THE NEED FOR CLINICAL TRIALS

BY

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The need for a clinical trial of a new drug is obvious. Well-designed clinical trials, however, are also needed to extend the evaluation of drugs and procedures beyond the largely empirical stage at which they may have been introduced and to assess as precisely as possible the frequency and severity of their side effects. It is worth noting that clinical trials may be applied not only to a drug, but also to any medical procedure ranging, for example, from operative interference and such specialized techniques as induced hypotension, hypothermia and hyperbaric oxygenation to such simple daily tasks as, for example, setting up an intravenous infusion and performing an endotracheal intubation.

CLINICAL IMPRESSIONS

The balance as between the “art” and “science” of medicine has during this century shifted steadily towards medicine as a science which is based on sound physiological and pharmacological principles. This progress was greatly accelerated after the Second World War by advances in technology and the better understanding of biological processes which resulted therefrom. In therapeutics this has been manifested by scepticism towards any worker who bases his statements solely on untested impressions derived from clinical practice, no matter how extensive or prolonged that clinical practice may have been. Impressions alone have often been the foundation upon which has been based much clinical practice and also a great deal of didactic teaching.

Nevertheless, having agreed to test and test again, it should not be forgotten that the impression may still be the original stimulus leading to a clinical advance; scepticism should not be allowed to produce a climate in which the observations of an alert clinical mind are undervalued. Careful investigation, however, should always follow a possibly significant clinical observation.

DRUG TESTING

To evaluate a need for clinical trials of new drugs, it is helpful to enumerate the stages through which a new drug must pass before it is released and approved for general prescription.

Chemical tests of purity are a first requirement. Recent mishaps from impurities in nitrous oxide (Lancet, 1966) have focused attention on the great responsibility carried by drug firms in this respect. A suspicion that hepatotoxicity of halothane might be attributable to impurities has also directed special attention to possible contaminants. In fact, the extraordinarily good record of the pharmaceutical companies in this respect should not be forgotten because of mishaps.

It is only after the substance has been prepared to a high degree of purity that clinical trials will be either needed or permitted. Tests for bacterial sterility of preparations for parenteral injection will also be required at this stage.

INVESTIGATIONS IN ANIMALS

Animal testing is a prerequisite before the administration of any substance to human subjects. The pharmacologists will have explored the activity and potency of the drug in respect both of its therapeutic action and of its side effects, but there remains a whole range of toxicity tests which modern drug control rightly demands. It may be that this already very long series of experiments will be extended as new knowledge accrues, for there is no reason to believe that the last word has been said with the discovery of teratogenic effects. The routine animal tests include estimations of minimum lethal dose on large populations of small animals, investigations into effects on cardiovascular, respiratory, central and autonomic nervous systems, as well as a search for hepatotoxicity, nephrotoxicity and teratogenic hazards.

It is, however, important to bear in mind the deficiencies inherent in testing drugs on animals.
There is a possibility that a desire to protect the public from experimentation or from unjustified enthusiasm for new products may result in useful therapeutic agents being overlooked. Anaesthetists will not need to be reminded of the extreme variation in drug action from one species to another, and results obtained in animals must not be applied to humans without a cautious appraisal of the whole situation. Had morphine been assessed by its action on the cat, it might never have been allowed to become one of the greatest blessings to mankind. It is at least arguable that if ether had been given a more extensive trial on cats or rabbits (animals notoriously susceptible) before the ether frolics and before Miss Parrot walked into Morton's surgery for a painful tooth filling, the discovery of anaesthesia might have been delayed indefinitely. This species difference is exemplified not only in the type of action exerted by the drug (as, for example, in the stimulant action of morphine in cats, or the contracture produced by suxamethonium and decamethonium in avians) but also, of course, in potency. An example was provided by a new relaxant drug which was found by the writer and his colleagues to have in the dog marked inotropic actions on the myocardium and little anticholinesterase effect, but in humans the former effect was not evident in therapeutic doses, but cholinergic effects were of such severity as to preclude its use.

The need for a cautious approach to and evaluation of the results of animal experimentation is further illustrated by the story of the introduction of curare into clinical practice. Very many years before it was successfully used in convulsive therapy and anaesthesia, attempts had been made to use its effects in the treatment of tetanus, hydrophobia and other spastic conditions. Failure to secure adequate pulmonary ventilation in human patients resulted in disaster, and this despite the fact that Sir Benjamin Brodie in 1811 had kept a donkey alive by intermittent lung inflation. An inherent danger of curare was apparently further demonstrated by West's (1938) experiments in dogs and guineapigs, which showed that the administration of curare led to the development of intense bronchial constriction and, as a result, all interest in the drug lapsed. Even after its clinical use had become accepted, Landmesser's (1947) demonstration of bronchial constriction in dogs influenced the use of this drug in some parts of the world. These results are not surprising in the light of later knowledge of the susceptibility of these two species to histamine, but they could have delayed the full exploitation in human patients of what is still the most useful muscle relaxant. Indeed the opinion is justifiable that had curare, digitalis and even possibly the first sulphonamide and penicillin, among other substances, been submitted to the full battery of animal tests demanded today, they might never have entered the pharmacopoeia.

A further deficiency in animal testing is that too often there is a failure to control all the variables which might influence the result. A good example is seen in the testing of a drug for hepatotoxicity by repeated administration to small animals without taking into account its possible respiratory depressant action and the consequent hypoxia.

In summary, the testing of drugs in animals for toxicity (acute and chronic), for potency and for side effects is at the best a gross admonitory procedure and at the worst may result in the by-passing of valuable therapeutic agents. The real worth of a drug can only be assessed by observation on the species for which it is intended—the human being. This can be done by carefully planned and cautiously undertaken observations on human volunteers.

**STUDIES IN HUMAN VOLUNTEERS**

Human volunteers are an essential part of the screening of some preparations before clinical trial. While removing most of the objections which have been described in relation to animal experiments they are still limited in scope. Whilst they reveal the significance in the human subject of side effects seen in the animal work, or unsuspected actions, and may also permit the use of refined techniques of monitoring not always possible in patients, they will not in most cases be practical as an index of therapeutic effectiveness. Whilst volunteers may permit themselves to be given a minor infection before the administration of vaccines or drugs, they are unlikely to permit, and ethically would be unjustified in permitting, the introduction of any serious disorder, although medical history is not without
many heroic examples of such extremism. Furthermore, the relatively small number of individuals who are likely to volunteer for experiments is always a limitation, and rules out human volunteers for the assessment of marginal differences in therapeutic effectiveness. The use of “volunteers” in prisons and mental hospitals is always suspect and is not likely to be ethically acceptable to many workers. To many problems, the clinical trial provides the only answer.

**Clinical Trials**

The purpose of clinical trials is to obtain the maximum amount of unbiased information concerning the principal action and side effects of a drug or procedure from the minimum number of patients in the shortest time and with the least potential hazard or inconvenience to them.

Each part of this definition presupposes that only “good” clinical trials should be considered. Any trial which does not produce the “maximum” amount of information from the effort put into it, or which is not “unbiased” and which exposes more than the “minimum number” of patients to any more than the “minimum hazard” is not justified. The other criterion, “the shortest possible time”, will be one that the investigator will surely require.

Clinical trials may be designed with three aims in view: (a) to assess the activity of a new product with an action which is unique or is present to a unique degree; (b) to compare drugs with a similar action, but with varying potency and side actions; (c) to re-assess more precisely drugs or procedures which are regarded as well established.

*The assessment of a new product with a unique action.*

The drug may have a completely novel effect, as, for example, ether when it was first used as an anaesthetic, or it may have a desired effect in a degree hitherto unknown. The clinical trials in such cases will be simple and straightforward. There may have to be comparative trials, but the more obvious the beneficial effect the less necessary these will be. Controls were hardly necessary with penicillin or insulin and were certainly unnecessary when curare was first given in anaesthesia.

**Comparison of drugs with similar actions.**

This is the most usual aim of a clinical trial. The differences between the drugs may be marked, as in the relative potency and duration of effect of the two analgesics, morphine and fentanyl, or marginal as in the case of morphine and methadone. The more marginal the differences, the more extensive will be the trial that is required and the more elaborate its planning and statistical pattern.

**The more precise re-assessment of drugs or procedures already established.**

There is always a need for clinical trials of this type as more highly developed and sensitive techniques for re-assessment become available. A case might be made out for the re-assessment, for example, of induced hypotension. How necessary, in fact, is this technique for many of the situations in which it is used, if adequate pulmonary ventilation and full muscle relaxation be ensured? There is obviously still a need for an adequate and well-designed trial to establish the need for or the required intensity of any supplementation of nitrous oxide-relaxant anaesthesia.

**The Limitations of Clinical Trials**

No matter how well designed, it will be recognized that a clinical trial will always have its limitations. It may not reveal all the effects of a drug, particularly if these are completely unsuspected. Thalidomide provided a tragic example. Side effects which occur only in special circumstances, as in this instance in early pregnancy, may only be revealed after extensive clinical usage.

A clinical trial may not reveal the biological variation which exists as between individuals. A rare allergic or immuno-chemical reaction to a drug, such as has been proposed to explain an apparent very rare connection between hepatitis and halothane, may not become apparent even after extensive clinical trials. Allergy to penicillin was not revealed in the early trials.

No matter how carefully designed, the trial may be limited by what it is possible to measure. It may, for example, be questioned whether the methods of pain assessment at present available are sufficiently objective.
Even in clinical trials human fallibility in interpretation will always be a limiting factor. Research workers are always open to the temptation of misguided enthusiasm. In this respect it might be doubted whether the prolonged administration of potent agents for conservative dental work has received the careful assessment that it merits. It could be that this is such a unique advance that a comparative clinical trial would not appear necessary. There is, however, in this field such an overlay of enthusiasm and such an emotive response to the apparent relief of anxiety in patients that there is a danger of overlooking the morbidity, and the possibilities of a fuller exploitation of good local techniques already available. Here indeed is a field ripe for a well-designed clinical trial. Only a short while ago, in anaesthesia, extravagant claims were made on the basis of clinical trials inadequately designed for the beneficial effects of various combinations of phenothiazines and analgesics (lytic cocktails). In the light of accumulated experience these claims have hardly been justified and the techniques have been, for the most part, discarded.

Finally, there will always be ethical limitations to clinical trials. The investigator must be on his guard lest his enthusiasm dims his conscience in regard to what is permissible. This problem has been fully discussed in the M.R.C. Report (1962) on the ethics of human experimentation, quoted in extenso in this issue. It is clearly not permissible to submit patients to known hazards, as, for example, those associated with large vein catheterization, where no clinical benefit is likely to accrue. Any consent given by the patients to such manoeuvres must be "enlightened", yet it is sometimes impossible and generally inadvisable to explain all the hazards, for this would create alarm and would certainly lead to the withholding of consent. It is not necessary here to do more than give a reminder of these problems and a caution to the prospective investigator that there should be no infringing of the rules which have been laid down.

CONCLUSION

With all their limitations, there will always be a need for clinical trials, both for the investigation of new substances and for the re-assessment of established drugs and procedures. The anaesthetist of today who has a lively mind will want to question many of the inviolable truths which have been handed down to him and which are so often based upon either empiricism or clinical trials very inadequately planned.

REFERENCES


PRELIMINARY NOTICE

A SYMPOSIUM

on

"THE ANAESTHETIC PROBLEMS FACING DEVELOPING COUNTRIES"

will be held at Addenbrooke’s Hospital, Cambridge,

on Saturday, June 10, 1967