The Child and Experimental Medicine

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The rules of conduct in human experimentation are attracting much notice at present both nationally and internationally (Beecher, 1959; Clegg, 1960; Roxburgh, 1963; *Brit. med. J.*, 1963), but the special problem of experiments involving children has not received the attention it deserves. The subject is a delicate one apt to evoke strong emotions and therefore seldom discussed in public. Nevertheless, it is important that it should not be shrouded in secrecy at a time when paediatrics is making increasing use of the great scientific and technical advances of recent years. Every doctor, and indeed every person, is likely to hold strong convictions on this topic, and the opinions expressed here represent a personal view based on experience of the practical and ethical difficulties of experimental work involving children, rather than an attempt to propound an easy solution.

It is true, of course, that clinical experimentation on infants and children has been going on for many years; it is equally true that public reaction to such experiments has always been ambivalent. On the one hand, more research is urged and money pours forth to finance the investigation of children's diseases. On the other hand, the mere mention of an experiment on a child raises cries of indignation and questions in Parliament. It is perhaps because the subject has not been ventilated enough that the public are uneasy about the activity of research workers, and their confidence is not restored by occasional experiments of doubtful propriety. Clinical investigators who breach morality in this way by thoughtlessness or misguided zeal do a grave disservice to medical science.

These matters must be brought into the open and frankly discussed, partly to help paediatricians to frame a code of standards acceptable to society in general, and partly to educate the public, and especially parents, to think rationally about such things and to appreciate the nature and objectives of paediatric research and the necessity for scientific experiments if standards of medical care are to be maintained and advanced.

Need for Paediatric Research

We are living on the threshold of an era of apparently boundless technological advance, in medicine as in other fields. Many of the techniques which to-day are experimental will to-morrow be commonplace. If the fruits of this progress are to be used for the benefit of infants and children, then they must be adapted to the special needs of the young. Valuable preliminary testing can be carried out on laboratory animals and adult human beings, but the ultimate observations or experiments must be made on children, since they may differ radically from adults in their responses.

Experimental work with young children and infants is not easy. Their small size makes the technical aspect of the

work difficult, while their inability to co-operate in tests or in the collection of specimens means that very close supervision is needed, and many failures and disappointments occur. These difficulties are sometimes advanced as reasons for not pursuing research in children, but this is a rationalization which often conceals ineptitude or apathy. There is no doubt, however, that the technical difficulties have deflected many of the best investigators into other fields, and paediatrics is the poorer for their going. It is all the more important that we who work with children should interest ourselves in these problems, seek to overcome them, and encourage those with special knowledge or technical skill to participate in paediatric research. Such specialists have often been working exclusively with adults and they may fear that their knowledge and skill will not be applicable in the children's hospital.

The well-worn paediatric cliché that "the child is not a miniature adult" has served its purpose in emphasizing the need for special consideration of the infant and child, but it may now be doing the advance of paediatric knowledge a disservice, since much that is known from clinical investigation of adults has not been applied to the child because the differences have been so heavily stressed. The similarities between adults and children are far greater than the differences, and much physiological and pathological knowledge may be applicable to children with comparatively little adaptation. Nevertheless, there are differences—above all, the fact of continuing growth and development—which make experimental research on infants and children indispensable if the new knowledge is to be used for their advantage.

Historical Background to Experimental Research in Children

Human experimentation is as old as medicine itself, but the experimental method of modern science is comparatively new. It is true that occasional experiments were carried out in ancient times and that Galen has been called the father of experimental medicine by virtue of his operations on living animals. Nevertheless, Galen was a clear thinker and observer rather than a clinical investigator in the modern sense, and for fifteen hundred years after his death medicine was a craft based on superstition and dogma. Men even lost the capacity for making clinical observations, and throughout Europe thought and inquiry were replaced by authority and theoretical disputation. Not until the Renaissance of the sixteenth century did medicine begin to emerge from its long hibernation. Throughout the seventeenth and eighteenth centuries men were keenly observing and recording the phenomena of disease, but few advanced further towards clinical experiment. Among those few, William Harvey stands out, for his demonstration of the circulation of the blood is one of the great landmarks of scientific medicine. James Lind is also of special interest to paediatricians, because his work on

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scurvy in sailors was the first recorded account of a clinical trial with carefully matched controls (Green, 1954).

Diseases of children were seldom the object of curiosity among these early medical scientists, for the care of sick children was largely in the hands of untrained women. The first real interest came from pathologists early in the eighteenth century. Morgagni is generally credited with being the first to perform necropsies on children; he remarked on the difficulty of persuading parents to agree since "mothers, from a false tenderness, constantly oppose the examination of the bodies of their children." One hundred years after Morgagni, Billard pioneered the systematic correlation of clinical paediatric data with morbid anatomical findings.

If the notorious experiments ordered by Queen Caroline on "charity children" (Sloane, 1755) be excepted, one of the first experiments performed by a physician on living children was the experimental inoculation of young children with measles by Dr. Francis Home, a member of the College of Physicians of Edinburgh, in 1759. Forty years later, as the eighteenth century drew to a close, Edward Jenner made medical and paediatric history by selecting a healthy 8-year-old boy, James Phipps, for the purpose of inoculation with cowpox.

Throughout the nineteenth century paediatrics advanced as a scientific subject, although the concept of the controlled experiment was not yet established. Following the lead of Billard, successions of physicians in the medical schools of Europe increased paediatric knowledge by the correlation of clinical and pathological findings. As the century wore on, emphasis changed from morbid anatomy to disordered physiological function, under the influence of such men as Bednar and Schönlein. With the development of bacteriology and biochemistry at the end of the century, the way was clear for the great advances in scientific paediatrics of our own century.

The first attempts at biochemical research in paediatrics were confined to comparatively simple measurements of the constituents of body fluids such as blood and urine. Paediatric journals of the early years of this century contain many reports of studies utilizing blood drawn from the superior sagittal sinus—a vessel first used for this purpose by Marfan in 1898—or from the jugular vein of infants. Very few articles refer to parental permission for these studies, and there is seldom any expression of doubt about the morality of the work. Children from orphanages and "foundlings" were commonly used as subjects for these investigations. It is perhaps not surprising that this type of research was accepted unquestioningly, for infant and child mortality was still very high and methods of therapy were often drastic. Moreover, medicine had but recently emerged from an era in which children were little regarded, a world where foundlings were bought and sold and child labour was the rule. It is salutary to recall that a hundred years ago the American Society for Prevention of Cruelty to Animals was empowered by the courts to act in a case of cruelty to a child on the grounds that a child is an animal. A society for the prevention of cruelty to children was not founded until 1875—nearly ten years later (Van Ingen, 1927). Against such a background, the use of orphans and foundlings for experiments would hardly have seemed to require permission or indeed justification.

With the advance of technology, research methods began to be more sophisticated. Techniques advanced from the mere withdrawal of blood to the injection of substances for experimental purposes. The first documented instance of this is probably the experiment by Oliver, who in 1894 injected crude extract of endocrine glands into his own son (Ivy, 1948). After 1900, studies on the newborn infant began to increase, and these often involved the injection of chemicals such as fluorescein or experimental nutrients such as fat infusions. Fortunately at the same time there appears to have been

some quickening of medical conscience, and the references to orphans and foundlings gradually diminished. Despite this, reports seldom referred to the obtaining of permission except, curiously enough, from medical staff. Thus there were frequent acknowledgments in the early paediatric journals of the kindness of obstetric staffs in giving permission for experiments "on their cases"—a possessiveness which still exists to some extent to-day among doctors, as though the undertaking of medical care somehow conferred ownership of the patient on the physician.

It is fortunate that paediatricians have become increasingly aware of their responsibilities at a time when research activity is growing and more potent tools are being placed in their hands. The recent enormous mushrooming of paediatric research is nowhere more evident than in the proceedings of the American Society for Pediatric Research, which now fill many pages of the *American Journal of Diseases of Children*. It is perhaps a commentary on the relative dearth of British paediatric research that, whereas the American Society has flourished for over 30 years, a Paediatric Research Society was founded in Britain only three years ago.

To-day, paediatric research faces a great future with powerful weapons to attack the many problems facing it. It will require wisdom and discretion to pick a way between the dangers of abuse and the neglect of the possibilities of these new methods.

What is Meant by an Experiment ?

Some of the opposition to experiments on children stems from ill-informed opinion on what constitutes an experiment. To many people the word implies the risk of death and carries horrifying echoes of the Nazi slave camps. To others it has the connotation of malpractice (Ladimer, 1962). In fact, an experiment merely means that the investigator makes observations under controlled circumstances instead of making observations of naturally occurring phenomena. In the experimental method a hypothesis is constructed and the conditions for its testing are specified. Variable factors other than those involved in the experiment are fixed as precisely as possible; it is not, of course, possible to control all variables, especially in clinical experiments, but an attempt is made to define the conditions and to adhere to them as closely as possible. Thus an experiment on a living mammal may involve control of food or fluid intake, both in quantity and in quality, control of activity, control of environmental temperature, and so on. Those variables which cannot be controlled may be measurable, so that working conditions are known as completely as possible.

The idea of controlling the environment of a child so that an experiment can be carried out may sound repugnant, but such control may simply mean putting the child on a diet—which need not be unpalatable or inadequate, but merely of known quantity or quality—fixing the temperature of his room, or specifying the amount of clothing to be worn or the amount of exercise to be taken during the period of the experiment. Once the conditions can be identified in this way, the experiment can proceed. This consists essentially of altering one of the variables to a known extent and in a known direction, and observing the result. Thus we might change the temperature of the air surrounding an infant and observe any change in body temperature—this would constitute a simple form of experiment.

Much fundamental research in paediatrics is concerned with social and behavioural characteristics or other attributes of the child as a whole. As simple examples of such work having a direct bearing on the care of children in hospital, the experiments of Prugh and his colleagues (1953) and of Vaughan (1957) may be cited. In these studies the effects of admission to hospital on the behaviour of groups of children were observed under controlled conditions. Such experiments as these do

not arouse the same antipathy in people's minds as do laboratory investigations and I shall therefore concentrate on the latter type of experiment. It must not be forgotten, however, that these constitute only a part, and not necessarily the most important part, of the sum total of experimental work on children.

Many experiments carried out on children involve measuring constituents of secretions or waste-products removed from the body. An enormous amount of data has accumulated from the analysis of stools and urine, and Hill (1960) has given a graphic account of the modern hospital with its white-coated workers hurrying to and fro clutching bottles of urine. Some measurements may be made without touching the child or by using instruments which are only attached to the child—for example, the recording of changes in the heart action or the blood-pressure. Other experimental methods may require analysis of blood, the insertion of recording instruments into the body, or the injection of chemical or other substances. It is these last types of procedure, which form only a small proportion of all experiments, that are likely to raise most apprehension in the minds of parents and doctors alike.

One of the simplest of such experimental techniques is a finger-prick to obtain a drop of capillary blood. When properly carried out, such a procedure is painless and free from risk. I see no practical objection to it as an experimental method in paediatric research. At a slightly more advanced level, a venepuncture to obtain venous blood may be considered—a procedure which is used daily in the routine care of infants and children. In skilled hands this is a safe procedure; its use in unskilled hands should never be permitted in experimental work or indeed in medical work of any kind with children. Even in skilled hands, however, there are certain objections in that venepuncture may occasionally cause pain and there may be other undesirable consequences in young children (Vulliamy, 1953), while in infants the procedure is not entirely devoid of risk. On these grounds—and this is a purely personal view—I have always considered that venepuncture in infants and young children for experimental purposes is hardly justifiable. Certainly if an alternative method using capillary blood exists or can be developed, there is no valid reason for even contemplating the use of venous blood.

At the other end of the range of possible techniques we may consider the use of radioactive isotopes in paediatric research. A doctor who is prepared to justify and carry out many kinds of experimental technique on children may hesitate at the thought of giving a radioactive substance to a child. Usually he is responding emotionally from prejudice and lack of knowledge; in other words, he is acting irrationally as the layman does when he shuns the whole idea of experiments on children—it is something he instinctively rejects without properly comprehending what it implies.

He would, of course, be right in doubting the extent to which the safety of the experiment could be determined or in refusing to accept any statement about its safety, however authoritative, without substantial evidence. Indeed, the scientific method depends upon the rejection of authority and the acceptance as evidence only of that which can be proved and repeatedly proved. The difficulty lies in determining what constitutes proof, because at any time further evidence may come forward which overturns previous evidence. All one can do is to form an opinion based on the best available information and be ready to change that opinion at any time in the light of new knowledge. We should not shrink from the use of radioactive materials in research simply from fear born of ignorance and emotion; we must, however, be most circumspect in their use because not enough is yet known about their potentialities and their long-term effects (Cranny and Farr, 1961; W.H.O., 1962). These tools have already proved useful in paediatric research but I suspect that they have been and are being abused, despite continuing warnings about their potential dangers (Fisher and Panos, 1962). Fortunately this has probably

happened little if at all in the United Kingdom owing to the vigilance of the Medical Research Council. Until such time as their safety is proved beyond dispute, the use of radioactive isotopes in infants and children should probably be restricted to investigations essential for diagnosis or therapy.

It will be apparent from the foregoing that an experiment may involve almost any procedure from alteration of the room temperature to the injection of radioactive isotopes. Any sweeping directive to the effect that no experiments are permissible on children might prevent a small number of experiments of borderline acceptability, but would certainly stop a great deal of harmless work of real value.

Purpose of Paediatric Experiments

Experiments carried out on children can be considered in five categories:

1. An experiment in treatment with the immediate aim of curing the child's disease.
2. An experiment on an ill child in order to find out more about his condition.
3. An experiment on an ill child in order to learn more about the disease from which he is suffering.
4. An experiment on a child who is either well or suffering from another disease in order to find out more about a particular disease.
5. An experiment, usually on a healthy child, designed to provide information about children in general.

Few would consider the first two unjustifiable; indeed, clinical medicine uses the experimental method to a far greater extent than many people realize and, as has often been pointed out—for example, Ivy (1948) and Green (1954)—the giving of any drug may be considered as an experiment since the doctor, although aware of the usual response to the drug, must observe how his particular patient reacts as an individual. Thus people who state categorically that no experiments must be carried out on children would deny to children the benefits of medical science.

Less prejudiced people might reasonably say that the first two categories of experiment were permissible because the child might benefit, whereas there might be no immediate benefit from the other types. This principle—that experiments may be carried out only if the subject is expected to benefit—has often been enunciated, but is open to abuse through rationalization of the purpose of the experiment. Moreover, more than one purpose may be served by the investigation, so that the line between categories 2 and 3 is not a distinct one. There may be a big step in principle between these two categories, but it can be very difficult in practice to separate them. If category 3 is accepted as reasonable, however, there is little fundamental difference between it and the next category. Thus, for example, if a metabolic balance study were contemplated on a child with hypercalcaemia, there might be genuine difficulty in stating whether it was for the child's benefit or for the acquisition of knowledge—obviously there might be a dual purpose. One might say to the child's mother: "This won't benefit your child directly, but what we find out may help other children with the same disease"; if a control study were required on a child without hypercalcaemia, one might say, "This won't benefit your child but what we find out may help children with other diseases." If the former is acceptable, it would seem illogical not to accept the latter as reasonable.

Some have tried to differentiate between the first four types of experiment and the fifth on the grounds that the former are concerned with disease and are therefore directly or indirectly aimed at the alleviation of human illness, whereas the latter merely seeks knowledge in the interest of medical science and therefore cannot be approved. This alleged difference is quite unreal, since a knowledge of the normal is essential to a proper understanding of the abnormal, and disease cannot be arbitrarily separated from health, except in the crudest sense. The idea

that an experiment for a medical purpose is somehow different from an experiment solely for a scientific purpose has been rendered totally obsolete by the increasing applicability of biological knowledge to medicine.

Because of these difficulties, I believe it is preferable to recognize experimental work for what it is, or should be—a carefully planned and controlled study designed to obtain information not otherwise available. It seems unrealistic to me to make a clear distinction, as the World Medical Association has done in its draft code of ethics on human experimentation, between experiments for the benefit of the patient and experiments conducted solely for the acquisition of knowledge. The motive behind the experiment may, of course, fall neatly into one or other category, but more often the distinction cannot clearly be made. Whether or not the information obtained will be of help to the subject of the study can only be determined after the results have been analysed and should not be made a condition of the experiment.

Conditions to be Observed

If it is accepted in principle that experiments may be carried out on children even although they have no immediate beneficial purpose, it becomes important to consider the circumstances in which such experiments may be justified, and the conditions under which they may be performed. Apart from the moral issues involved, the practical objections to experiments on children are that they may be attended by risk, and that they may cause pain or fear.

If the extreme view is taken that no risk at all is permissible, then no experimental studies could be undertaken, since there is risk in everything we do. There is risk in all our daily activities—in crossing the street, in eating, even in breathing. Most of these day-to-day hazards are accepted without thought because they are known to be very small—that is, they are calculated risks. There is a risk in coming into hospital, but it is not calculated by the patient, who puts his trust in the doctor, believing that he has calculated the risk. If the doctor took an uncalculated risk, the patient would be justified in losing confidence. If any individual takes an uncalculated risk he is acting foolishly. Thus there is nothing reprehensible about a calculated risk, and to say that we take a calculated risk when we carry out an experiment should increase rather than diminish confidence. Thus if we collect urine from a child there is a very small risk that the collecting vessel may break and cut him. If we merely ask him to stand on a stool for some experimental purpose the stool may overbalance and he may be injured. These are the ordinary risks of everyday life, and it appears to me reasonable to say that an experiment on a child is permissible provided that the risk does not exceed the ordinary risks of daily living. Children should never be submitted to more hazardous experiments such as adults may voluntarily undergo, even although the parents are willing to consent. Indeed such a proposal should never be made to a parent. Experiments carrying a greater risk may, of course, be permissible if an ill child is expected to benefit directly, and here the calculated risk must be weighed against the benefit anticipated.

There is another kind of risk to which the child may be exposed—the risk that withholding standard treatment for the purposes of an experiment may prolong or aggravate his symptoms or even delay his recovery from the illness. Some experimental investigations may necessitate the withholding of drugs for a period, since they may interfere with the experiment, but it should be axiomatic that such action must never be taken if it is likely to prolong distressing symptoms or influence recovery adversely. Experiments which cause pain are sometimes carried out on adults, who voluntarily accept the discomfort but may object to it if it becomes too severe. Great care must be taken that the volunteer understands what is

involved and is not overawed or otherwise influenced so that he hesitates to object. A child may not understand the experiment and may not object, so that I believe an experiment causing pain should never be carried out on a child. Even discomfort is not permissible in small children, although an intelligent older child may accept moderate discomfort if the reason is explained to him.

The question of fear is more difficult, because children in hospital, with the memory of recent unpleasant experiences, may be apprehensive even at the approach of the physician. If such slight apprehension can easily be dispelled by reassurance or increased familiarity with the doctor, then it may be reasonable to proceed, but anything more than this should be regarded as a contraindication to the experiment.

At no time should the potential scientific value of the work be used as an argument for or against carrying out an experiment. Any work may prove to be of value unexpectedly and any apparently important study may be useless. The judgment of the value of a piece of research should be kept apart as a separate issue. It may be necessary for a grant-giving committee to assess the possible value of work they are proposing to support, but the importance or otherwise of the work should never be allowed to influence the decision on whether it is justifiable. I agree with Clegg (1960) in doubting the wisdom of Nuremberg Rule No. 2, which states that “the experiment should be such as to yield fruitful results for the good of society.” I believe it is dangerous to suggest that an experiment which might otherwise be unjustifiable is justified because it is for the common good. As Clegg (1960) says, any investigator can claim that what he is doing is for the good of society. Certainly an increased risk must never be accepted simply because the project is believed to be of great importance or value to the community.

More important considerations than its possible value are (1) whether it is well conceived and planned, (2) whether thought has gone into the framing of hypotheses to be tested, (3) whether the experiment is designed to answer the questions posed, (4) whether the same information could be equally well obtained by experiments on laboratory animals or adults, and (5) whether the investigator has the skill and knowledge necessary to conduct the experiment properly. Failure to satisfy any of these criteria may disqualify the experiment, but even if a project satisfies all these, it may not be justified if the basic requirements outlined above are not fulfilled.

Permission for Experiments

Most authoritative statements on the need for permission for human experimentation have been made without due consideration of the special case of children. Thus the Nuremberg Military Tribunal (1947) at the Nuremberg Trials pronounced that the voluntary consent of the human subject was absolutely essential. The Judicial Council of the American Medical Association (1958) similarly stated that the voluntary consent of the person on whom the experiment was to be performed was required in order to conform to the ethics of the American Medical Association. If these pronouncements were taken literally, experiments on infants and young children would not be possible. It is indeed an assault even to touch a person without his consent. However, a child without sufficient understanding is in law considered as incapable of giving consent, so that the power to give or withhold consent to treatment is vested in the parent (*Brit. med. J.*, 1961). Whether or not parental consent can be given to an experiment may be disputed on philosophical grounds. According to Ladimer (1959) it has been ruled in a series of cases that no one may consent on behalf of a minor where the proposal or trial is not directly or indirectly beneficial. The World Medical Association (1962) in its draft code of ethics on human experimentation states categorically that persons incapable of giving consent because

of age should never be used for human experiments which are conducted solely for the acquisition of knowledge.

Attention has already been drawn to the undesirability of differentiating between potentially beneficial and merely informative experiments, and it seems more reasonable to accept the view of Shimkin (1953) and others that in this, as in other spheres, parents can give consent on behalf of their children with the same provisos as would pertain if they were giving permission for experiments on themselves. In the case of older children permission should also be obtained from the child after careful explanation of what is required of him and the reason for the experiment.

When an experimental procedure is simple and completely harmless the investigator may be tempted not to tell the parents, because they might object irrationally or might be disturbed unnecessarily. It should be accepted as a fundamental principle, however, that no experiment involving a child should be undertaken without the parents being fully aware of what is proposed and having ample opportunity to prevent the proposed experiment should they wish to do so. The physician must make sure that the parents realize the procedure is primarily experimental and not therapeutic, and that they have no feeling of constraint or fear of penalty should they decide not to allow their child to participate. This obligation inevitably increases the difficulty of investigative work, but the additional burden must be accepted and allowance made for the extra time and effort required.

It is equally clear that direct permission from the parents does not absolve the physician from any part of his responsibility, because the parent, from his limited knowledge of medical science, is not usually in a position to understand and assess the proposed work and has to rely on the doctor's judgment. Moreover, a parent who is quite willing to allow an investigation may nevertheless withhold permission because she feels that by giving it she is assuming some of the responsibility. In a different category is the parent who will cheerfully consent to any procedure without considering its effect on the child; such behaviour may have its origin in a disturbed parent-child relationship. It is preferable, therefore, to give a full explanation to the parents of what is intended, making sure that they understand the implications, and to give them the opportunity of refusing to allow their child to participate if they wish to do so. The question of whether the experiment is justified must be decided by the investigator himself.

It may be added that, by the same token, the approval of an experimental project by a research organization does not absolve the investigator from moral responsibility for the proposed experiment.

Character of the Investigator

A spirit of inquiry and experiment is in no way incompatible with a moral and humane attitude to patients and there is no need to postulate a conflict between the two, for the interest of the individual child must, and in my experience always has, come first. As Roxburgh (1963) says, the relationship between subject and experimenter is the same as that between patient and physician, so that ethical considerations apply to the former relationship as to the latter. The popular image of the children's doctor as a kindly benevolent old gentleman sitting by the sick child's bedside may indeed be contrasted with that of the clinical investigator, portrayed as a ruthless, cold-blooded fanatic. This idea of a split between physician and experimentalist is a comparatively new one; the early physicians from William Harvey onwards were often experimentalists by nature, and the whole-time scientific research worker in medicine only developed because clinical medicine did not keep pace with the advance of scientific technology. Some of the reasons for this divergence have been given by Pickering (1949), and McCance (1951) has drawn a vivid picture of the difficulties of clinical research when

the physician and the experimenter are out of sympathy with one another's aims. The doctor of the future must be properly grounded in scientific method, which is the basis of all branches of medical science, so that he can combine in one person physician and scientist. Such a dual role need not be difficult, as has been suggested by Fox (1960), whose analogy with Dr. Jekyll and Mr. Hyde is an unfortunate one.

Physicians, like other scientists, must have the capacity for concentrating on one object at a time, but they must equally be able to switch from one clinical problem to another demanding an entirely different approach. I do not believe that the mature doctor has difficulty in distinguishing his experimental interests from his duty to his patient. An interest in experimental medicine need not be a dehumanizing process nor need it be demoralizing, as has been suggested by Jaspers (1959). The concept of the inhuman scientist stems partly from fiction and partly from a small number of unscrupulous investigators who have brought great discredit to science and the experimental method. One occasionally meets young investigators with an arrogance foreign to the spirit of science, but the mature scientist is a humble man inspired by intellectual curiosity and a desire for truth, which are attributes equally desirable in the practising doctor. In the words of Gaddum (1954), "All good doctors are really doing experiments all the time."

It has sometimes been stated that it is undesirable for the physician in charge of patients to conduct experimental studies on his patients himself. Guttentag (1953) and Fox (1960) have clearly stated the case for separation of the physician from the experimenter. Contrary to this view, I believe that the physician in charge is the right person to be responsible for the experiment, whether it be carried out by him as an individual or by a team. Such a man is sufficiently mature to see in its proper perspective what is being done, and to modify or abandon the experiment at any time if this should be in the patient's interest. Moreover, it is he who should explain the investigation to the parents and it is to him personally that they give their consent. He is usually a man of assured position, so that success in his research field is not vital to his own security. The dangers of the younger independent clinical investigator are his unbridled enthusiasm, which may override his judgment, his lack of experience, and the fact that his career may depend on the results of his research, so that he has a strong incentive to transgress the bounds of morality if this should prove necessary to achieve his objective. Ambition for renown is not a good motive for scientific research and it becomes a positive menace in clinical research.

Even the senior scientifically trained clinician is not immune from such influences, and sometimes so much money and skill may be committed to a project that he is tempted to allow these considerations to influence his judgment; in such circumstances he should have an independent adviser who is not involved either financially or professionally to give impartial advice on the justifiability of the proposed experiment. The suggestion by Shimkin (1953) that research on human beings should be a group effort supported by a proper consultative body has much to commend it, provided that responsibility is not thereby shifted from the physician's shoulders.

Choice of Children for Experimental Work

In many instances experimental studies of disease in childhood will be made on children who are suffering from the disease under investigation. It is usually when control observations are required or basic physiological data are sought that the question of choice arises. For these purposes there are no "inferior" children who are more suitable for experiments than others. If the proposed experiment may justifiably be carried out on a child, it may be carried out on any suitable child. When deciding whether an experiment is justifiable, the old question: "Would you subject your own child to this?" is

still a good yardstick for most moderately minded people. It should be remembered, however, that some zealots may be prepared to submit their own families to indignities which the average man would consider excessive. The experiment referred to above, in which Oliver injected his own son with a crude extract of endocrine glands, is a well-known example (Ivy, 1948).

The former practice of subjecting "charity children," orphans, or mentally defective children to procedures which would be considered undesirable for more fortunately placed children is wholly objectionable and morally indefensible. By the same token, however, there is no fundamental reason why children in hospital should be considered ineligible, since no unethical experiment should be contemplated in any case. There are certain disadvantages in this practice, however, apart from the obvious scientific one that children in hospital are seldom "healthy." The hospital is a friendly and homely place to the paediatrician and others who spend their lives in it, but it may be terrifying to some young children, who appear docile and co-operative but are really fearful and resentful. Unnecessary investigation must be kept to a minimum in such children, so that they are generally unsuitable for experimental investigation unless this is essential for their recovery. On the other hand, many older children really enjoy life in hospital and are pleased to be the centre of attraction in the ward. After years of working in children's wards, one learns to recognize the different reactions of children and the meaning of different sorts of behaviour—this is one further attribute of the paediatrician as investigator, that he knows which patients are emotionally suited to participation in experimental research. Special care must be taken, of course, that children in hospital are not used in preference to other more suitable children simply because they are accessible, and the difficulties inherent in obtaining observations on healthy control subjects must be faced squarely, even at the cost of greatly increased effort and expense.

Discretion must be exercised when experiments on infants are contemplated, because, although apprehension is not a problem in young infants, they can neither complain nor resist effectively. Sometimes it is suggested that experiments of doubtful propriety are permissible on babies with severe malformations. To me, this is an affront to the whole concept of the individual as a person, and I do not believe that any experiment should be carried out on a malformed child which would place the malformed child in a separate category, thus creating two types of human being and paving the way for Hitlerian ideas of inferior beings.

Importance of Maintaining Public Confidence

Many people are fearful of the very word "experiment" and recoil with abhorrence from the idea of an experiment on a child. At the same time the public subscribe vast sums of money for paediatric research, perhaps not fully appreciating that this inevitably means experiments on children. If paediatrics is to advance as a science, and if the children of the future are to be healthier, we must ask the public to look dispassionately at the issues involved and to appreciate that the medical research worker is not a soulless scientist callously and inquisitively probing the secrets of nature, but a reasonable and responsible man who is trying to do the best possible for his patients of the present and for his patients of the future. If we are to convince the public that their trust is not misplaced, we must be very sure that we are not projecting a false image, and that everything we do is based on the very highest ethical standards. We must discuss our work openly among ourselves and be prepared to modify or abandon without hesitation any project which is generally condemned as morally unacceptable by our colleagues. In particular, we must restrain the young, overenthusiastic, and unprincipled research worker whose anxiety is his own advancement rather than the well-

being of the patient. Fortunately, such men are very few, but the activities of only one may be sufficient to destroy the confidence in a hospital which it has taken many years to establish.

It is worth repeating the words spoken by Sir Harold Hims-worth (1953) on the subject of the Hippocratic Oath: "The spirit of the Hippocratic Oath . . . can be given in one sentence. *Act always so as to increase trust.* That is the first and paramount law of social ethics. . . . In your research act so as to increase confidence in scientific integrity."

Perhaps most of all, we must retain the confidence of parents. For them, the admission of their child to hospital is a time of apprehension and emotional stress, which will only be increased if they suspect that things may be done to their child without their knowledge or agreement. Some of their fears can be allayed by careful explanation at the time of admission, or shortly afterwards, and this is an important way of maintaining good relations and increasing rather than diminishing their trust in the hospital. Such parents might be addressed somewhat as follows:

"This is a teaching hospital and the advancement of medical knowledge is one of our responsibilities, in addition to and second only to the care of patients. Research is being carried on into many diseases of childhood, and observations made on your child while he is in hospital may help in the work, which may eventually lead to the saving of lives. You may be quite sure, however, that nothing will be done to your child, except what is urgently necessary for his own care, without your knowledge, and you will be given every opportunity to object if you wish to do so. We hope, however, that if you are asked you will give the matter your earnest consideration, since the research may be helpful in saving the lives of other people's children. You may feel completely confident that nothing which may harm or cause pain to your child will be suggested."

Whether parents are able to accept ideas of this sort at such an anxious time is difficult to judge, and depends on many factors such as the nature of the child's illness and the character of the parents themselves. Very little is known about the effects on parents of their child being sent to hospital (Robertson, 1958), and the subject is one badly needing further study.

The children's hospitals of this country have a high reputation. It would be tragic if confidence in them were so shaken that parents feared to entrust their children to the hospital staff. It would be an even greater misfortune if experimental work were stopped, for inevitably the standard of care would decline. Neither of these things need happen if paediatricians give full and careful thought to their responsibilities and if the public recognize the need for paediatric research and are satisfied that it is carried out according to the highest ethical standards.

Recommendations

The Ethical Committee of the World Medical Association is at present preparing a code of principles and definitions as a guide to doctors on the ethics of human experimentation (*Brit. med. J.*, 1962). Because of its world-wide application, however, such a code can only be stated in the broadest terms. The Medical Research Council, the Ministry of Health, and other bodies have declined to lay down definite rules about human experimentation in this country, wisely stating that reliance must be placed on the conscience of the individual doctor. There is no doubt that the vast majority of doctors are highly principled, but there are many aspects of this difficult problem which cause real anxiety and much heart-searching to the paediatrician who is trying to carry out clinical research on infants and children. I believe, therefore, that statements from individuals who have faced these difficulties may be helpful, and, as a purely personal code of conduct, I would suggest the following guiding principles for experimental work involving children.

An experiment may be considered justified if:

1. The experiment is properly designed and appropriate to its objective.
2. The risk incurred is no greater than the ordinary risk of daily living.
3. The child is not subjected to pain or discomfort (slight discomfort may be permissible for an older child who understands and agrees).
4. The child is not frightened by the procedure (initial apprehension which is easily allayed may be permissible).
5. The parents are aware of what is contemplated, understand the nature of the experiment, and have had a genuine opportunity to object.
6. The information desired cannot be obtained by experiments on laboratory animals or adult human beings.

I would add four further recommendations:

1. The physician in charge of the patient should be responsible for the research work, either as an individual or as a member of a team, should participate fully in the work, and should be aware of any procedure contemplated as part of the study.
2. An impartial adviser or advisory board should be asked to pronounce on the justifiability of the project at an early stage.
3. All technical methods employed should so far as is possible be practised first on animals or adult volunteers, so that the research worker is fully proficient in the techniques.
4. At all times the nursing staff should be fully informed of the reasons for and the objectives of the research.

Conclusions

I have tried to discuss a difficult subject honestly and fairly. It would be very easy simply to agree with those who say: "Experiments must never be performed on children." This opinion is often readily and thoughtlessly expressed by physicians whose interests lie in other fields, but those of us who work in paediatrics cannot shrug the matter off so easily. The same opinion may be held by some paediatricians who have pondered the matter deeply, and their views must be respected. It may also be asserted, however, by doctors who are hostile to scientific medicine or who are not interested in advancing knowledge and seek to impede those who are. One wonders if such men ever stop to think that they themselves are constantly performing crude, dangerous, and uncontrolled experiments on the children under their care, with only their own subjective impressions as a guide. Does the excuse that these activities may benefit the patient really make them more acceptable than carefully designed experiments with no such claim, but with a clearly defined objective which may add some new fact to the total of paediatric knowledge? In the words of Bradford Hill (1952), "it may sometimes be unethical not to experiment."

We must accept, and we must try to get others to accept, the fact that no experimental work with children means depriving them of the advantages of medical progress and inevitably a decline in the quality of paediatric care. Experiment is necessary if a critical and inquiring attitude is to be maintained; in the absence of such an attitude among physicians, standards of medical practice must deteriorate. As Sir Henry Dale (1951) has said, the movement from an empirical art to an exact science is inevitable in medicine and it has already been, and will continue to be, on balance, of immense advantage to medicine.

If we accept that the advance of medical knowledge by planned observation and experiment is a desirable goal, we must also accept the principle that carefully designed and controlled experiments on children are permissible, since they are essential to the advancement of knowledge of disease in childhood. In accepting the need for research, however, we must always keep in front of us the obligation to protect the individual child to our utmost ability. We must never forfeit the confidence that parents have in us: indeed, by explanation of our motives and methods, we ought to be able to enhance their trust in us as worthy to protect the lives and health of their children.

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