Several guides on ethical matters already exist, but they are either limited or need to be interpreted against the background in which they were formulated. The question of children is referred to in only some of these. The Declaration of Helsinki allows the legal guardian to consent to non-experimental clinical research on those legally incompetent to give consent. The M.R.C. document states the legal position about informed consent and expressly forbids non-therapeutic research "which might carry a risk of harm." The interpretation of the word "harm" can vary so widely that in practice the phrase is not helpful. The editorial, "Treatment-Research-Experiment?" used as a guide for acceptance of work for publication in the *Archives of Disease in Childhood*[5] allows parents to consent to "procedures not in the ordinary course of medical care."

Overlooking the problem of those incompetent to give informed consent, there are impediments in both areas of "informing" and "consenting."

(1) To give full information concerning a study may result in distressing information being revealed prematurely. For example, it may be desirable to try new treatments for leukaemia in a child whose parents have just discovered he is "anaemic." Similarly, experimental therapy in children with progressive mental disorders diagnosed before the onset or at an early stage of clinical involvement, may call for detailed discussion of the outcome should no treatment be attempted before this is acceptable to the parents. (This should not be used as an excuse for not giving information because this would reduce the changes of obtaining the desired consent).

(2) Almost all procedures have some, albeit very slight or unsuspected, "risk of harm." It may be slight in the sense of anaphylaxis after injection of penicillin or slight in the sense that an unnecessary venepuncture by a white-coated doctor may unsettle a child when he needs medical attention in the future.

(3) Knowing that in law the doctor who conducts non-therapeutic clinical research on those incompetent to give informed consent exposes him to the possibility of a charge of assault can affect the manner in which the legal guardian is "informed."

(4) In many instances the technicalities of a study cannot be assessed by the subject and he is likely to decide whether to agree to it on his assessment of the personality of the doctor. Here other pressures, such as not offending the doctor on whom his subsequent care depends, inevitably influences his decision.

In practice the doctor must give a balanced view of all the considerations, a situation comparable to the direction given by a judge to the jury before they retire to consider their verdict.

Just as there are national differences in temperament, ways of life and standards of living, so the establishment of ethical standards can be expected to vary. It should be the right of each national group to determine its own standards, but this need not preclude attempts by other groups to improve those standards by education and external pressures such as restricting either financial support for research or the publication of results in international journals. Nevertheless, policies concerning these pressures should be determined by the profession rather than by the public, who are inclined to give an emotional rather than a rational opinion.

For the future, the profession must seek to educate the public in the need to join with it in a common exploration of medical problems. Meanwhile legal considerations which totally prevent progress in medical science should be disregarded and in the words of the editor[5] of the *Archives of Disease in Childhood*, "the protection of the public" must "continue to rest upon the maintenance of a collective tradition for honest dealing."

Illustrative Case Histories

RELATION OF LEAD INGESTION TO FEBRILE CONVULSIONS

Object.—to discover if children presenting with febrile convulsions had previously been subject to unusually high lead ingestion.

Procedure.—blood taken at time of admission with febrile convulsions for usual investigations and for lead determination. One month after recovery blood to be taken for further lead determination. This result should reflect the base line level of lead and will be unaffected by fever. Where opportunity presented blood would be taken from febrile children who did not have fits.

Objection.—the venepuncture one month after recovery does not contribute to the well-being of the subject. The project was abandoned.

TREATMENT OF HAEMOLYTIC URAEMIC SYNDROME

This may be treated by (1) supportive therapy and dialysis; (2) administration of heparin as an anticoagulant; (3) administration of streptokinase as a more potent anticoagulant and lytic agent. Several individual centres each claim good results with each of these forms of treatment, although the best results are quoted by centres using the potentially dangerous streptokinase. Only a randomized trial will decide whether the theoretically more dangerous drug has any advantage. The success claimed for the three orders of treatment can be explained if one is treating a mild case by dialysis, a case with limited thrombus formation with heparin, and a severe case with streptokinase.

Individual paediatricians, who are generally more protective towards their patients than adult physicians, may object to a controlled trial because it means that a mild case—which they consider, probably erroneously, they can recognize on the severity and duration of symptoms—may be chosen for treatment with streptokinase. Conversely a severe case may be selected for treatment with dialysis which the clinician feels is inadequate. A well-planned trial is necessary as it may provide guidelines to the selection of the best form of treatment for individual cases. Thus it may be possible to treat mild cases with dialysis alone and restrict the use of streptokinase to severe cases with extensive fibrin deposition.

TREATMENT OF SICKLE CELL CRISES

A preliminary communication suggested that patients with painful sickle cell crises showed rapid clinical improvement when treated with ancrod, an anticoagulant. Other investigators were doubtful of this and feared the possibility of a serious bleed into an infarcted tissue. It was considered important to establish the value or otherwise of the drug by conducting a controlled trial on as few patients as possible. A semiquantitative scoring system for clinical symptoms was devised as part of a double-blind trial and this allowed a valid conclusion to be reached after only five patients had been treated with the drugs. As the results did not differ from those in five untreated patients it is considered that therapy was not justified in a larger number of patients. Thus a properly controlled trial limited the risk to a minority of patients.

Appointments of Speakers

ALFRED WHITE FRANKLIN, M.B., F.R.C.P., Consulting Paediatrician, London

ALAN M. W. PORTER, M.D., General Practitioner, Camberley, Surrey

D. NOEL RAINE, M.B., M.R.C.PATH., Consultant Chemical Pathologist, Children's Hospital, Birmingham

Discussion

DR. FRANKLIN: The debate on this topic has recently become much more acute because of the development of academic child-health departments, which didn't exist before 1950. I'm very glad about this evolution, because to learn about the abnormal you need to know the normal; you can save the lives of many newborn babies and prevent mental handicap as the result of careful research—there's no other way.

CHAIRMAN: When you talk about research do you mean a deliberate programme of research, or studies done en passant, say, on blood specimens taken for therapeutic investigation?

DR. FRANKLIN: I mean both. If you are in a hurry, and the implications of the study are important, there is a temptation to use normal babies for taking specimens with no purpose other than research. In maternity hospitals this leads to objections on ethical grounds and I know of many projects that have been stopped by hospital medical committees.

DR. PORTER: Was this done before ethical committees were established?

DR. FRANKLIN: Yes; quite a number of hospitals have had strict rules about research studies on children for a long time, and after discussion have usually vetoed work not directly in the baby's interests. I think this was a correct procedure.

DR. RAINE: Establishing normal values is a great problem and quite frankly paediatric biochemists have had to work without knowing many of them—particularly in toddlers. But this isn't because of outside restrictions: one's own conscience has stopped one doing those studies.

DR. PORTER: This is a very great pity. Two or three apparently normal infants out of every 1,000 die of "sudden and unexpected" causes; if we knew the normal biochemical values for this age group we could then investigate children and see if there were any biochemical clues to this mystery.

DR. RAINE: We now know that this information can be obtained in a totally different way—by computer analysis of all the data on children in hospital and deriving a Gaussian curve for the normal range. This is obviously second-hand but the approach can yield useful results.

CHAIRMAN: But so far many children have been submitted to venepuncture not for their personal benefit, but for the greater good?

DR. PORTER: So far the whole of medical ethics has evolved to protect the individual, but there is room to consider the needs of society in general. The reasons why we've neglected these are due partly to revulsion at the Nazi experiments, which were publicized at the same time as there was an explosion in scientific medicine—this is why ethical codes which evolved at the time concentrated on the individual.

DR. FRANKLIN: I've always said that if somebody wants to take blood specimens from normal children, besides getting the parents' consent he should hold a children's party and venepuncture his own children first. Doing something for the greater good rather than the individual patient can have a bad effect on the doctor concerned: if he says "I am here to benefit society" he gets used to saying "I am allowed to take blood from my patients for whatever purposes I think fit."

The Willowbrook Project

CHAIRMAN: I think that Beecher's remarks are relevant here: "If a study is unethical, it does not become ethical because it produces useful results." These have been applied to a discussion of the Willowbrook programme.[6]

DR. PORTER: I remember the correspondence about the Willowbrook programme, which I consider was totally wrong.

DR. RAINE: Why?

DR. PORTER: Because it's totally wrong to expose a child deliberately to a disease unless it's clearly to his benefit; it's the antithesis of what medicine is about.

DR. RAINE: I hold no brief for Willowbrook either, but you have to judge some decisions on the background from which they emerge. Krugman made the valid point that any child going into this hospital ran a high risk of acquiring hepatitis.

DR. FRANKLIN: I'm sorry about this condemnation of Willowbrook. Your point about the background is most important—more than 60% of children were infected within six months of arrival in the institution, which had a population of 5,000. This is not a situation which is comparable to anything in normal life—except perhaps smallpox in Jenner's day. The Willowbrook project was a small, carefully controlled trial and it showed that children could be protected against the naturally acquired infection by an artificially given one. Nobody objected when much the same programme was carried out with the trials of measles vaccine.

Krugman also deserves a great deal of credit for his scrupulous care in securing the truly informed consent of the children's parents—certainly more than we do in health centres when we recommend children to have triple vaccine.

DR. RAINE: On the other hand, there was a danger with giving hepatitis virus of enhancing its virulence by human passage.

DR. FRANKLIN: I think there's a good case for a general service hospital not to get the reputation for doing a lot of research investigations on children—it's bound to affect the parents' confidence. Perhaps most of this work should be done in special research hospitals, where research work is done quite openly and parents would recognize this before the child went in.

Vaccine Trials

CHAIRMAN: What are your views on taking blood from controls—say, in a trial of a new vaccine. The procedure can't possibly benefit them?

DR. PORTER: I see nothing ethically wrong in this, if you have the parents' informed consent. The possibility of good emerging from the trial is great; the possibility of harm is remote.

DR. RAINE: One has to be very careful about using mentally defective children in this work: there's a temptation to say "because they're a drain on society they should repay part of their debt in this way"—and this is an entirely wrong attitude.

CHAIRMAN: Plotkin has stated[7] that an article of his about rubella vaccine was rejected on the grounds that "the unvaccinated controls had undergone a venepuncture unnecessary to their health."

DR. PORTER: I think this was a wrong decision, because it denied practicising doctors valuable information.

DR. RAINE: But if children start to associate hospitals with venepunctures they'll be less willing to come in if ever they are ill—this is why the second blood samples weren't taken in the Case 1 I mention in my working paper.

DR. PORTER: Even so, Dr. Raine, I think it was wrong not to have gone ahead and done the second venepuncture in this case. We now do not have some potentially valuable clinical information that we could have had. If it was a worthwhile study you should have gone ahead; if it wasn't you shouldn't have started it.

DR. RAINE: It was the ethical committee's decision, and one understands the reasons for it.

DR. PORTER: It all comes down to the advice given by the M.R.C., which I quote in my working document. This stricture has been applied throughout paediatrics, and is based on advice given by the late Sir Harvey Druitt. Obviously he was a man of great legal eminence, but his opinion has virtually gone unchallenged—though he was unable to give statute or case law for it when Dr. Beecher wrote to him.[4] Indeed, Sir Harvey clearly had some doubt on whether these strictures applied to minor procedures. He replied to Beecher: "Researchers may feel ethically justified in subjecting babies and small children to trivial procedures regardless of the strict legal position, but these are unlikely to cause harm and therefore unlikely to lead to lawsuits. Without lawsuits there can be no deciding cases on the principles involved." There's an element of doubt here, and the defence organizations say that they will indemnify you if you ask the parent's permission. What's more, if you ask the public for their views, as I did,[8] they can see nothing wrong with trivial procedures—provided the "risk-benefit ratio" is low.

DR. RAINE: Certainly the M.R.C. Document influenced the decision in my Case 1.

CHAIRMAN: Dr. Franklin, are your views changed in the child who is mentally defective?

DR. FRANKLIN: Only in the sense that an older defective child might be more upset by a venepuncture.

DR. RAINE: We have to remember that properly done a venepuncture is a relatively non-traumatic procedure—much less so, for example, than the two or three finger pricks required to obtain more than a few drops of capillary blood.

DR. FRANKLIN: The same criteria can't apply to preventive medicine as to curative medicine. We've accepted the practice of giving people diseases artificially for the general good, and not just for their own good.

CHAIRMAN: Difficulties arise about trials of new vaccines against more trivial diseases, such as mumps. Mumps itself doesn't carry a great risk of morbidity—and certainly not mortality—so how far do you go in telling the parents of the possible risks of an untried vaccine?

DR. FRANKLIN: You must take them into your confidence completely, and tell them, for instance, that theoretically there is a risk of encephalitis.

DR. PORTER: This is shifting the responsibility from the doctor to the parent, who is in no position to make such a decision. A sound medical decision must be taken.

DR. FRANKLIN: Of course. The responsibility does remain mine, but the parents must know the risk but that I am advising them that it is so small that it will be outweighed by the benefits.

DR. PORTER: One of our duties as clinicians is not to terrify our patients.

DR. FRANKLIN: Nevertheless, it's malpractice not to tell the parents or patients what we know.

DR. PORTER: It assumes that you have accurate knowledge of the likely risks.

DR. RAINE: I would agree with Dr. Franklin about the trial of a new agent, but with Dr. Porter where a well-established schedule is being used.

CHAIRMAN: Dr. Porter, when you give polio immunizations do you tell the parents that there's a one in a million risk of some sort of paralytic accident?

DR. PORTER: Certainly not: there has to be a degree of discretion. Does a surgeon read out a long list of complications of a varicose vein operation? If he did, I would send my patients to another surgeon.

DR. FRANKLIN: He doesn't need to spell them out, but he's very unwise not to tell them that every anaesthetic and every operation does carry a small risk.

DR. RAINE: This raises the fundamental point in every discussion on ethics: that you have to apply the written code to the individual situation.

DR. FRANKLIN: It emphasizes the difference I make in my working paper between what doctors are allowed to do in the name of investigations directed towards treatment, and the same sort of thing in research, when you come up against a whole lot of committees. Many routine clinical procedures done without sufficient thought, for little purpose other than keeping the records tidy, are far worse than many research investigations. Lumbar punctures, for instance, on babies with convulsions—a junior houseman might say: "dare I not do this?" whereas somebody more experienced would know that it will be of no value.

DR. PORTER: This is a question of experience rather than ethics. The increasing use of medical audit should help to solve this problem.

Role of the Press

DR. RAINE: It's more likely to come from moral pressure by his colleagues than straight analysis.

DR. PORTER: What's more, the press is always on the look-out for examples of frank human experimentation.

CHAIRMAN: Danish press reports of immunization accidents did lower the acceptance rate of routine innoculations, so much so that there's now compensation of $6,000 a year for these victims.[9 10]

DR. FRANKLIN: That's a splendid attitude, because the immunization was undertaken not only for personal good but for the good of society in general. After all, Jenner is generally accepted as having done something rather wonderful. By modern criteria his work was entirely unethical. He took an 8-year-old child, gave him cowpox (a disease which as a child he wouldn't have been exposed to), and then six weeks later he exposed him to an insertion of variolous matter—a risky undertaking. The only ethical justification of this was for the greater good, and I doubt whether today the experiment would have been passed by an ethical committee.

CHAIRMAN: How do you scrutinize paediatric research projects in Birmingham, Dr. Raine?

DR. RAINE: The division of paediatrics monitors its own ethical problems—not through a separate committee, but through the existing committee of physicians. It doesn't scrutinize all projects, but is there to give advice when needed. We have to remember that any hospital wouldn't have survived with the reputation it has if unethical research had been going on.

CHAIRMAN: Dr. Porter, you have done a small research project on public reaction to research on children?

DR. PORTER: I had a project for research on the siblings of children who'd succumbed to "cot death". I was told by a paediatric authority to whom I showed my protocol for comment that venepuncture on these children was inadmissible under the M.R.C. code. This astonished me so much that I asked the reaction of the first ten colleagues I met; the instinctive reaction of nine out of ten of them was "of course you may." What's more, a professional market research worker in the course of her duty asked 10 laymen the same question—and all of them said that I could.[8] It was Justice Weddell Holmes who said last century that the advantage of the jury system was that it kept the law in touch with public opinion—and I think that medical opinion in ethics has now wandered rather far from what the public think is right.

DR. RAINE: The question of the ethics of screening is a new and sensitive topic. We started a mass screening project in Birmingham, fully aware that this was a reversal of traditional medicine, where the patient comes to meet the doctor.

DR. FRANKLIN: This is whole-population screening?

DR. RAINE: Yes—screening for phenylketonuria, and in our case for a whole host of other diseases. This is done on a capillary blood specimen taken by the midwives; so far as the patient is concerned, it's exactly the same as the routine Guthrie test.

DR. PORTER: Does this raise ethical problems; surely the problems are just over patient management?

DR. RAINE: Not in taking the sample—that's all right—but a large number (5%) of babies have an abnormal result from their first test. Then you have to repeat the test, but from that moment the mother is worried, and you have problems unless she gets a definitely normal result back very quickly. Occasionally you have to do a third test, and very early on we got into the practice of bringing mother and baby to the clinic for a full explanation from the doctor, and the opportunity to ask questions.

DR. PORTER: This is still a question of handling patients, not medical ethics.

Experimental Approach

DR. FRANKLIN: No, ethics do come into this, because our ignorance of many of these conditions really make this approach an experimental one. I'm sure that the mothers must be allowed to opt out of these programmes.

DR. PORTER: Is the programme primarily for the patients' welfare or primarily experimental?

DR. RAINE: This started in an effort to improve the Phenistex test for phenylketonuria, which everybody agreed needed doing. But during the research the Department of Health suggested that the Guthrie test should become the standard, so that our

primary reason was removed. However, we also found that we were picking up other conditions and were beginning to ask questions about their prevalence in the population and whether they could be treated.

DR. FRANKLIN: You are discovering the extent of the problems and whether they are preventable; you must know what you are dealing with before you can begin treatment.

CHAIRMAN: Aren't we back at the greater good concept?

DR. PORTER: The greater good concept is secondary, surely; when these tests are done on babies in my practice I've never been conscious of the slightest difficulty or anxiety, but perhaps I haven't been looking.

DR. RAINE: There is a lot of anxiety, generated particularly by an occasional midwife, who says: "oh it's just a test to see if your baby is mentally handicapped." You couldn't conceive of a worse presentation than this. We tried in the early stages to have a lot of publicity—talks, newspaper articles, and television programmes—but we've got a bit lax about this.

DR. PORTER: But surely the individual paediatrician needs to know whether a child has an inborn error of metabolism?

DR. RAINE: Yes.

DR. PORTER: Therefore this test is for the welfare of that child and not an experiment. The greater good for society is secondary, and so no ethical questions arise.

DR. FRANKLIN: But you can't always treat what you discover.

DR. RAINE: We found that histidinaemia and prolinaemia were as common as phenylketonuria—that was new knowledge. There's probably a good case for treating histidinaemia, and so we did, but nobody knows about prolinaemia, so we decided not to treat these babies, but are following them up.

DR. FRANKLIN: What is your incidence of phenylketonuria?

DR. RAINE: One in ten thousand.

DR. FRANKLIN: So there are 9,999 babies having pricks for the sake of one.

CHAIRMAN: Shall we ever get to the point where a venepuncture for research on a normal child is accepted as right?

DR. FRANKLIN: I'm not sure that they are considered to be wrong; but you need to defend your position clearly if you do one—and that's as it should be.

DR. PORTER: At present they are regarded as wrong mainly because of what I regard as wrong advice to the M.R.C.

DR. RAINE: We also need to think carefully before we bring the child to the hospital for an unnecessary visit. A lot of our effort goes into managing the child with a metabolic disease at home.

DR. PORTER: This emphasizes that a lot more research should be done where these difficulties are much less—in general practice.

CHAIRMAN: I think that is the subject of another discussion.

References

1 *British Medical Journal*, 1964, **2**, 177.
2 *British Medical Journal*, 1964, **2**, 178.
3 *Lancet*, 1970, **1**, 822.
4 Curran W. J., and Beecher, H. K., *Journal of the American Medical Association*, 1969, **210**, 77.
5 *Archives of Disease in Childhood*, 1967, **42**, 109.
6 *World Medicine*, 22 Septemeber 1971, p. 23.
7 Plotkin, S. A., *New England Journal of Medicine* 1972, **287**, 205.
8 Porter, A. M. W., *British Medical Journal*, 1973, **1**, 46.
9 *British Medical Journal*, 1973, **1**, 794.
10 *British Medical Journal*, 1973, **1**, 758.

General Practice Observed

Iatrogenic Disease in General Practice: Its Incidence and Effects

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Summary

A year's survey of iatrogenic disease in general practice showed that one consultation in every 40 was the result of iatrogenic disease. Iatrogenic disease may affect the doctor/patient relationship, often leading the doctor to feel guilty or the patient to become aggressive.

Introduction

Reports and discussion of the adverse effects of medical treatment form a substantial part of both lay and medical literature. Remarkably little is known, however, of its incidence in the community, the reports published by the Committee on Safety of Medicines probably indicating only the tip of the iceberg. Several surveys have dealt with the incidence in hospital practice. Hurwitz and Wade[1] observed 1,268 hospital inpatients, and drug reactions were found in 10·2% of all patients receiving drug therapy (digitalis, ampicillin, and bronchodilators particularly). In medical wards the incidence was 16·4%. Surveys in other hospitals showed considerable variation in incidence, probably because of different methods of reporting the side effects. Hurwitz[2] found that 2·9% of 1,268 patients in hospital were admitted because of adverse reactions to drugs given for therapeutic reasons (digoxin, antibiotics, corticosteroids, anticoagulants, analgesics, and tranquillizers were the commonest offenders). A further 2·1% of the patients were admitted with self-poisoning.

This survey attempts to estimate the prevalence of iatrogenic disease in general practice and draws attention to the effects on the doctor/patient relationship.

Method

The practice under study consists of 6,200 patients and is mixed rural and industrial on the edge of the South Yorkshire coalfield. Patients move freely among the three partners, whose prescribing habits are similar. Comparison between the prescribing habits of the practice and the national pattern is shown in fig. 1, where the figures are taken from a sample

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