization of these purposes. In this context I believe it is fair to state that the questions which have been raised concerning clinical investigation involving human subjects have occupied the thoughts of our membership and, indeed, those of all members of the research community, to a greater degree, than any other single subject during the past year. It is this issue which I wish to discuss as it relates to pediatric research.

At the outset I believe that several generalizations, perhaps obvious, must be made:

1. It is our special task to serve children through science.

2. We, in this Society, have dual obligations as our name implies; first, those of pediatricians charged with responsibility for providing optimal treatment for each *individual* child placed in our care, and second, those of investigators charged with the responsibility and the duty of advancing medical knowledge for the benefit of *all* children through research.

3. We work with the full knowledge that the fruits of our labors, if they are ever to serve the purpose for which they were undertaken, namely, to benefit children, must at some point be tested *in* children, no matter how complete the preliminary evaluations in the test tube, in animals or in adults. And certainly it is easy to document instances where failures to realize this have resulted in tragedy.

4. We work with the full knowledge that those whom we serve, children, have no choice in the matter and are placed in our hands by third parties whose legal right to do so is at best only hazily defined.

Against this background, which has always characterized pediatrics as a special discipline, the statement of Public Health Service Policy, issued on February 8, 1966, had perhaps even greater impact on us than on our colleagues in other areas of clinical investigation:

'No new, renewal or continuation research or research training grant in support of clinical research and investigation involving human beings shall be awarded by the Public Health Service unless the grantee has indicated in the application the manner in which the grantee institution will provide prior review of the judgment of the principal investigator or program director by a committee of his institutional associates. This review should assure an independent determination: 1. of the rights and welfare of the individual or individuals involved; 2. of the appropriateness of the methods used to secure informed consent; 3. of the risks and potential medical benefits of the investigation.'

The responses to this statement were immediate and widespread, but by no means uniform. One type of response is epitomized by two quotations from a very recent issue of Perspectives in Biology and Medicine [4]:

'No physician-investigator with pride in the ethical standards of his practice could be thought paranoid when reacting defensively in today's climate. With the laudable purpose of protecting the citizen's rights, frightened federal administrators have promulgated rulings which apply selectively to patient-doctor relationships in clinical investigation. These regulations may well persuade so many physicians to abandon their careers as clinical investigators that the progress in some aspects of medical research will be seriously retarded.'

'The clinical investigator who considers his program and examines his motives in the darkness of his bedroom before falling asleep, looks into his own eyes when

shaving the next morning and into those of his colleagues and students at work, would not go far wrong. The Washington medical administrators either never had such experiences or have forgotten them.'

This type of reaction serves neither science nor society. It is the response of a self-righteous ostrich and indicates little realization of where we are or how we got here, and certainly offers no suggestion of where we are going and how we are to get there. The second quote is shockingly simplistic and disgracefully unfair.

It seems evident, I believe, that the government's action represents a response to today's climate and is certainly not the cause. The questions which have been raised are not the response to suddenly discovered, widespread abuses of the power which society has traditionally placed in the hands of the physician, nor are they selectively directed against science. They represent, as stated by WOLFENBERGER, among others, 'only one expression of broader current re-examination and formulation of the rights of the individual. Related expressions may be widespread interest in draft laws, civil rights, the right to privacy, compensation to victims of crime and the concern expressed by both the public and various professional and scientific bodies to update or establish professional codes of ethics in general [7].' As this general re-examination involves clinical investigation, there is little doubt that the central issue is that of consent.

The first of the current attempts at codification followed the Nuremberg trials and resulted in the ten point Nuremberg Code. Rule I of this code stated 'Voluntary consent of the subject is absolutely essential'. The remaining nine rules were concerned primarily with safeguarding the welfare of the subject by demanding careful preparatory study, exacting experimental design, skilled and qualified investigators and, particularly, the considered evaluation of risk as balanced against the importance of the anticipated results. There seems little doubt that the failure of any professional society officially to adopt the Nuremberg Code, stems not from any disagreement with the basic principles but rather from the great difficulties encountered in applying the first rule without simultaneously inhibiting scientific progress. For Rule I also defined the quality of consent in very specific terms as described below:

'Rule I. Voluntary consent of the subject is absolutely essential.

This means that the person involved should have the legal capacity to give consent, should be able to exercise full power of choice without the intervention of any element of force, fraud, deceit, over-reaching or other forms of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved so as to make an under-

standing and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration and purposes of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon health and person which may possibly come from his participation in the experiments [5]'

The dilemma which may confront even the most conscientious investigator attempting to apply these principles needs no documentation to this audience. Suffice it to state that the problems are so complex that some have seriously questioned whether any consent by a subject can ever be considered valid [2]. It is evident, too, that strict adherence to Rule I would preclude any investigation involving infants and children.

The Recommendations Guiding Doctors in Clinical Research, issued by the World Medical Association in 1964, and commonly known as the Declaration of Helsinki, sought to establish more workable rules, while still preserving the rights and welfare of the subjects. This Declaration distinguishes between the clinical research which is combined with patient care, and clinical research which is not for the immediate benefit of the subjects. In clinical research combined with patient care the Declaration of Helsinki states that *if at all possible* consistent with patient psychology the consent of the patient should be obtained. It thus recognizes that in the therapeutic situation there may be circumstances where the seeking of consent and the explanations which would have to accompany this might be detrimental to the patient. Further, it recognizes that in cases of legal or physical incapacity consent may need to be procured from a legal guardian. In non-therapeutic research the Declaration states that consent must be obtained, this consent freely given by individuals or their legal guardians who have been fully informed of what is being asked of them and what they are consenting to and who are in such mental, physical and legal state as to be able to exercise the power of choice.

The Declaration of Helsinki was officially adopted by this Society last year and also by most, if not all, of the other Societies representing clinical investigation in this country. However, it has been most evident in the past year that the public does not regard endorsement of these principles as constituting an adequate guarantee that the rights and welfare of individuals who are subjects in clinical investigation will be assured. It has become equally evident that additional guarantees will be demanded, and it is important for all to note that this will occur in a time when access to the highest quality of health care has also been defined

as a basic right, and when the President of the United States has urged that we accelerate the pace at which new medical advances are transferred from the laboratory to the bedside. Some proposals have already been made:

Dr. WILLIAM SILVERMAN seriously and sincerely proposed a means of providing help for parents who are, in his words, 'forced into the role of arbiters required to make exceptionally difficult judgments in situations which increase in complexity each day that our knowledge increases' [6]. Dr. SILVERMAN suggested that a physician other than the investigator, perhaps the family physician, assume the responsibility of acting to defend the patient's rights and personal welfare when an investigative procedure is proposed. He also suggested that the consent-giving responsibility be placed in the hands of this personal physician. In the same vein, but going, I believe, much beyond the intent of Dr. SILVERMAN's proposal, Dr. MICHAEL ALDERMAN, writing in *The New Republic* stated that 'no single individual should be required to play the role of both scientist and doctor' and recommended that 'it would be wise to interpose between subject and scientist another physician to serve as counselor before the experiment is begun, one who is exclusively concerned with the patient's welfare throughout the experiment' [1].

These recommendations I must reject. I believe that the essence of good clinical investigation is that the physician is a scientist and the scientist is a doctor. From the direct confrontation of patient and clinical investigator arise these questions which demand answers from those concerned with patients, present and future. And from the doctor-scientist combination comes the drive which leads to discovery. The imposition of barriers between the patient and the investigator will, I believe, ultimately deprive the patient.

A second proposal for providing further guarantees recommends the establishment of review bodies and it has been recognized by many, including the National Institutes of Health that, what has been termed an 'external check of other echelons of medical approval' may be both necessary and desirable. Some, however, have gone beyond this. Dr. ALDERMAN, for example, states that review boards *must not* be identified with the sponsoring institutions and that they 'should represent the public as well as the profession and should be appointed by an appropriate public body or bodies.' Further, this 'committee should be directed to pass on the propriety and the value of the project initially, and also required to review regularly research in progress. It should have the authority to instruct the Public Health Service to withdraw support from any project at any time'. These proposals I emphatically reject. Certainly continuing dialogue between the public and

the clinical investigator is needed in order to refine existing codes and to develop new ones, but most importantly for mutual education. But such deliberations should be for the purpose of developing broad legal, moral and ethical guidelines designed to facilitate the advance of medical knowledge while certainly protecting individual rights. The proposal for complex and heterogeneous review committees in each institution, scrutinizing each proposal, threatens to throttle research without providing any additional significant assurances concerning individual rights.

The third method suggested for providing additional guarantees is of course through the passage of new laws. As was indicated before, a special problem confronting pediatric investigators arises from the fact that the legal right of a parent to consent to investigation on a child has not been clearly established in law. The law, according to Professor PAUL FREUND of Harvard University, has stated that parents may consent for the child if the invasion of the child's body is for the child's welfare or benefit [3]. We know, too, that if the child's welfare is jeopardized the right of consent may be taken from the parent by law. What remains to be clarified is whether the parent may consent for the child on the basis of possible future welfare or benefit; and most difficult of all whether the parent may consent for the investigation of a child in circumstances where the individual child will probably never benefit but where the information gained may benefit other children in the future. Professor FREUND has stated that the law cannot be expected to yield precise answers to ethical problems of medical experimentation. At present, however, until greater precision is developed and until more detailed guidelines are evolved, it seems clear that in all circumstances not for the immediate benefit of the child we must obtain informed consent, we must conduct complete and painstaking evaluation of risk, and we should invite the approval and surveillance of non-involved professionals in order to protect both the subject and the investigator. I would like to submit, however, that laws which deprive the parent of the right to give consent, which deprive them of the right to invest in and participate in the future health of their children, and which inhibit the development of knowledge of children, for children, must be condemned and must be opposed.

I do not intend today to present to you a specific code which might serve as a guide for future behavior, nor could I. However, from the writings of many thoughtful individuals who have addressed themselves to this subject, I have selected three quotations which I believe describe well the situation in which we and the Society we serve find ourselves and which point the way in which we both must go:

1. 'The controversy regarding conduct of research

has served to increase the tension between the long-range interests of society, science and progress on the one hand and the rights of the individual on the other. It is important that this tension should be a creative one, resulting in a higher order of problem solving that safeguards both interests, rather than a solution that gravely impedes the progress of science. Society must preserve the delicate balance between these interests, realizing that the cost of excessive restriction of research can come very dear' [7].

2. 'There is a danger that, if scientists do not respond to the public's concern about research conduct, research rules will be imposed on science from without. Such rules may be formulated in an emotional atmosphere, may be selective, inconsistent and inadequate, and may be enacted into law in such a fashion as to be unnecessarily burdensome, restrictive and rigid' [7].

3. 'The law on the whole subject of experimentation will be worked out in close reliance on the moral sensibilities of the community. It, therefore, behooves the medical profession to take the public into its confidence and to educate public opinion rather than to risk the shock and explosion of pent-up revulsion if the lid is pressed down on information and then blown up by some melodramatic case. The primary step is to recognize that difficult moral dilemmas do exist on which help and guidance may be sought from many sources' [3].

Taking these principles of behavior as a charge, I am proud to announce that those professional groups which bear the major responsibility for pediatric education, research and patient care in the United States, the Society for Pediatric Research, the American Pediatric Society, the American Academy of Pediatrics, the Association of Medical School Pediatric Chairmen and the National Institute of Child Health and Human Development, have formed a Joint Committee on Clinical Investigation in Children. Appointed to represent the Society for Pediatric Research will be Dr. ROBERT GREENBERG of Stanford; The Association of Medical School Pediatric Department Chairmen, Dr. CHARLES A. JANEWAY of Harvard; The NICHD, Dr. GERALD LA VECK; The American Academy of Pediatrics, Dr. WILLIAM SILVERMAN of Columbia, and the American Pediatric Society, Dr. ALBERT SOLNIT of Yale. It will be my great privilege to serve as Chairman.

It should be emphasized at the outset that it is our

intent to add to this Committee members representing interested non-medical groups: The law, the clergy, the social and behavioral sciences, the media of communication and the public at large. This Committee was formed in recognition of the fact that moral dilemmas do exist and it intends indeed to seek help and guidance from many sources. Certain goals are already evident: To us must come the realization that we can no longer afford the luxury of speaking only to each other; to the public must come the realization that medical progress through research cannot be bought only through payment of taxes and by contributions to voluntary health organizations; between these groups must emerge dialogue which will reduce fear and distrust, and from this dialogue must come rules and laws which foster rather than inhibit the progress of science.

As we begin our meetings, to which 392 abstracts, the largest in our history, have been submitted, I have every confidence that the work of this Society will go on with the support, encouragement, and fuller understanding of the total society we serve.

References and Notes

1. ALDERMAN, M.: Medical experiments on humans. *The New Republic*, Dec. 6, pp. 10-12 (1966).
2. BEECHER, H. K.: Editorial: Some fallacies and errors in the application of the principle of consent in human experimentation. *Clin. Pharm. Therap.* 3: 141 (1962).
3. FREUND, P. A.: Ethical problems in human experimentation. *New Engl. J. Med.* 273: 687 (1965).
4. LANDAU, R. L.: Editorial: Civil rights and the clinical investigator. *Perspect. Biol. Med.* 10: 137 (1967).
5. Nuremberg military tribunals, trials of war criminals (the medical case), vol. 2, pp. 181-84 (U.S. Government Printing Office, Washington 1947).
6. SILVERMAN, W. A.: Informed consent. *Pediatrics* 38: 373 (1966).
7. WOLFENBERGER, W.: Ethical issues in research with human subjects. *Science* 155: 47 (1967).
8. Delivered at the time of the Annual Meeting of the Society, April 28, 1967, in Atlantic City, New Jersey.
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