CLINICAL TRIALS IN THE ASSESSMENT OF DRUG EFFICACY AND SAFETY

PETER R. B. NOEL, M.B., B.S.
Clinical Investigation Unit,
Huntingdon Research Centre, Huntingdon

NEW drugs must be tried out adequately in two or more unrelated animal species before the compound is administered to man (Noel, 1962). The extent of such testing depends on the proposed duration of clinical use.

In man the phases of introduction of new compounds may be divided into three:

1. initial human administration;
2. clinical trial to assess efficacy;
3. general medical use.

The amount of toxicological (animal) testing required to cover the safety aspect of each phase will obviously differ, as will the total quantity required differ, according to the probable fields of use of the drug. Before initial administration to man, a short-term, subacute animal test is necessary; however, this may be run concurrently with the chronic test for safety. When these pharmacological and toxicological studies are complete, subsequent stages depend greatly on the proposed use of the drug, and, in this respect, drugs may be subdivided into two main groups:

Group 1. Drugs to be used on severely ill patients who would normally be in *hospital* and in whom the risk of side-effects may be accepted because facilities are available to counteract them, and because it is important to improve the patient's probability of recovery.

Group 2. Drugs to be used on patients who are not severely ill, where the risk of life is by no means immediate or certain; therapy which is essentially within the sphere of *general practice*, where only minor side-effects are acceptable.

The term "new drug" has become almost synonymous with

drugs in the first group, especially to those in hospital practice.

Drugs in group 1

Trials of these drugs are basically simple. Patients in hospital with severe illnesses usually exhibit measurable changes over short periods of time, so that numerical grading of severity is a simple procedure. The course of subacute and chronic ailments is followed by appropriate pathological or radiographic procedures which again allow numerical assessment, important in statistical analysis.

First administration to man usually presents little difficulty. When pharmacological and animal toxicity data indicate an advantage over existing medication or an entirely new type of activity, the hospital practitioner has evidence of probable drug value. He can then give the drug in increasing dosage to patients in whom other therapy has failed. The absence of direct toxicity in man may therefore be established quickly and trial continued on patients less severely ill. Quite soon, the drug may be placed in one of three categories, by clinical impression alone:

(1) Drugs whose value is obvious—as was the case for example with sulphonamides and penicillins, mustine and aminopterin, liver extracts and hexamethonium bromide.

(2) Drugs which appear quite active, whose place in therapy has to be ascertained by more extensive clinical trial. Such drugs are frequently alternatives to existing drugs such as the later antibiotics, busulphan and mercaptopurine, cyanocobalamin and mecamylamine.

(3) Drugs which appear to have little or no activity or those where dosage is limited by side-effects to such a degree that they are unlikely to be useful adjuncts to therapy.

Thorough clinical investigations at the outset may avoid the necessity of obtaining repeated confirmation of the results before acceptance. Formal clinical trials will then be needed for drugs in category (2) alone before value is certain, and this usually means a comparison with the results of standard medicaments. Where the drug is merely part of a therapeutic regime, all additional therapy must be identical in both cases (only later should the necessity of additional therapy be assessed). Such trials are most commonly " between-patient ", so that patients must be paired within various subgroups. This subdivision is necessary when factors such as age, sex and severity of disease are thought to alter the clinical indications for use, but unnecessary subdivision only prolongs the trial and reduces the significance per subgroup, unless the disease itself is very common. Double-blind procedures are rarely necessary when the data collected is known to be reliable

and the allocation of patients to a particular therapy is strictly controlled.

On the surface such trials appear foolproof, yet faults do occur; some obvious, some hidden. Many isolated or collective, well-organized hospital trials have been reported and these have become examples of how good trials should be conducted. It does not, however, follow that because a trial was carried out in hospital, it must be good. The two principal faults are selection of patients, and unreliable data. Double-blind techniques do much to remove the doubt in such cases, provided the drugs are not identifiable by associated pharmacological or other side-effects. Radiographic interpretation is known to be variable and a number of independent opinions may be necessary before assessment is possible. Less known, however, is the variability of clinical pathology results, so that single results at intervals may need more than statistical analysis before the meaning is clear. The variation of results reported from the same specimen has already been demonstrated between laboratories (Wootton and King, 1953). Clinical measurements are frequently accepted, but can we be certain that when basal blood pressure readings are recorded, they were correctly taken? Did the same physician really carry out the same time-consuming procedure on every occasion? Observations by the nursing staff are used, but to what extent may these be relied upon when the wards are full and trained staff short?

In view of the current acceptance of results of hospital trials the attitude of the reader should be critical, so that when no faults are found the results may be accepted and acted upon.

Drugs in group 2

There is no doubt in my mind that drugs which are to be used primarily in general practice should be assessed in general practice. This seems obvious but great difficulties exist in present circumstances, all of which must be taken into account.

The general practitioner has no registrar or houseman to keep detailed records for him, to delve into small points in the patient's history and assess the urgency of complications developing during the patient's current illness. He has no nursing staff to carry out his instructions, and on whom he may depend to inform his staff when the patient's condition deviates from that expected. In addition, he is usually extremely busy and may be working very long hours. Nevertheless, he is the only practitioner with the requisite type of

patient for these trials, therefore all that can be done is to beg our colleagues to co-operate, and do *all* that is possible to reduce the extra work required to an absolute minimum. This implies that the work to be done in carrying out a trial in general practice must be divided into two separate parts, viz. (1) the planning, organization and analysis; and (2) the collection of data. This dichotomy appears to work well, as in our own case, the Unit performs the former functions whilst a group of interested practitioners observe and record. Any doctor interested in participating in such trials will be welcome to join our group.

The initial administration of a group 2 drug does not concern the general practitioner. At the moment such work is frequently undertaken by volunteers, and the establishment of specialized centres for this purpose would add greatly to the safety of the procedure. The data collected from this initial administration must be more comprehensive than is necessary for group 1 drugs despite the fact that only safety is being assessed. No subdivision of the drugs into categories can result from these initial studies, so that all drugs in this group need clinical trial to establish efficacy. As with animal toxicity testing, these minor drugs which arouse least clinical interest require the major amount of assessment to establish safety.

For a clinical trial to establish efficacy, the first step is to define the object of the trial accurately. It is no use enquiring generally whether drug A is better than drug B; the limits of the objective must clearly be stated. Since the practitioner's time is at a premium, the questions he is asked should be kept to a minimum. Apart from data identifying the patient, the information required is usually in three parts, viz. (1) a direct answer to the main question asked by the trial: (2) supporting evidence of this result or another aspect of assessment; (3) an unbiased record of side-effects. The most convenient way of obtaining the information is to channel the data into required forms by providing the alternative answers possible, from which the practitioner may choose, and allow additional space for comments. In trials of this nature it is virtually useless asking for extraneous recordings " in the hope that they may yield additional information ".

The trials most suitable to general practice assessment under present conditions are those of short duration, concise requirements and minimal investigation. The drug should be of established safety and the information regarding safety should be available

(both animal and human) and where the slightest danger exists, no risks should be taken. At the present moment, misreading of press reports has led to worry over teratogenic effects (even in males). Whilst doubt exists of this nature, it might perhaps be wiser to exclude women in the first trimester of pregnancy from drug trials, provided of course that it is realized that any drug given to a woman in the first 3 months of pregnancy is in fact a trial, if she did not have the same drug during the previous trimester.

Numerical expression of clinical findings is less common in general practice trials although certain " times " may be recorded and other clinical measurements made. The most important measure, however, is not numerical, rather an overall assessment of symptomatic relief, thus if we are to use general practice techniques we must accept that *the patient himself is the most important indicator of drug efficacy*. How much relief is obtained from anxiety symptoms on sedative "A" as compared with sedative "B" can only be assessed by the patient himself; the same applies to antitussive activity, antipruritic activity, analgesia, and so on. Since the patient always assesses his doctor's treatment himself, why has such antagonism grown against the patient's opinion? Undoubtedly it is in part due to the past use of unsound procedure and we can state dogmatically that all such trials must be *double-blind*, as well as *controlled* and *statistically analysed.*

Since the majority of these drugs give symptomatic relief in long-standing conditions, " within-patient " trials are more often possible, thus near perfect " pairing " results. Selection is avoided by complete randomization of drug allocation, the various treatments being similar in taste and appearance. Positive control drugs are always preferable on ethical grounds but where no active control is recognized a placebo must take its place, in which case the objective of the trial is to establish the presence of activity rather than comparative efficiency. In the latter case, it is important for the practitioner to have an escape clause allowing the patient to continue with the next drug, should one appear detrimental to his condition.

If we accept that group 2 drugs should be tried out in general practice, and we overcome the difficulties inherent in such a procedure, the trial is of limited value until the results are published. This major obstacle will remain until it becomes generally recognized that certain forms of patient-preference have similar values to numerical assessments. Statistical techniques may be used to avoid bias within the trial, but the bias against " preferences " without the

trial, is as yet uncontrolled. Every clinician finally chooses his drugs on the basis of preference (or personal impression) which after all, is the art of medical practice. " Accepted therapy ", too, is only the statistical result obtained from analysing the procedures followed by the medical population, which again, are based on personal preferences.

Safety

Finally, of great immediate importance, is the final assessment of drug safety; the " trial " of the drug in man himself, *after* release for general use. As yet, no other means of assessing hypersensitivity reaction is known. The blood dyscrasias, probably allergic in origin, exfoliative dermatitis and drug fever are among the conditions that cannot be detected as yet in animals, and the incidence is frequently too low to be detected with certainty in the patient-sample used in normal trials. Thalidomide has demonstrated a new group of toxic effects which were not detected despite very thorough testing at the time and it will still be some years before the true clinical value of teratogenic tests in animals can be evaluated. Other drugs may adversely affect man in a manner not yet thought of. All drugs administered to a patient for the first time are trials. The likely effects and relative efficiency should be known before administration, therefore deviations are important. Recognition of such unknown effects has led to the discovery of new groups of drugs. Adverse effects must also be recognized, considered part of a universal trial, and reported, but to whom?* The disease notification scheme is limited but has already proved its worth; extension of its activities might well be the answer to the early detection of these toxic effects in man.

Summary

The programme of new drug introduction may therefore be summarized:

1. Pharmacological testing to help establish the metabolism of the drug, its range of activity and its efficacy compared to compounds having similar activity.
2. Toxicity testing in animals, using an adequate number of animals and species to indicate direct toxic action during growth, adulthood, pregnancy and foetal life.
3. Initial administration to man under conditions of maximum safety to indicate the presence or absence of acute toxic changes and rarely efficacy.

*Since this was written, the Committee on Safety in Drugs has been established, one section of which deals with " adverse reactions ".

4. Clinical trial to establish relative efficacy; these trials being carried out in the field of proposed medical use.
5. Publication of data.
6. General medical use when the adverse effects of long-term administration in man or reactions which appear to be unique to man will be detected.

It is advantageous, both to patient and to doctor, that drugs used therapeutically should be of known safety and efficacy. It is therefore necessary for *all* concerned to co-operate in the various stages of drug assessment.

Deficiencies now exist and to overcome these, it is suggested that:

1. More attention should be given by the pharmacologist to the absorbtion, metabolism and elimination pathways of new compounds.
2. Some degree of standardization should be agreed as to what are the minimal requirements for toxicity testing in animals.
3. Selected teaching and non-teaching hospitals should provide facilities for the initial administration of new drugs to man, so that the procedure is performed under conditions of maximum safety.
4. Clinical trials should be so organized that the information required is obtained and the results are not indecisive personal impressions.
5. General practitioners should accept that they are in a unique position, not only to participate in organized trials of drug efficacy but also to supply the data from which the final assessment of drug safety may be made.
6. Patients should be educated so that they may understand the processes involved, and are encouraged to participate in organized trials, knowing that such procedures are in fact often safer than the indiscriminate prescription of new drugs by individual doctors.
7. Space should be made available in the medical literature for the results of clinical and pre-clinical investigations.
8. A nation-wide notification scheme should be set up to collect, investigate, and correlate the information obtained with regard to toxicity; after a drug has been made available to medical practice. A start might well be made by making all congenital abnormalities notifiable.

REFERENCES

Noel, P. R. (1962). *Lancet*, **2**, 824.
Wootton, I. D. P., and King, E. J. (1953). *Lancet*. **1**, 470.