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Clinical Pharmacology – Scope, Organization, Training

Report of a WHO Study Group

Summary. 1. The effective and safe use of drugs is seriously impeded by a lack of clinical pharmacologists.[1] — 2. The need to develop clinical pharmacology is due largely to *a*) the increasing number of drugs; *b*) the realization that the effective and safe use of drugs can be greatly improved by scientific study and teaching; *c*) the occurrence of several therapeutic disasters. — 3. The scope of the clinical pharmacologist's work includes: *a*) Research into the action of drugs on the body, and of the body on drugs; initial studies of new drugs in man; comparative therapeutic trials; and drug monitoring. *b*) Teaching of students, hospital staff, and practising physicians in the application of scientific knowledge to therapy. *c*) Services, including provision of information on drugs; measurement of drug levels; advice on design of clinical drug studies; drug monitoring; preparation of pharmacopoeias and formularies; and advice to governmental drug control organizations and industry. — 4. New clinical pharmacology units are needed. These may be started within clinical and/or pharmacology departments, and either remain there or develop into independent departments. — 5. Facilities needed include laboratory and office space, hospital beds, and out-patient facilities. The clinical pharmacologist must have access to patients and be responsible for their care. — 6. Training programmes must be expanded to meet the need for clinical pharmacologists in medical schools, hospitals, governmental organizations, and industry. — 7. To safeguard individual and public health, an immediate and substantial expansion of clinical pharmacology is essential.

A Study Group on clinical pharmacology was convened by WHO in Geneva from 8 to 12 December 1969. Dr. H. Halbach, Director, Division of Pharmacology and Toxicology, opened the meeting on behalf of the Director-General.

The meeting was held at this time mainly for the following reasons: first, the need to remedy the shortage of clinical pharmacologists that was impeding the implementation of the various WHO resolutions on therapeutic efficacy and safety of drugs; second, the need to demarcate clearly the scope of the new discipline of clinical pharmacology; and thirdly, the need for drug studies to be carried out in all parts of the world in a scientific and co-ordinated way, since drug responses in man are influenced not only by his genetic constitution but also by environmental and economic factors.

1. Introduction

In recent years, widespread concern has been developing amongst medical and other scientific workers, and the general public, about the effective, safe, and rational use of drugs.[2] The development, surveillance, and use of drugs affect the welfare and rights of both the individual and society, and involve scientific, ethical, and legal problems of great importance and complexity.

The ways and means by which WHO can contribute to the more effective and safe use of drugs have been discussed by the various governing bodies of the Organization.

The Seventeenth World Health Assembly[3] stated that international co-operation is essential if man is to be provided with the best opportunity to benefit from drugs with the minimum risk. Such co-operation would, for example, eliminate wasteful duplication of research and promote rapid dissemination of information on therapeutic efficacy and hazard. A number of resolutions in this field have been officially endorsed. For example, the Seventeenth World Health Assembly (1964) adopted a resolution requesting the Director-General, *inter alia*, "to undertake, with the assistance of the Advisory Committee on Medical Research, the formulation of generally acceptable principles and requirements for the evaluation of the safety and efficacy of drugs."[3] The Twenty-second World Health Assembly (1969) requested the Director-General "to examine possible ways of providing advice to governments in developing machinery for evaluating the therapeutic safety and efficacy of drugs."[4] In compliance with these resolutions several meetings of experts have been convened by the Organization and their reports have been published.[5]

Various attempts to promote drug research and therapy have been made by the governing bodies and scientific groups of the Organization. In the course of

1 See p. 242.

2 A WHO Scientific Group on Principles for Pre-Clinical Testing of Drug Safety defined a drug as "any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient". (Wld Hlth Org. techn. Rep. Ser. 1966 No. 341, p. 7).

3 Resolution WHA 17.39 (Off. Rec. Wld Hlth Org. 1964, No. 135, p. 17).

4 Resolution WHA 22.41 (Off. Rec. Wld Hlth Org. 1969, No. 176, p. 20).

5 Principles for Pre-Clinical Testing of Drug Safety (Wld Hlth Org. techn. Rep. Ser. 1966, No. 341); Principles for the Testing of Drugs for Teratogenicity (Wld Hlth Org. techn. Rep. Ser. 1967, No. 364); Principles for the Clinical Evaluation of Drugs (Wld Hlth Org. techn. Rep. Ser. 1968, No. 403); International Drug Monitoring (Wld Hlth Org. techn. Rep. Ser. 1969, No. 425); Principles for the Testing and Evaluation of Drugs for Carcinogenicity (Wld Hlth Org. techn. Rep. Ser. 1969, No. 426). The report of a WHO Scientific Group on the Evaluation of Dependence-Producing Drugs (Wld Hlth Org. techn. Rep. Ser. 1964, No. 287) is also relevant.

these attempts, a serious lack of specialists has become evident in the various fields of drug research and therapy, especially in clinical pharmacology.

The WHO Advisory Committee on Medical Research stated that there is a constant shortage of research workers in clinical pharmacology, and recommended that WHO continue to encourage the training of specialists in this field. It endorsed the conclusions of the WHO Scientific Group on Principles for the Clinical Evaluation of Drugs[6] that "More and better trained personnel as well as improved laboratory facilities are needed to improve the evaluation of drugs in man. As one method of achieving this objective, consideration should be given to forming more clinical pharmacology units in medical centres. Attention should be given to developing better techniques for measuring absorption, distribution, and excretion of drugs and their metabolites, and for the detection of toxic effects of drugs. Where it is impracticable to establish clinical pharmacology units, consideration should be given to the inclusion of therapeutic research in specialized units or centres, equipped for thorough investigation of diseases that are important in particular areas of the world."

The present Group was convened to review and delineate the scope, function, and organization of clinical pharmacology, and to make recommendations for the training of clinical pharmacologists.

2. General Considerations

Clinical pharmacology is concerned with the scientific study of drugs in man. Its scope is set out below (see section 3). Despite the fact that clinical pharmacology is already an established medical discipline in some countries, it has not yet been recognized in most and its development has lagged. Clinical pharmacology in its modern form began in the 1930s, but it was not until the early 1950s that it became widely recognized as having a distinct contribution to make to medicine.

Such development of clinical pharmacology as has already occurred, and the present demand for trained specialists, are largely due to:

(1) the increasing number of new drugs produced by the pharmaceutical industry;

(2) the realization that the choice, and the safe and effective use, of drugs depend on knowledge that can best be obtained by systematic scientific study;

(3) the occurrence of several therapeutic disasters.

In increasing efficacy, and reducing hazard due to inadequacies in development, manufacture, distribution, and use of drugs, clinical pharmacologists contribute particularly in the following areas:

(1) clinical investigation of new and existing drugs;

(2) instruction of medical students, hospital staff, and practising physicians in the scientific application of drug therapy;

(3) consultative activities for drug regulating agencies, and for research and development in the pharmaceutical industry.

The need for clinical pharmacologists in these fields exceeds the capacities of existing facilities. New units must be established and existing ones expanded. Since the need can only be met by allocating technical resources, both in manpower and in material, it must be realized by governments, universities, and medical schools that clinical pharmacologists make a contribution that is not forthcoming from other clinical and nonclinical scientists.

There are several reasons why trained clinical pharmacologists are particularly well qualified to help solve some of the most pressing problems concerning drug use.

As scientists who have been trained in methods of studying drug responses in man, they can undertake studies of absorption, distribution, metabolism, and excretion and have special knowledge and experience of designing and carrying out therapeutic trials.

The concern of the clinical pharmacologist with drugs in general, as opposed to special areas of therapeutics, equips him to co-ordinate the teaching of pharmacology and therapeutics throughout undergraduate and postgraduate medical education. His general pharmacological interests and experience make him the most suitable person to co-ordinate the detection and quantification of adverse reactions to drugs in hospitals, and to set up experimental investigations to determine their cause.

Recent years have seen a great increase in knowledge of drugs, both old and new, and centres are needed from which such knowledge can be made readily available to all who require it. Clinical pharmacology units are well suited to this purpose.

3. Scope

The functions of the clinical pharmacologist are (1) to improve patient care by promoting the safer and more effective use of drugs; (2) to increase knowledge through research; (3) to pass on knowledge through teaching; and (4) to provide services, e.g., analysis, drug information, and advice on the design of experiments.

3.1 Improvement of patient care

The multiplicity of drugs poses serious problems for both the physician and his patient. The quality of patient care could be greatly improved by taking full advantage of existing knowledge about the efficacy and safety of a drug, its indications and contraindications, dosage schedule, and interactions with other drugs. The clinical pharmacologist can greatly assist the practising physician in achieving this goal.

6 Wld Hlth Org. techn. Rep. Ser. 1968, No. 403, p. 30.

3.2 Research

3.2.1 Pharmacokinetic studies

Pharmacokinetics is the study of the absorption, distribution, metabolism, and excretion of drugs. Since these processes determine the concentration of the drug at the site of action, much additional information can be obtained by combining pharmacokinetic with pharmacodynamic measurements, e.g., measuring the plasma concentration of a drug in relation to its pharmacodynamic effect. Pharmacokinetic studies "contribute to the safer conduct and more efficient design of human drug studies. . ."[7] The rates of drug metabolism and elimination vary widely in different species, and are often more rapid in commonly used experimental animals, e.g., rat and dog, than in man. Pharmacokinetic studies must be performed in man, therefore, in order to obtain information that is relevant to clinical practice.

The rate and amount of drug absorption from the gastrointestinal tract may vary according to the pharmaceutical formulation. Hence collaboration with a pharmaceutical scientist is often important in studying such problems.

Many drugs are bound to plasma proteins from which they may be displaced by other drugs, leading to an increased drug concentration at the site of action and to a change in duration of action.

Some drugs accumulate in certain tissues or organs and can persist there for a long time (e.g., tetracyclines in teeth and bone, chloroquine in the retina). Such accumulation has important implications for drug toxicity.

Many factors influence the metabolism and excretion of drugs. For example, genetic factors are responsible for substantial differences in the rate of metabolism of isoniazid and suxamethonium. Exposure to drugs (e.g., phenobarbital) or other chemicals (e.g., DDT) may lead to an increase (induction) of drug-metabolizing enzymes and so alter the rate of metabolism of a whole range of drugs.

Some drugs (e.g., monoamine oxidase inhibitors) may inhibit metabolizing enzymes. Others may alter drug elimination (e.g., probenecid).

The kinetics of a drug may be affected by the age and developmental state of the individual to whom it is administered. This is of particular importance in pregnant women, in children, and in the aged.

Drug elimination may be altered by environmental influences, diet and disease. Renal failure, for example, may greatly increase and prolong the effect of a drug which is normally excreted unchanged in the urine.

Pharmacokinetics are not merely of theoretical but are of considerable practical importance in drug intoxication. By altering the urinary pH, the change in tubular reabsorption of a drug can be so great as to be life-saving (e.g., in poisoning by salicylates or phenobarbital).

Sensitive new techniques, e.g., gas-liquid chromatography and radioisotope methods, have made it possible to measure extremely small concentrations of drugs in biological fluids, thus greatly increasing the usefulness of pharmacokinetic studies in clinical practice.

3.2.2 Pharmacodynamic studies

Pharmacodynamics is the study of the biological and therapeutic effects of drugs. The measurements to be made depend upon the type of drug being studied. With new drugs, especially, a broad range of pharmacological activity should be covered, and observation and measurement should not be confined to the expected effect alone. Pharmacodynamic studies can also elucidate the mechanism of action of a drug.

Measurements that can be made range from simple clinical observations of pulse rate, body temperature, and blood pressure to studies requiring complex equipment.

3.2.3 Individual variations in drug response

There are marked individual differences in drug responses. A given dose of a drug may be toxic to one patient and without effect in another. Such differences may be pharmacokinetic or pharmacodynamic. As an example of the former, patients treated with the same dose of some antidepressants have regularly been found to show more than 10-fold differences in steady-state plasma levels. As an example of the latter, hereditary resistance to dicoumarol-like anticoagulants has been reported. Interactions with other drugs, geographical and nutritional factors, and disease states may also profoundly influence drug response at the receptor level. Results obtained in one population cannot always be extrapolated to another having a different genetic constitution or living under different environmental conditions.

3.2.4 Early studies in man

The aim of early studies of a new drug in man is to find out if it has a potentially beneficial effect. Special training and experience are necessary to conduct these studies in such a way that they yield the maximum information with the minimum risk. The clinical pharmacologist is particularly well qualified to carry out such studies.

Studies of a drug in man must be justified by the demonstration of a potentially useful effect in animals, or by theoretical considerations about its mode of action. Administration to man must be preceded by investigation of toxicity in animals and by specification of the chemical structure, purity, and stability of the drug. In most cases information should be available about absorption, metabolism, and excretion in animals; data may also be useful concerning the plasma concentrations at which the potentially beneficial and the toxic effects appear. The clinical pharmacologist must satisfy himself that these pre-clinical studies are adequate.

7 Wld Hlth Org. techn. Rep. Ser. 1968, No. 403, p. 15.

The clinical pharmacologist should design his investigations in consultation with scientists who have studied the drug in animals. If several clinical investigators are involved, arrangements should be made to exchange information and co-ordinate their efforts. Early clinical findings may necessitate further animal experiments; in some cases clinical studies must be interrupted until these have been completed.

When a drug is first administered to man, this should be done under circumstances in which all important, relevant information can be collected. Regular observation of blood and urine composition may be supplemented by function studies of organs, such as the liver or kidney, which are especially prone to damage. If animal toxicity tests suggest that an organ is particularly vulnerable, special efforts must be made to record its function.

It is essential to begin with low doses, increasing them cautiously until a measurable effect appears and watching for unexpected actions of the drug. These studies should be combined, if possible, with measurements of plasma concentration and metabolism in man, thus permitting a comparison to be made with data obtained from animals.

Initial clinical studies may sometimes be carried out, after relatively short-term animal toxicity tests, to determine whether there is a potentially useful effect in man. Not more than a few doses should be administered until longer-term toxicity tests have been completed.

If the action in man appears promising, an attempt must be made to define the dose-response curve and the type of disease that is most responsive, and to obtain evidence concerning the mode of action. Once satisfactory information on these points has been obtained, it is necessary to proceed to a formal therapeutic trial in order to define the position of the drug, both alone and in relation to existing methods of treatment.

3.2.5 Therapeutic trials[8]

If the initial studies in man are promising, a therapeutic trial must be undertaken to compare the drug with either a placebo or existing therapy. The trial may be carried out by a clinical pharmacologist or a clinical specialist but in the latter case the clinical pharmacologist can often give useful advice concerning the design and execution of the trial.

The first step in designing the trial is to formulate precise questions. It is wise to limit their number or the trial may become so complex that the answers will prove inconclusive. The variables to be measured must be selected and the end-point defined. Precautions are needed to prevent bias in the collection of data and to evaluate errors.

Criteria of diagnosis, and the range of severity of disease, must be defined. If some factor (such as duration of disease) is thought likely to affect the response, subgroups may be formed in allocating treatments. Random allocation must be employed to prevent conscious or unconscious bias in the selection of treatment. Randomization is also necessary to ensure that the groups will be roughly equivalent and to allow the application of statistical tests of probability and significance.

Since a therapeutic trial involves comparison of the new drug with either a standard treatment or a placebo, it may be necessary to disguise the identity of the drug from the patient and from the doctor or observer to prevent bias in the assessment of results. The placebo provides a control both for suggestibility and for spontaneous changes in the signs and symptoms of the disease under study.

The number of patients that need to be included in an investigation can be estimated if the variability of the measurements, the size of the desired effect, and an acceptable probability of detecting the latter are defined. The size of the sample to be studied should be specified in advance, to prevent bias caused by the physician deciding to stop the trial when a particular result occurs. If a fixed sample trial is not wanted (e.g., for reasons of ethics or convenience), results can be analysed as they are obtained (i.e., sequentially) by special statistical tests. Fewer patients are needed, on average, if a sequential design is used, but the results may have wide confidence limits and only a single endpoint can be used for terminating the trial. The design is complex, and expert statistical knowledge is required.

In many studies it is necessary to vary the dose until a desired effect is achieved, rather than to use a single dose. Provision for altering the dose complicates the design of a trial, but may be essential if the result is to be useful in clinical practice.

Multicentre trials involving a number of medical centres are especially helpful in uncommon diseases or where very large numbers are required. A central organization is essential to co-ordinate the trials and ensure that the participants adhere to the protocol.

Once the plan of a therapeutic trial has been agreed upon, it is necessary to prepare the forms on which the results will be recorded. Skilful design of these forms will save much time in checking and analysing results, and it is often wise to arrange them so as to facilitate the transcription of data to punch cards for computer analysis.

3.2.6 Relations between pre-clinical and clinical studies

Drug development and usage require a constant integration of animal and human data, and the clinical pharmacologist has an important role to play in accomplishing this. The selection of drugs for clinical trial by animal screening procedures, animal models of human disease states, or molecular modification of an accepted remedy must be repeatedly scrutinized to assess the validity and predictive value of pre-clinical

8 Wld Hlth Org. techn. Rep. Ser. 1968, No. 403, p. 20.

studies. A proper correlation of observation in man with effects in animals demands that clinical and preclinical data be comparable in terms of chosen variables and the quality and quantity of the evidence.

Information on the absorption and metabolism of drugs in animals will facilitate the work of the clinical pharmacologist in his own investigation of these aspects of drug action.

Where effects that had not been predicted by animal studies occur in man, additional animal experiments are necessary to investigate the underlying mechanisms.

3.2.7 Additional research functions

The clinical pharmacologist may be concerned with research on the monitoring of adverse effects. Examples include the early detection of unsuspected drug toxicity, the accurate epidemiological quantification of adverse reactions, tests for predicting drug toxicity, and efforts to confirm suspected cause-and-effect relationships (see also section 3.4.4).

The clinical pharmacologist is also concerned with monitoring the therapeutic use of drugs and the pattern of drug prescribing, including indications, contraindications, and suitability.

His interests may also involve research in epidemiology and social medicine. Examples include incidence of drug toxicity, factors influencing doctors' prescribing and patients' self-medication, errors by patients in following directions for taking drugs, dispensing errors by nurses or pharmacists, and the abuse of drugs by society.

3.3 Teaching

3.3.1 Teaching medical students, hospital staff, and practising physicians

Basic pharmacology is usually taught as a preclinical discipline. Its scientific and educational value are unquestioned, but the therapeutic use of drugs in patients cannot be adequately taught or understood by a student who has no knowledge of disease and its modification by drugs. In many medical schools, however, during his clinical studies the undergraduate hears little of the therapeutic use of drugs, save perhaps for a few cursory remarks at the end of a ward round or patient demonstration. Yet it is extremely important nowadays that medical students be thoroughly instructed in the potent pharmacological tools of their trade. They must understand how to use drugs properly, their mode of action, and their adverse effects. They should also be trained in the critical evaluation of claims made for drugs. Unfortunately, instruction in therapeutic pharmacology during the clinical years is totally inadequate in many medical schools. Even after graduation, some doctors read little about the subject and rely too much their for information on the promotional efforts of the pharmaceutical industry. This problem was less important thirty or forty years ago when there were few effective drugs, but is now of crucial importance, for many inadequacies in the use of modern drugs stem from the inadequacy of undergraduate and postgraduate instruction about them. The clinical pharmacologist can do much to remedy this state of affairs by developing an interdisciplinary programme in co-operation with clinical specialists. Through formal lectures, seminars, and informal bedside consultations he can revise basic knowledge of pharmacology and aid in the choice of drugs. Special efforts should be made to teach pharmacology and therapeutics to interns, residents, and other physicians. All practising doctors need continuing education throughout their careers in this as in other spheres, and there should be no hesitation in using modern auditory and visual teaching techniques. It is now possible to teach pharmacology as a practical science in a clinical context.

3.4 Services

3.4.1 Provision of information concerning drugs

Clinical pharmacologists should play an active part in planning the provision and dissemination of information about drugs. Thousands of different pharmaceutical preparations are already available for prescription by doctors and their number continues to increase rapidly. Provision of readily accessible sources of information about these preparations is an important part of the continuing education of doctors, and will help them to use drugs to the best advantage.

Hospital pharmacies and medical libraries should maintain a file of up-to-date manufacturers' data sheets and package inserts, and a small library of reference books on drugs. Some large hospitals may be designated as poison information centres, and maintain files on the ingredients and toxicity of domestic and industrial products.

Doctors need a regular source of information about drugs, both new and old. Many currently used drugs were not available during the training of doctors who qualified only ten years ago, and the optimal use of older drugs may be revised in the light of new knowledge. Publications are needed that provide such information in short, easily digested articles. These are already available in some countries. Programmes on advances in drug therapy have been included in services for the medical profession on several national television channels. Other methods, such as video-tape recordings or closed-circuit television coverage of lectures, are also useful. Such methods are, however, most likely to appeal to those doctors already concerned with continuing their own education. More effort is needed to bring these educational activities to the attention of the others, and research should be carried out to discover which methods are most effective.

The growth of knowledge about drug actions, interactions, and toxicity cannot be put to effective use unless it is quickly accessible. Unaided human memory is now insufficient for this task. It may be feasible to write computer programmes that incorporate guidance

to the prescriber in the selection of the best treatment, where factors such as diagnosis, severity, age, sex, and drug interaction are specified. In the future, computers may increasingly be used in large hospital pharmacies to check prescriptions for potential interactions and unusual dosage regimes. Terminals in wards or doctors' offices could be used to interrogate computer memories concerning the indications for and contraindications to the use of particular drugs.

3.4.2 Measurement of drug levels in body fluids

Standard doses of drugs may produce widely different plasma levels in different patients, and some drugs, e.g., phenytoin, may produce severe adverse reactions due to very high plasma levels. The analysis of drug levels in body fluids has been shown to be important for the care of individual patients. The clinical pharmacologist has an essential role to play in the practical application of pharmacokinetic data.

3.4.3 Advice on design of clinical drug studies

Although some clinical trials are carried out by clinical pharmacologists, many are conducted by clinical specialists. The clinical pharmacologist is a source of advice to doctors who are going to conduct such trials.

3.4.4 Monitoring drug usage

Clinical pharmacologists can fulfil an important service by surveying prescribing patterns and the incidence of adverse reactions. Collaboration between local and international centres may help to minimize delays in recognizing drug toxicity. Clinical pharmacology units also provide trained personnel who can quickly begin an investigation of a suspected adverse reaction.

3.4.5 Preparation of reference books on drugs and manuals on prescribing, e.g., pharmacopoeias and formularies

Such works may be international, national, or local. The clinical pharmacologist helps to decide which preparations should be included, and their dosage schedules and clinical recommendations.

3.4.6 Advice to governmental drug control organizations

The services of the clinical pharmacologist are necessary for the following purposes:

(1) to decide whether animal data on a drug are adequate to justify administration to man;

(2) to decide whether therapeutic trials justify release for general use;

(3) to work on drug monitoring (see section 3.4.4);

(4) to advise on the restriction of drugs or their withdrawal from the market.

Governmental organizations may employ clinical pharmacologists as full-time staff or use them as independent consultants. When difficult decisions have to be made, it is desirable that responsibility be shared with independent advisers rather than being borne by one or two government officials.

3.4.7 Advice to the pharmaceutical industry

Clinical pharamcologists are of value to industry in both full-time and part-time consultative capacities.

4. Organization and Facilities

4.1 Organization

Most clinical pharmacology departments have grown from small units established within departments of medicine or pharmacology either individually or jointly. Nevertheless, the evolution of a satisfactory organization for clinical pharmacology has presented problems common to all specialties which employ both clinical and non-clinical scientists and cross the boundaries of clinical specialties. Before making recommendations for the future, the present position will be reviewed.

4.1.1 Present organization

a) Division of Clinical Pharmacology sponsored equally by the Department of Pharmacology and a clinical department (usually the Department of Medicine).

Many programmes began with this type of structure. It can work well when the chairmen involved agree on what the clinical pharmacologist should do and allow him sufficient time to do it. It is important, therefore, that the functions of the clinical pharmacologist should be decided before the programme is begun.

The advantage of this arrangement is that the clinical pharmacologist has full membership of both a basic and a clinical department, and thus should have ready access to laboratory and clinical facilities. He should also have the opportunity of integrating basic and clinical teaching. The viability of this structure obviously depends upon the continuing goodwill of both sponsoring departments.

b) Division of Clinical Pharmacology within the Department of Pharmacology.

In some centres, the Department of Pharmacology has assumed the principal administrative responsibility for the development of clinical pharmacology. It has provided space and obtained curriculum time for clinical pharmacology. The clinical pharmacologists also have secondary appointments in clinical departments, depending upon their interests. A serious danger exists, however, of their being isolated from clinical departments.

c) Division of Clinical Pharmacology in a clinical department (usually the Department of Medicine)

In some centres, the initiative in establishing clinical pharmacology has come from a clinical department. This type of arrangement also has a simple administrative structure and enables easy access to patients and clinical facilities. However, isolation from pharmacology and other basic disciplines may occur and it may be difficult to develop a programme which involves other clinical departments.

4.1.2 Proposal for development of clinical pharmacology units

A medical school which proposes to establish clinical pharmacology should usually begin by appointing one or two staff members who will be attached to existing departments. In most instances, the individuals should have joint appointments in a department of pharmacology and a clinical department (usually medicine), both of which should provide facilities, budget, and curriculum time. These facilities may initially be limited to attachment to an existing clinical service with shared laboratory space for animal, chemical, and clinical studies. Clinical pharmacology will often expand rapidly, however, and provision should be made for the establishment of specialized out-patient clinics for therapeutic trials, the admission of patients for clinical drug investigations, and laboratory space designated for clinical pharmacology.

In some medical centres, clinical pharmacology groups have grown large enough to undertake a wide range of research, teaching, and service functions.

These larger units have reached a stage that makes it necessary to consider alternative methods of organization. They are often able to carry out complete biochemical and pharmacological investigations of drugs in man. They may be responsible for co-ordinating the teaching of applied pharmacology and therapeutics throughout the medical school. The staff may consist of a nucleus of fully trained clinical pharmacologists, chemists, and biometricians, with attached research workers in different clinical departments.

The functions of such a unit spread beyond the boundaries of any existing department and have substantial responsibilities in teaching, research, and service. A separate department may be the most satisfactory administrative arrangement.

4.1.3 Proposal for departments of clinical pharmacology

A formally established Clinical Pharmacology Department should offer career academic positions to clinical pharmacologists, chemists, and biometricians. It should also provide shared facilities for clinical and non-clinical scientists who prefer to remain within departments such as paediatrics, psychiatry, internal medicine, biochemistry, and statistics.

The Clinical Pharmacology Department should collaborate with the Pharmacology Department. Of prime importance is the provision of continuing undergraduate and postgraduate instruction in pharmacology. The Pharmacology Department can greatly assist in providing a basic science background for trainees in clinical pharmacology, and can provide clinical orientation for postgraduate students in basic pharmacology, especially those who wish ultimately to teach in medical schools.

Besides clinical facilities and laboratory space for its full-time members, a Clinical Pharmacology Department should also provide space for those who have shared appointments in other departments. Only a structure such as this will provide the chairman of Clinical Pharmacology with the opportunity to increase his departmental staff and space on an equal basis with other departments.

4.1.4 Organizational structure in non-academic institutions

Clinical pharmacology units may provide service functions in hospitals not affiliated to academic institutions. They may participate in staff training, provide a consulting service for therapeutic problems, and organize drug monitoring. They may also co-operate in research projects with academic centres and with industrial and governmental laboratories. Similar considerations apply regarding space, and clinical and laboratory facilities, as in academic institutions.

A special development in several countries has been the establishment of clinical pharmacology units financed by pharmaceutical firms. Some of these are primarily concerned with early studies in healthy volunteers, others with patients. Such units require trained medical and nursing staff to look after the subjects and patients and to make clinical observations, as well as laboratory staff and equipment for biochemical measurement.

4.2 Facilities

The clinical pharmacology unit, whatever its organizational status, should have laboratory and office space for its exclusive use. The amount of space assigned will depend upon its size and functions. Like other clinical scientists, the clinical pharmacologist should have access to an animal laboratory whenever necessary. Since the clinical pharmacology unit may grow rapidly, provision should be made for expansion. Ideally, all clinical pharmacology personnel should be housed in a single area convenient for both the pharmacology department and the clinical departments with which they are particularly concerned. In medical centres where the basic science and clinical departments are widely separated, laboratory and office space will be required in both areas. Space is needed in the clinical area for clinical investigations and the preliminary processing of specimens.

Hospital beds and out-patient facilities must be available for clinical studies, and the clinical pharmacologist should be fully responsible for his patients.

5. Training

5.1 Training clinical pharmacologists

Clinical pharmacology is interdisciplinary by nature. These disciplines include two essential ones, pharmacology and clinical medicine, and also physiology, biochemistry, genetics, and biostatistics.

Clearly, no-one can become an expert in all aspects of these varied disciplines. A training programme should not attempt to cover them all, therefore, but should

take into account the trainee's background and anticipated career, and the capabilities of the training unit.

The training of a clinical pharmacologist should correspond in extent to that of other clinical scientists; excessive training requirements in both experimental pharmacology and a clinical specialty may unduly prolong the training period and therefore deter interested candidates.

The clinical pharmacologist must be competent to care for the subjects of his investigations. The healthy volunteer and the patient are entitled to expect a person who invites them to submit to investigations to have clinical competence. For this reason, the clinical pharmacologist should have undergone substantial clinical training.

An alternative view is that the clinical pharmacologist should be trained primarily in pharmacology, with a relatively brief clinical training. In this situation he must rely completely on the co-operation of those responsible for patient care.

An integrated training programme in clinical pharmacology comprises at least two years spent in a fully equipped unit in a major medical centre. Each trainee has an individual programme, which depends upon his previous experience in clinical medicine and basic sciences. Some trainees may wish to spend part of this period in a basic pharmacology department.

The following general scheme of training has been adopted in several clinical pharmacology units:

Trainees take part in the regular seminars and teaching rounds of the unit. They are assigned a research project involving clinical and laboratory work. Attempts are made to provide them with experience in all stages of clinical trials, in addition to which they may attend courses of instruction in biometrics, statistics, pharmacokinetics, physical chemistry, etc. They may also require further clinical training, which can be obtained by attending the clinical practice of the hospital, working in clinics, and investigating patients appropriate to their research projects or future careers. This period can be shortened if special training in pharmacology has been acquired as an undergraduate.

5.2 Training of physicians

A general physician or a specialist may spend one or two years working in a clinical pharmacology unit. Such training would equip him to participate in clinical trials, the teaching of graduate doctors, drug monitoring schemes, and clinical units for the treatment of poisoning.

5.3 Training for industrial and governmental careers

Physicians who intend to pursue a career in industrial or governmental regulatory or monitoring agencies will also benefit from a training in clinical pharmacology. For some of these, full training of the type described in section 5.1 will be appropriate. For others more limited training, e.g., in the design and analysis of clinical trials, will suffice.

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