INVITED ARTICLE

EXPERIMENTS ON HUMAN BEINGS

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The concept that human experimentation is an ethically acceptable practice was rudely shaken by the exposure of some researches carried out on involuntary subjects during the Second World War. The memory of what can happen still causes doubt in the minds of some persons as to the morality of using human beings as subjects for experiment in any circumstances.

It is, therefore, important to achieve an overall justification of the practice before going on to the particular and I suggest we can call upon at least three arguments to support the case. The first, perhaps rather negative but, nevertheless, widely held view is that it is no less immoral to use animal subjects for the benefits of humans than it is to use humans themselves. I doubt if this would have carried much weight 10 or 20 years ago but, certainly in Europe, the animal rights campaign is rapidly becoming more aggressive and influential. The second justification to some extent springs from this and rests on the fact that human beings are not merely intelligent animals. Their way of life, their feeding and their reproductive cycle are different from those of the lower animals. There is no reason to suppose that experimental results in animals are immediately transferrable to humans; the ultimate test of a medical or surgical treatment designed for numans is whether or not it will work in humans. Thirdly, we have to consider the morality of accepting a particular treatment without adequate analysis of the alternatives (1). We live in an age of competition for resources — certainly in the United Kingdom — and we are, therefore, bound in honour to deploy those resources economically. We should find out whether a superficially attractive but resource intensive procedure is, in fact, better than one which is less flamboyant before we compete with each other to introduce it on a wide scale.

If, then, we accept the generalisation that human experimentation is both necessary and, on a utilitarian basis, also ethical, we must look to its particular regulation. The original, largely lay influenced, Nuremberg Code was replaced in 1975 by the revised Declaration of Helsinki prepared by the World Medical Association (2). This remains our guide although I suggest that it is only a guide and that international declarations, which are often inspired by a single objective, must be interpreted in accordance with the public policy of the time and with individual national circumstances.

As is well known, the major contributions of the Declaration of Helsinki were, firstly, to lay down basic principles and, secondly, to distinguish between therapeutic research and non clinical or purely scientific research. From this it follows that there are two quite different experimental populations — the patients themselves or healthy volunteers — and these will demand different ethical appraisal. In the interests of space, I propose to limit my remarks to the rather more controversial areas.

Research and experimentation on patients is of two main types — that devoted to the individual case and that designed for the benefit of sufferers as a group. One would have thought that the treatment of the individual patient presents no major problem. But we can look at a quotation from the statement by the British Medical Research Council:

> 'In the case of procedures directly connected with the management of the condition in that particular individual, the relationship is essentially that between doctor and patient. Implicit in this relationship is the willingness on the part of the subject to be guided by the judgement of his medical attendant. Provided, therefore, that the medical attendant is satisfied that there are reasonable grounds for believing that a particular new procedure will contribute to the benefit of that particular patient... he may assume the patient's consent to the same extent as he would were the procedure entirely established practice' (3).

That was written in 1963 but we are now nearly a quarter of a century further on and it seems doubtful if such blatant paternalism is now acceptable. The patient has a right to choose even death in preference to a procedure which may have unpleasant side effects. The assessment of the risk/benefit ratio of an innovative treatment is essentially one to be made through a doctor/patient relationship; the so called 'therapeutic privilege' can hardly extend to the introduction of experimental techniques.

But our main concern as regards adult patients must lie in the field of group treatment — in short, in the conduct of the clinical trial. Again in the interests of space, I will not discuss the better appreciated and accepted problems associated with clinical trials but will pick out those which seem to me to be particularly significant. The first of these is the potential conflict between the physician responsible for primary care of the patient and the research group. It would seem that the primary and, indeed, major, ethical responsibility rests on the former because it is he who must agree to admitting the patient to the trial and he who must counsel the patient as to acceptance of the situation. For a trial to be ethical, the researchers must either believe that a new treatment is preferable to one that is already accepted as standard or they actually do not know which treatment is to be preferred. Knowledge, is, however, different from instinct and the primary care physician must have a 'gut feeling' as to what is best for his patient. I believe, in effect, that, while we discuss at great length the ethics of the researchers, we often forget that the major problem exists a stage further back at admission to the project. This is particularly so if the best is to take a long time. Can a general practitioner randomise his patients to assist in a trial to discover, say, whether high vitamin dosage in pregnancy reduces the incidence of neural tube defects? If he believes it might be so then, clearly, *all* his patients should be so treated. And what if a suggested supplement *might* be harmful — is he to wait until the major research project achieves statistical significance before withdrawing his patients? The dilemma is acute (4).

It follows that patient care and research care are uneasy bed fellows in the context of clinical trials. It is true that every time a doctor prescribes a drug for the first time he is conducting an experiment — but it is an experiment devoted to a particular patient in the particular context of patient care. It is not the same thing as a randomised trial which must, I believe, be undertaken by those who are not responsible for primary care.

Nevertheless, although not everyone is in agreement — it has, for example, been asked whether it is right to assume that every problem has a scientific solution (5) — it seems to me that, given the assessment and balancing of the purpose, the benefits and the risks associated with a novel procedure and its alternatives (6), the randomised clinical trial is acceptable with two possible special considerations. The first of these is the use of placebos, in which context it has been questioned whether deliberate deception of the patient is ever acceptable (7). This is, I suggest, too narrow a view. So long as the result obtained is measured in symptomatic terms, the placebo is a necessary part of the research and carries with it the possible fringe benefit of discovering harmful effects of the substance or treatment under test. Nevertheless, there are good reasons for suggesting that the use of placebos should be strictly limited; there must be few circumstances in which a genuine reference substance is not available. And I would suggest that this limitation should be even more strictly observed in relation to placebo therapy.

The second special care would seem to be the double blind trial in which the caring physician is, himself, unaware of the treatment being given. I would suggest that the ethical acceptability of the double blind decreases as the severity of the condition under research increases. And if, at the other end of the scale, the results of the research are so trivial that the caring physician may reasonably be left in doubt as to the treatment his patient is receiving, then it is questionable whether the research was worth undertaking.

It is apparent that there are essentially two hurdles which the randomised trial has to overcome — the potential affront to the doctor/patient relationship and the problem of consent (8). I suggest that it is in the latter field that ethics and, ultimately, the law, as opposed to clinical judgement, become most concerned. In the present climate of opinion it seems to be beyond argument that patients should know they are concerned in a research programme and that they should have sufficient information on which to determine their participation. Once again, however, we have two hurdles to cross. The first refers, again, to the question of 'therapeutic privilege' — are there times when the prognosis is such that the patient should not be informed of the details and of its possible amelioration? My own feeling is that discussion of medical matters in the media is now so widespread that there can be few patients who are not aware of the inferences to be drawn from their symptoms; it seems to me, also, to be relatively immoral to suppose that it is

right to withhold from patients the information that they are suffering from a potentially lethal condition. Yet, such a premise would seem to be the only justification for such remarkable instances as that reported by Brahams (9) where treatments, which included the portal infusion of effective cytotoxins, were allocated randomly to patients without their knowledge or concurrence (10). And it is important to appreciate that this particular experiment came to public notice only because a death occurred; one must assume that many undoubted experiments are being similarly undertaken without public knowledge and it is encouraging to note that the most distinguished research investigators are moving towards the view that full consent of the subjects is essential to an ethical research programme (11).

It does, however, lead to the second problem which asks whether a patient can ever give so-called informed consent to a trial in which even the doctors are divided (12). It has been suggested that only those actively involved in the caring professions are capable of so doing and I have, myself, gone on record as wondering whether the ultimate test of the ethics of a randomised trial might be to see how many physicians' wives were enrolled as subjects (2).

The concept of 'randomised consent design' has recently been introduced in an attempt to evade the difficulties of informed consent — both from the physicians' and the patients' viewpoints — and, in practice, to increase the accrual rate to therapeutic experiments (13). This strategy, which is also known as pre-randomisation, involves the designation of patients to a particular therapeutic regimen *before* they enter the trial; as a result, the patients can be informed of what is proposed for them as individuals rather than they be asked to make an almost impossible choice. But it is then, equally, impossible for the physician or surgeon to avoid bias in the presentation of his case to the individual patient and, for myself, I would agree with those who doubt the validity of methods designed to increase patient participation which would not have been forthcoming had the device not been used.

Thus far, we have been concerned only with the strictly therapeutic trial. The non therapeutic trial, however, introduces several more ethical dilemmas, the particular ones which I would like to pick out being the use of 'captive' populations. The first of these includes actual patients who, by virtue of already being in hospital, may well be the practical ideal as test subjects for research which has no connection with their reason for being in medical care. There are many, and I would align myself with them, who would regard the acceptance of such research as one of the major grounds for criticism of the Declaration of Helsinki (Part III, para 2) (14). I find it hard to see many circumstances in which one could say with absolute certainty that an extraneous experimental project would have no effect upon the well being of the patient.

I also isolate prisoners as a special group because they have been, and possibly are being, used for experimental purposes and because they illustrate most vividly the difficulties of dissociating consent from inducement in any non therapeutic situation (15). Prisoners are, moreover, liable to volunteer for experiments which are inherently dangerous because it may well be advantageous in a prison situation not only to feel ill but actually to be ill. In short, it is far from convincing that prisoners can ever give wholly autonomous consent to experimental projects and, while it may be permissible to conduct research and treatment aimed, say, at reducing recidivism, paralogisms in favour of the use of prisoners which are based on such grounds as that giving a service to society conduces to an acceptance of society are, at best, unconvincing.

The less therapeutic and the more hazardous an experimental protocol becomes, the more it behoves the researchers to involve themselves as subjects. But the dangers must always be equilibrated with the anticipated value and no researcher is entitled to place either himself or others at a probable risk of severe injury. It was George Bernard Shaw who wrote 'No man is allowed to put his mother in the stove because he desires to know how long an adult woman will survive the temperature of 500°F, no matter how important or interesting that particular addition to the store of human knowledge may be'. ('*The Doctor's Dilemma*').

The lady in question is not likely to have consented to the procedure and it is clear that consent lies at the heart of any ethical experiment; many would hold that the information to which an experimental subject is entitled is greater than is that owed to the patient (16). What, then, of those who are unable to consent — that is, particularly, the child, the fetus and the embryo? Each of these groups merits consideration in their own right. Moreover, the attitudes to research in such fields are so conditioned by individual national attitudes and, in many instances, actual legislation, that it is extremely difficult to generalise.

Again in the interests of space, I will confine myself to expressing some personal opinions, the first of which is that patients ought to be able to consent to research on their children and this, again, is accepted in the Declaration of Helsinki. This assumes, however, that the risk/benefit ratio is grossly imbalanced in favour of benefit and that, when a child is capable of understanding, he or she should not be involved in an experimental procedure if there is any conflict between that child's wishes and those of its parents (17). The problem of fetal research is particularly emotional and, again, I offer no more than my own opinion — invasive and potentially damaging fetal experimentation is permissible only if the fetus is dead or during the phase in the non viable fetus which can be regarded as that period existing between somatic death and cellular death. As to the embryo, I have stated elsewhere my firm agreement with the majority of the Warnock Committee (18) that research and experimentation are morally acceptable at least up to the fourteenth day of existence provided that existence has been in vitro and not in vivo; I believe, however, that this applies only to the embryo rendered 'spare' in the therapeutic process — I cannot condone the deliberate production of embryos for the sole purpose of research and experimentation (19).

The public surveillance of research becomes particularly important whenever there is a doubt as to the validity of consent. The concept of the research ethical committee is particularly relevant to research on children and, equally, on the aged or any others who may not be totally in control of their lives. I would not like to see the role of the ethical committee extended into that of a prognostic committee as has been the tendency in the United States (20). I would, however, suggest that the function of research ethical committees should be standardised at national level, that they should be — and be seen to be — wholly independent of the researchers themselves and that such committees should contain a reasonable element of responsible non medical opinion. The latter are there to ensure that research is limited to that which does not offend the susceptibilities of the public. But research much continue and one would hope, with the leader writer of *The Lancet* that all the members of ethical committees should be not only well meaning but also well informed.

Research must go on but we should bear in mind the

cautionary words of the British Medical Journal which advised us: 'At a time when there is so much public questioning of medical traditions... research workers need to be especially careful not to offend these hightened susceptibilities' (21).

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