CLINICAL PHARMACOLOGY

G. A. ELLIOTT, M.D., F.R.C.P., *Professor of Medicine, University of the Witwatersrand, and Chief Physician, Johannesburg Hospital*

During a study tour from October 1964 to April 1965 I visited the USA, Canada, the United Kingdom, Holland, Sweden, Switzerland, France and the Federal Republic of Germany, studying the production, control and use of drugs. My main purpose was to obtain a comprehensive picture of the functional operating relationship between the drug industry, State drug control bodies and the medical profession. From the professional point of view I was anxious to ascertain what are the training and functions of the clinical pharmacologist, particularly in view of the recent establishment in the Department of Medicine of the University of the Witwatersrand and the Johannesburg Hospital of a new post, that of Therapeutic Trials Physician. The original defined functions of this post conformed in most respects to what I found on my study tour to be the functions of the clinical pharmacologist as outlined below.

THE FUNCTIONS OF CLINICAL PHARMACOLOGY AND THE CLINICAL PHARMACOLOGIST

Clinical pharmacology, like pharmacology, has no fixed definition. It has been said that 'pharmacology is what the pharmacologist does'. A similar definition might be applied to clinical pharmacology and the clinical pharmacologist. Clinical pharmacology, however defined, is an interdepartmental subject, and the clinical pharmacologist should be diplomatically suited to collaboration with many departments. The subject bridges the gap between academic pharmacology and clinical drug therapeutics.

By present convention, the clinical pharmacologist studies mainly chemical substances used as drugs (pharmaceutical specialties) and some 'biologicals'. The definition of a drug in terms of the South African Drugs Control Act of 1965 is 'Any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in (*a*) the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man; or (*b*) restoring, correcting or modifying any somatic or psychic or organic function in man'. This definition conforms in general to the definition of a drug in the drug control regulations of most countries.

What Does the Clinical Pharmacologist Do?

A. *He tests drugs in man.* The simple stated purpose of pre-registration clinical trials is to investigate pharmacological activity, toxicity and side-effects, safety and therapeutic efficacy.

The first clinical trials of a new drug, based upon the evidence provided by the chemist, experimental pharmacologist and toxicologist, aim at the investigation of pharmacological activity and toxicity on a small number of normal subjects for about 2 weeks per subject. The choice of subjects raises ethical moral and legal problems. They may include drug-industry staff, students, nurses and prisoners, but all are voluntary subjects.

The selection of the dose of a new drug to be administered for the first time to man presents problems. The prediction index of pharmacological activity, toxicity and the optimum safe initial dose from the evidence provided by the experimental animal pharmacologist remains low. Owing to species difference, the safe dose in man, expressed in mg./kg. body weight, may vary from 10% to 500% of the dose suggested by animal experiments in spite of the most careful and expert advice. It is common practice to use as an initial dose in man 10% of the dose in mg./kg. body weight predicted from animal data. No reliable formula for the prediction of animal:man dose has yet been evolved. To predict the therapeutic, teratogenic and carcinogenic activity in man from the chemical formula and from the results of animal experiments is, with few exceptions, not yet possible.

The first phase of a new drug investigation in man is referred to by some as 'human pharmacology' since therapeutic efficacy and safety are as a rule not studied.

Some clinical pharmacologists confine themselves to these earliest trials, but the majority also conduct the first phase of clinical therapeutic trials in those conditions for which, from knowledge of pharmacological activity in man and animals, it is anticipated that the new drug may have a symptomatic, curative and preventive effect and be reasonably safe. Having established *prima facie* evidence of possible therapeutic effect and of safety, the drug passes to the phase of widespread therapeutic trials conducted inside and outside hospitals. These trials are required to be planned and conducted on a controlled basis if they are to support a drug company's application to the State drug control body for registration and marketing of the new drug.

Evidence of efficacy is required by all State regulations. It is not always easy to prove. Relative efficacy is a still greater problem. Efficacy must always be considered in relation to safety and to the nature of the disease being treated. Greater calculated risks may be taken in drug trials for metastatic carcinoma than for diabetes.

In regard to safety, certain commonly used terms require definition. 'Toxic effect' is a noxious effect which may become manifest during a clinical trial and which would become manifest regularly if the drug dosage were raised sufficiently. 'Side-effect', which may be toxic or non-toxic, signifies an effect on a target organ other than the target for which the drug was intended, for example, drowsiness is a side-effect of an antihistaminic. 'Adverse reaction'

signifies a noxious effect that becomes manifest while the patient is on the normal accepted dose. It may be due to idiosyncrasy, to interaction with other drugs being administered simultaneously, to food and drug interaction, as in the case of monoamine-oxidase inhibitors and cheese, or to background disease, for example renal failure. It is unintended and usually unpredictable, being noticed after the drug has been registered and is in wide clinical use. An adverse-reaction reporting system at hospital and national level is essential today if drugs are to be used as safely as possible.

At any stage of the pre-registration clinical trials, the investigation (and the drug) may be abandoned owing to inefficacy and undue toxicity. Few people outside the drug industry realize how many drugs fall by the wayside, not only in the phase of pre-registration clinical trials but also at some point between their conception and synthesis by the research chemist and the initial trials in man. A major drug company regards itself as fortunate if it is able to register with the State and therefore be entitled to market one new drug a year. This is the sole survivor of some 2,000 - 4,000 that were synthesized by the chemist 5 - 10 years before. The chemist, pharmacologist and toxicologist decide, often on rather arbitrary grounds in the present state of knowledge, which of their new chemicals should be biologically screened. These are a fraction of the number synthesized. The pharmacologist and toxicologist investigate the action, toxicity and metabolism of the few selected for their particular tests; toxicity and insufficient activity result in more being abandoned.

It is appreciated that animal tests do not necessarily relate to man. The pharmacologist, toxicologist and clinical pharmacologist then decide which of the remainder should be subjected to first trials in man for pharmacological activity and toxicity. Perhaps 20 of the original several thousand reach this stage. Those which are found to be unduly toxic or pharmacologically inactive, or less active than existing similar drugs, are abandoned. Half or less of the 20 go to early therapeutic trials by the clinical pharmacologist.

Insufficient therapeutic efficacy leads to more being abandoned. Five may be left for expanded controlled therapeutic trials, and only one may fulfil the standards that justify application being made for registration and marketing.

Over 50% of registered new drugs from all sources each year are 'buried' 2 - 5 years after registration because they are superseded by better drugs. A small handful survive.

Taking into consideration all the above factors, the responsibilities of the clinical pharmacologist are considerable, and it is not surprising that he has anxious moments about the welfare of the normal subjects and the patients on whom he conducts his tests.

Lastly, the clinical pharmacologist often confines the trials in which he actively participates to drugs related to his own clinical or research experience. His function as a designer of trials for others is described in paragraph (C).

B. *He investigates the mechanism of drug action*, and for this must have adequate laboratory and metabolic ward facilities. Ignorance of the mechanism of a drug's action does not necessarily obstruct its registration by the State drug control body, but it is generally accepted without question that knowledge of mechanism of action promotes knowledge of safety and efficacy. In such studies the resources and the collaboration of the chemist, biochemist, enzymologist, physiologist, pharmacologist, pharmaceutist, immunologist, embryologist, electron microscopist, clinical pharmacologist and other clinical investigators are required, making use of the test tube and of biological models grading from tissue culture to man.

The study of interaction between drugs is rightly receiving increasing research attention. One drug may enhance or inhibit the activity and/or safety of another. The mechanism of interaction may be reasonably well understood as in the case of probenecide enhancing the effect of a given dose of penicillin by reduction of the renal excretion rate of the latter. Other interactions are less well understood. Monoamine-oxidase inhibitors potentiate sometimes dangerously the action of such commonly used drugs as hypotensive agents, central nervous system depressants including alcohol, sympatheticomimetics, procaine, chlorothiazide and meperidine (pethidine, demerol). These perfectly accurate clinical observations which have everyday practical implications still require basic study of the mechanism of the interaction of the drugs concerned.

Enzyme induction in relation to drug action is a fruitful field for clinical pharmacological research. Phenobarbital administered over a period induces the production of liver microsomal enzyme which increases the rate of metabolism of simultaneously administered long- or short-term dicumarol. This may well explain our own experience in a respiratory resuscitation unit of the failure of dicumarol to reduce the prothrombin index when administered in normally accepted dosage for deep or superficial venous thrombosis complicating attempted suicidal barbiturate coma. Most of these cases have been on long-term barbiturates and have collected a supply of the drug from their regular dose for the suicide attempt. The study of this particular problem is complicated by the considerable individual differences in man in the rate of dicumarol, and other anticoagulant drug, metabolism, based possibly on genetic factors. Numbers of other commonly used drugs such as some analgesics, tranquillizers, antihistaminics and oral hypoglycaemics have an enzyme-induction effect in animals certainly, in man possibly. Repeated doses of one drug, for example phenobarbital or tolbutamide, may in some species stimulate the drug's own rate of metabolism probably through enzyme induction, successively larger doses having to be administered to maintain pharmacological activity. J. J. Burns quotes animal pharmacological experiments which indicate that some drugs may inhibit the activity of drug-metabolizing enzymes in liver microsomes; this increases the duration and intensity of pharmacological action of other drugs by slowing their metabolic detoxification. Examples of enzyme-inhibiting drugs are iproniazid, nialamide, chloramphenicol, para-aminosalicylic acid, meperidine and morphine. The application of these observations to man is a matter for extended research.

In all these research problems the clinical pharmacologist has a part to play as a team member.

C. *He designs trials* and their protocols for himself and others, and consequently must have a knowledge of biostatistics. In designing a trial he must plan for random selection and know when and how to apply double blind cross-over methods, sequential analysis and the 'patient is his own control' approach. He must appreciate that double blind studies are only as good as their design, and must know when it is unsafe to use a dummy placebo. Above all he must apply common sense. Today it is necessary for him to know the principles of computing, particularly the assembly, analysis and coding of what goes into the computer. 'Put garbage in and garbage comes out' is an aphorism to remember. Other functions which he may share with the specialist biostatistician are described in a later paragraph.

The others for whom he may design protocols include specialists who are likely to be the best qualified to study drug efficacy and safety in their own fields of research or clinical interest, and general practitioner groups who alone are in a position to collect cases for controlled trials of drugs in conditions met in general practice such as the common cold or epidemic influenza.

D. *He teaches postgraduates* and undergraduate medical students in their pharmacology and clinical years; one of his objectives is to help to produce a breed of medical practitioner who will use drugs critically and with understanding, and who will know how to assess efficacy and safety. He should have research fellows under his tutelage conducting research into drugs and participating in clinical trials. He should be encouraged to recruit trainee specialists (registrars) to design and participate in controlled trials as an exercise in methodology that will serve them in good stead in their profession. He may be able to arrange that medical students participate in simple drug research projects during their spare time or vacations. Through the medium of a hospital-medical school newsletter and the medical press he can disseminate drug knowledge.

E. *He should have time to do his own research* even if it has no direct bearing on drugs. It is however surprising how many research projects can in fact be drug-slanted, and how many projects unrelated to drugs lead to better understanding of drug action. The potential careerist in clinical pharmacology is more likely to stay in that career if permitted to continue his primary research interest as part of his day's work. Those with no basic research interest should have time to practise their branch of clinical medicine.

F. *He has administrative responsibilities* but under no circumstances must he be a full-time administrator out of touch with the practice and realities of clinical pharmacology. Administrative duties include advising through an appropriate committee on hospital pharmacy and formulary matters, and participation in the hospital adverse-reactions reporting system which is so vital to the interests of drug safety.

Clearly, no single person can carry out all these functions. Each clinical pharmacologist, be he employed part-time or full-time, will select his functions according to his talents and according to what is required of him in the hospital in which he works.

What is the Training of a Clinical Pharmacologist?

Here opinions differ. All agree he must have formal clinical and pharmacological training. The majority view is that he should be a medical graduate with experience in internal medicine up to being a specialist physician (internist), who then proceeds to study pharmacology in a department of pharmacology for 1 - 4 years, not necessarily aiming at acquiring a degree in pharmacology. Then he returns to function from a clinical department such as internal medicine or an autonomous department of clinical pharmacology.

The minority view is that he should be primarily a pharmacologist with a medical degree, proceed to 1 - 2 years of clinical training in internal medicine at 'registrar' level, and thereafter function from a department of pharmacology. This minority view tends to the opinion that he should not practise therapeutic trials but rather confine himself to the earliest trials in man, studying pharmacological activity and toxicity.

His training must include an introduction to the State drug control regulations of his own and other countries.

The term 'drug investigator' is commonly mentioned. The clinical pharmacologist is of course a drug investigator, but many competent clinical drug investigators have had no formal training in pharmacology. They may be specialists or general practitioners working in hospital, consulting room or domiciliary practice, and do not necessarily have or require laboratory facilities. The 'testimonial writing' type of investigator who, after administering a drug to a group of patients in a more or less haphazard way, reports favourably on little objective evidence is being gradually eliminated in most countries by the statutory requirement of proof of efficacy and safety by controlled trial.

An interesting group of investigators falling under the definition of clinical pharmacologist as regards their function, and usually as regards their training as well, are those employed full-time by drug companies. The drug company provides working facilities which may include company sponsorship of up to 30 beds in a teaching hospital, provision of nursing and technical staff, metabolic ward, laboratories and sometimes a small pharmacy and staff to facilitate proper control of drug administration. These investigators conduct pharmacological and early therapeutic trials in man on drugs referred by the company's committee which assesses dosage, method of administration, possible pharmacological and therapeutic activity on evidence submitted by the chemist, experimental pharmacologist and toxicologist. The company clinical investigator may reject the drug without clinical trial or at any stage of the trials which he may undertake. I was not impressed by the oft-stated fear that this type of investigator is influenced by drug-company management. All clinical pharmacologists in this category whom I met had been awarded teaching hospital and university status. One held a professorship and was director of medical education at a well-known university medical school.

Clinical Trials of Registered Drugs

The State may require re-evaluation of efficacy of registered drugs. The Food and Drugs Administration of the United States of America has listed 8 groups of drugs requiring re-evaluation; tranquillizers and antidepressants heading the priority list. The other groups are progestational agents, drugs used in pregnancy, topical antihistaminics and '-caines', some sustained-release drugs, paediatric drugs, and non-prescription drugs (commonly known as 'over the counter' or OTC drugs).

A drug company may wish to re-evaluate one of its own registered products.

Registered drugs may be used as an instruction medium in controlled-trial methodology. There are probably enough new unregistered drugs at any one time to use for this purpose.

Biostatistics and the Clinical Pharmacologist

The trained clinical pharmacologist and the specialist biostatistician appreciate and give consideration to such biological peculiarities as the rating of subjective sensations in contrast with the measurement of objective observations, patients' preferential ratings, and the variable environmental and iatrogenic 'x' factors which may apparently enhance or inhibit the effect of a drug or cause an inert placebo apparently to have a therapeutic effect. Such

factors may be responsible for bias on the part of the observer.

Factor x may appear in several guises particularly where subjective symptoms are under observation as in trials of psychotropic drugs. The attitude of the physician, be it warm, cool or indifferent, may be responsible for an apparent effect of drug or placebo. The attitude or the very presence of other patients who are not in the trial but are neighbours in the same hospital ward or outpatient group, and a change for purposes of the trial from a poor to a better environment may also influence the results.

Another factor x concerns the selection of the optimum dose of a drug for each patient in the trial. The usual procedure of giving each patient under trial the same dose schedule results in some patients receiving their individual effective dose, some receiving more and some less. A short series of cases and controls is likely to give indecisive results. But if the maximum safe dose for each patient is found before the trial and each patient enters the trial on an individualized dose, a small series is more likely to give a conclusive result, be it favourable or unfavourable to the drug.

The biostatistician is subjected to informed and uninformed criticism. All the world cannot be wrong in assigning him a necessary place in the design and interpretation of clinical drug trials. Nevertheless, it is well to remember the comment of Laplace, the French mathematician, that 'the theory of probabilities determines with exactness what a well-balanced mind perceives without the mathematical calculation'.

The State and Clinical Pharmacology

State drug control regulations have as their main objective the protection of the public against inefficacious or unduly toxic drugs. Efficacious drugs are rarely free from hazard. Inefficacious drugs may be administered when an efficacious drug is specifically indicated.

The very presence of drug-control regulations encourages the drug industry to continue its high standards of drug production and quality control, and supports the industry's inherent wish to avoid false claims of efficacy and safety by conducting controlled clinical drug trials which will at least satisfy if not more than satisfy State requirements. The State in this indirect way promotes high standards of clinical pharmacology.

Some States go further and positively assist the promotion of drug research and pre-registration clinical trials by providing posts in approved institutions for the modern skilled clinical pharmacologists and posts for their training.

With the acceptance by Parliament in June 1965 of the Drugs Control Act, South Africa has joined the many countries that have regulations to control the production and registration of drugs for use in man. Although a beginning has been made with the production of certain antibiotics from basic fermentation processes, we have still a long way to go to develop a drug industry with all the research and development facilities and expert personnel necessary for the production of new drugs from their conception and synthesis by the chemist to the phases of testing pharmacological activity and toxicity in animals. There are, of course, many manufacturing companies in South Africa producing pharmaceutical specialties (under full quality control) which have already been registered in countries with registration requirements. Clinical trials have been conducted on numbers of drugs still in the pre-registration phase in the country of origin, and these trials have doubtless been included by the company in its application for registration of the drug in the home country of the company. Such trials are likely to continue after the introduction of drug legislation in South Africa, in addition to trials which will be required by our own legislation. For the above reasons the demand for pre-registration trials in South Africa is likely to increase and we must start to make provision for posts and facilities for more trained and trainee clinical pharmacologists.