Clinical Pharmacology: Present Status and Future Development

On 4 June 1965, a small group of university scientists gathered in Basin Harbor, Vermont, to discuss the status of the clinical pharmacologist in the American academic community, his current and potential contributions to medicine, and his present and projected needs. The participants (*1*) worked for the most part in small sub-groups, gathering together at the end of the day to report on their separate deliberations. The report which follows is a summary of the conclusions of the sub-groups.

Training Programs, Student Teaching

Training in clinical pharmacology is intended to prepare physicians for careers as teachers and investigators in the area of human pharmacology and experimental therapeutics. These goals require that training programs provide already competent clinicians with the special training in basic and human pharmacology necessary for them to carry out studies in man related to the efficacy and safety of drugs and their mechanism of action.

Since each trainee is expected to develop a broad perspective and knowledge of general pharmacology and since the clinical pharmacologist must maintain and increase his own pharmacological expertise, it is desirable that training programs be located in medical centers with vigorous pharmacology departments vitally concerned with the training of clinical pharmacologists, and in such proximity to clinical facilities that communication and travel between the clinic and the pharmacology department can readily occur.

Whether clinical pharmacology training programs are to be primarily housed in the pharmacology department or in the clinical department will depend on local circumstances, such as the availability of space. As time goes on and circumstances change, the bases of operations for clinical pharmacology may also change. It is important, however, that at least one major clinical department and the department of pharmacology accept the premise that the training program will develop optimally if it has strong support from the chairmen of these departments. This statement is made with the realization that useful units have been established with support primarily from either a clinical department or the department of pharmacology, but the long-term development of this field demands strong bilateral support.

Ideally, the trainee should interact with the faculty of the department of pharmacology throughout his training period, and consider himself to be a pharmacologist as well as a clinician. Trainees can participate in the teaching of the general medical school pharmacology course; seminars and advanced courses in pharmacology should be made available to them. Courses in biostatistics, especially as related to experimental design and data analysis, are necessary for most trainees. The core of the training program, however, is the trainee's participation in research projects. In carrying out a specific project the trainee learns the philosophy and techniques of pharmacological experimentation in man. He comes to grips, under supervision, with the problems of clinical and pharmacological literature assessment, experimental design, measurement techniques, errors of measurement, data analysis, data interpretation, manuscript preparation, and data communication.

It is desirable for each trainee to engage in various phases of drug evaluation, from the comparative clinical trial to studies of drug mechanism. Since one of the greatest handicaps to rational therapeutics is the lack of acceptable scientific evidence on drug effects in man, it is essential to produce investigators who are interested in therapeutic trials and competent to design, carry out, and evaluate such trials. Each division of clinical pharmacology should develop and teach the methodology of controlled drug evaluation in man in one or more areas, the latter to be dependent on the clinical and investigative interests, skills, and facilities of the clinical pharmacology unit and the opportunities for collaborative therapeutic studies with other clinical specialties.

The trainee should be exposed to the full scope of services provided by clinical pharmacology. In this regard, the trainee should be made aware of the service functions in which his own mentors engage. For example, trainees can participate in the monitoring and evaluation of adverse drug reactions, in pharmacy committee meetings where requests for the addition of drugs to, or the deletion of drugs from, the formulary are considered, and in departmental or medical center committees where protocols are reviewed for design and safety. The trainee should also participate in teaching medical students and house staff a critical approach to the use of drugs in man.

The duration of training in clinical pharmacology will vary, but will usually be more than one year. If a clinical pharmacology unit is to offer supervised training in research, teaching, and service functions to a number of trainees, it must have a sufficiently large faculty to make this task possible without destroying the research potential of the unit. A clinical pharmacology unit can be started with one man in charge of the program, but it must soon expand to include other fulltime faculty members.

It should be emphasized that clinical pharmacology units will vary in the specific training offered, depending upon the investigative interests and backgrounds of the men in each unit. These differences in interest are to be encouraged, although all clinical pharmacology units will have, as a common goal, the development of rational therapeutics based upon scientific studies on the effects of drugs in man.

The minimal requisites for admission to a training program in clinical pharmacology include an M.D. degree and an internship, although it is often desirable for the trainee to acquire sufficient clinical training to be board-eligible in one of the specialties. It is also eventually desirable, but not essential, for the clinical pharmacologist to have some special clinical skills. As a nonspecialist working in a highly structured and sub-specialized clinical department he may find it difficult to gain sufficient access to patients to make a continuing clinical research pro-

gram possible. Special clinical skills may also make it easier for the clinical pharmacologist to gain the confidence and respect of the clinical faculty and house staff, and hence their cooperation.

To recruit physicians into clinical pharmacology, an enticement could be offered in the form of financial support during the residency training period. Precedent exists for this type of support in psychiatry, ophthalmology, and some units in clinical pharmacology. The urgent national need for recruitment of physicians into clinical pharmacology makes it important to consider this approach. Holders of Ph.D. degrees who might be recruited into clinical pharmacology should receive adequate financial support throughout the medical school and clinical training necessary to develop careers in this field.

It is important to remember that the influence of the clinical pharmacologist in training physicians goes far beyond his obligation to the trainee and his program. He can, for example, play an important role in teaching sophomore pharmacology, a point in medical school where the student wants and needs to have his pharmacology related to man.

During the clinical clerkships, students can have basic principles of pharmacology reinforced for them, as the clinical pharmacologist discusses such things as drug absorption, drug metabolism, and interaction between drugs. The clerkship is perhaps the best place to instruct students in a critical approach to the use of drugs in man. Various techniques are available to the clinical pharmacologist for achieving this goal, including the manner in which he approaches the care of patients during periods when he serves as attending man on the wards and in the clinics. The house staff can be instructed by the clinical pharmacologist in correct drug usage through his participation in conferences and ward rounds. When the talents of the clinical pharmacologist are properly used in the medical school, he will be found interacting with the embryo physician throughout most of his training.

Finally, in his efforts to implement rational therapeutics in his medical center the clinical pharmacologist can coordinate the teaching of therapeutics within his own clinical department and in other departments as well. The clinical pharmacologist cannot be an expert in every aspect of therapy, but he can, through special conferences and collaborative research with individual faculty members, encourage a more scientific approach to the use of drugs by the faculty in general.

Academic Structure and Interdepartmental Relations

Because the clinical pharmacologist must devote a considerable portion of his time to the development of interdepartmental programs, he should not restrict his activities to any single department in the medical school. At the same time, he must find professional acceptance in one or more departments, and must have advancement opportunities equivalent to those of other faculty members. Interdepartmental status poses special problems to faculty members in clinical pharmacology, to departmental chairmen, and to the dean of the medical school. It is important that these problems be discussed openly during the formative phases of a clinical pharmacology program, for the long-term success of this discipline is dependent upon a harmonious working relationship among these key people.

The administrative structure of clinical pharmacology programs cannot follow a rigid, arbitrary pattern. Nonetheless, sufficient experience has accumulated from existing programs to suggest that a productive unit is most likely to develop if the university or medical school accepts clinical pharmacology as a discipline requiring a well staffed and permanent academic unit, if the unit is closely associated with both the department of pharmacology and a clinical department (such as internal medicine, anesthesiology, pediatrics, psychiatry), and if the clinical pharmacology unit is formally responsible for certain areas of teaching, research, and patient care.

The manner in which these requirements are fulfilled will necessarily vary from institution to institution. However, certain features would be desirable for most programs. In addition to formal academic structure (separate departmental status is not precluded, but neither is it indispensable to success), the unit should have a budget and should be assigned clinical and laboratory space from preclinical and clinical departments committed to clinical pharmacology as such. The director of the unit should be trained in both pharmacology and a clinical specialty, and hold a joint appointment in both departments. Other members of the unit may hold appointments in either or both departments, depending upon their interests and qualifications. Members of the unit should participate in the teaching and seminar programs of the department of pharmacology and in clinical teaching (especially of therapeutics) in areas appropriate to their interests and abilities. They should also be able to carry out pharmacologic research in animals as well as man. This means adequate laboratory space, clinical research facilities, and access to clinical material.

Although members of the unit should participate in patient care in the subspecialty areas of their interest and competence, the clinical pharmacology unit should ordinarily not have prime responsibility for a major subspecialty area such as cardiology or infectious disease. It is important to have sufficient time to pursue aspects of clinical pharmacology which fall outside the usual subspecialty area (for example, drug metabolism in man, pharmacogenetics, the epidemiology of drug reactions).

The clinical pharmacologist must have academic status comparable to other faculty members and be assigned similar degrees of responsibility. It is expected that responsibility for academic advancement will rest largely with the chairman of the department in which the clinical pharmacologist has his primary appointment.

Finally, it must be recognized that the clinical pharmacology unit has to develop in addition to, and not at the expense of, existing departmental budgets and faculty posts. By virtue of his status and his control over budgets, the dean of the medical school is best able to assure that the clinical pharmacology unit will thrive as a welcome addition to the primary departments to which it is attached.

Services

The clinical pharmacology unit plays an important role in providing advice to the university hospital community concerning problems in experimental design. It should provide liaison with departments such as biostatistics and epidemiology when these departments can provide knowledge relevant to a given research project. Clinical investigators from other disciplines may thus be assisted in their research, be it laboratory experimentation or therapeutic trials. Research colloquia on a regular basis or informal, irregularly

scheduled discussions may be held to allow students, house officers, trainees, and investigators to discuss specific projects before they are started, while they are in process, and after they are completed. In this way, fundamental aspects of experimental methods can be discussed in detail and in proper sequence. These aspects include: constructing a protocol, considerations of the accuracy of measurements, appropriate controls for variability, unforeseen problems which arise during specific projects, analysis of data, and medicolegal and ethical considerations in clinical research.

The clinical pharmacologist can also serve as the person in the hospital whom the students, house officers, and faculty contact for information about the use of drugs in man. To facilitate this function, a library of pharmacology and toxicology textbooks, drug reaction reports, and filed data from the drug industry and the Food and Drug Administration should be readily available. In those cases where the clinical pharmacologist is not able to supply the information himself, he should be able to refer the questioner to a proper authority either in the university or elsewhere. A clinical pharmacology unit may wish to emphasize this effort by providing available publications and local announcements to students, house staff, and faculty.

Many clinical pharmacologists now serve on one or more university committees organized to review proposals for the study of new drugs or therapeutic procedures in man. Such committees include those concerned with therapeutic trials, with the study of new drugs, and with the use of a clinical research facility. Clinical pharmacologists should take an active role in these various committees, emphasizing constructive criticism of design and appropriate methods of study, rather than "police action" or censorship.

Other types of committees on which the clinical pharmacologist may serve or to which he may offer advice are those which play service roles in the medical community (for example, hospital pharmacy committees). Here he can be a consultant in regard to the safety and efficacy of drugs so that sound administrative decisions as to the hospital formulary can be made. His role is not to displace but to supplement existing mechanisms for studying and controlling drug usage in the institution.

There is need in the medical community for reporting of adverse reactions to drugs, for gathering toxicological information, for the development of "poison center" facilities, and for the continued critical evaluation of old and new drugs in the therapeutic armamentarium. Maintaining service functions of this nature in the medical community at large should not usually be the primary obligation of the academic clinical pharmacologist, who has as his main responsibility the teaching of pharmacological principles to clinical investigators and future practitioners. He can, however, serve as an adviser, on both local and national levels, for the development of improved systems for meeting such community needs. Individual clinical pharmacologists who have special research interests in the specific areas described will naturally devote greater time to them in their training and teaching activities.

The clinical pharmacologist can facilitate liaison between the Food and Drug Administration and investigators in the university hospital by keeping the latter informed on current FDA regulations and providing additional detailed information when it is required. The complexity of some rulings and the likelihood of further changes in the regulations have increased the importance of this function.

The drug industry can also interact usefully with the clinical pharmacologist, who will have knowledge of the capabilities and interests of other investigators in the academic community, and who should be willing to collaborate actively in the search for new drugs at all levels from theoretical formulations to the accumulation of clinical data. The clinical pharmacologist, in turn, will benefit from this relationship not only because it enables him to learn about new and possibly interesting drugs in fields different from his area of specialization, but also because it allows him to develop collaborative projects which broaden the spectrum of activities that are available to his trainees.

In addition, the clinical pharmacologist can improve overall drug usage in the medical community through participation in programs of postgraduate education. Finally, the various consultation services offered by the clinical pharmacology unit can be extended to community hospitals in the university area, within the limits of available time and personnel.

Financial Support and Space Needs

At present, salary support in clinical pharmacology is generally available from training grants from the National Heart Institute, the National Cancer Institute, and the National Institute of General Medical Sciences for partial or total support of one faculty member of the group. This type of support is renewable at the end of granting periods. In addition, special or senior fellowships and career development awards are available from the National Institutes of Health. These are self-limited types of salary support and there is nothing in this category for support of clinical pharmacologists at the associate or full professor level, that is, those who are beyond the career development stage. Support for faculty members at the immediate post-trainee level is available but inadequate.

Burroughs Wellcome Clinical Pharmacology Grants are available, but in small numbers, and are currently limited to one 5-year period. Salary directly and completely from the university in support of clinical pharmacology personnel is unusual at present.

In regard to trainees in clinical pharmacology, support at the postdoctoral level is provided by the Training Grants and Fellowship Programs of the National Institutes of Health referred to previously. These trainee stipends are also available to predoctoral trainees who are receiving training in clinical pharmacology outside the regular medical curriculum. The availability of such funds seems adequate to meet current needs. Tuition for such trainees is also available when needed.

In addition, Merck, Sharp & Dohme international fellowships in clinical pharmacology are also available annually in small numbers. They are limited to foreigners. A few fellowships are available from other pharmaceutical firms.

Other sources of support include funds from training grants for some secretarial and technical personnel, as well as some funds to support laboratory research. Although specific research grants to support long-range projects are being utilized, such support is often not adequate to finance the cost of investigations on certain problems in clinical pharmacology and clinical toxicology which arise suddenly, having been unforeseen at the time of grant application, and which demand that answers be sought quickly to min-

imize risk to patients. The negotiation of additional long-term grant support can pose serious time problems in such instances.

Funds from the pharmaceutical industry are available in small amounts for specific studies, and are unquestionably useful in covering the expense of some investigations. Such funds do not, however, provide a sound continuing base from which to obtain salaries for trained investigators or for research assistants.

Many clinical pharmacology units have entered the initial stage of their development. With small staffs (often one man) they are making a modest beginning in meeting the needs in the area of predoctoral and postgraduate teaching of clinical pharmacology, the recruiting and training of well qualified clinical pharmacologists, and research on drug action, comparative efficacy, mechanism of action, structure-activity relationships, toxicity, and pharmacologic interactions in man. Most urgently needed at this time is the type of support which will facilitate the development of more adequate staffs in those university clinical pharmacology units which have demonstrated potential in their training and research activities.

By bringing additional well trained and capable faculty members into these groups, the clinical pharmacologist could give more attention to such things as his function as an interdepartmental catalyst, mechanisms of drug toxicity, and the investigation of drug action in depth. Only through effective teaching programs and the impact of investigative programs which attract students and house staff can clinical pharmacology exert maximal appeal and recruit talented people.

There is a recognized need for more well trained clinical pharmacologists to meet the current demands of teaching and research, to develop programs in the many medical schools currently without them, and to staff future centers, such as the proposed regional complexes which are charged with bringing research advances more effectively and safely to therapeutic application.

To meet these needs, the most fruitful approach at this time might well be to foster the development of well staffed clinical pharmacology units to attract capable people and to train them effectively. Despite the sources now contributing toward this goal, additional support is clearly required. Funds are needed for the stable support of senior faculty positions in those clinical pharmacology units which have demonstrated potential in their training and research programs. *The lack of such funds is the single greatest limitation in the next stage of the development of clinical pharmacology.* In addition, support for young clinical pharmacologists at the immediate post-trainee level is often lacking, and many of the research functions of the clinical pharmacology unit are not readily supported by long-range research grants. Funds for new studies are generally available from the pharmaceutical industry only if the interests of the firm in question and of the investigator coincide. Support is also not readily available for the important service functions provided by the clinical pharmacology unit. A special type of unit or program support would be extremely helpful to provide funds for such activities on a continuing basis.

The location of space for the laboratories, offices, and clinical research units needed by clinical pharmacology groups differs considerably from institution to institution. Many groups have research space available within the department of pharmacology or in an area immediately adjoining the research space of the pharmacology department. The ideal location of space for a clinical pharmacology unit would be close to both the department of pharmacology and the research area related to clinical investigation. Clinical facilities are obviously of great importance, and in selecting the site for such facilities, consideration should be given both to the needs of the investigator and the physical and psychological comfort of patients.

Some units have inadequate space for their current programs, and most units would find the expansion of their faculty sharply limited by the shortage of space and facilities for additional investigators.

Space for specific clinical research projects is primarily available at the present time in categoric disease-oriented clinical research units (such as those for cancer chemotherapy) or in the multidisciplinary clinical research areas. Where such facilities are not available, they will have to be provided.

Because of the interdepartmental nature of clinical pharmacology it is suggested that responsibility for development of space for such groups be a function of the dean of the medical school in cooperation with the chairmen of the department of pharmacology and of the clinical department or departments most directly involved. *It is suggested that those groups interested in fostering the development of clinical pharmacology recognize that lack of space currently limits the adequate staffing of most clinical pharmacology units.*

If one accepts the general philosophy and specific needs described above, it is difficult to avoid the conclusion that the welfare of the American public demands that means be found to expand clinical pharmacology. There are two major sources of available funds: the government and the pharmaceutical industry. Both sources are now making contributions, but grossly inadequate ones. The cost of establishing clinical pharmacology units in all U. S. schools would not be high, and the potential benefits would be immeasurable.

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1. Daniel L. Azarnoff, U. of Kansas; Paul Calabresi, Yale; Edward A. Carr, Jr., U. of Michigan; Thomas C. Chalmers, Jr., Tufts; J. Richard Crout, U. of Texas, Southwestern Medical School; Thomas E. Gaffney, U. of Cincinnati; Leon I. Goldberg, Emory; Glenn W. Irwin, Indiana U.; Harris Isbell, U. of Kentucky; Hershel Jick, Tufts; Walter M. Kirkendall, Iowa U.; Louis Lasagna, Johns Hopkins; John A. Oates, Vanderbilt; John A. Owen, Jr., U. of Virginia; Lawrence G. Raisz, U. of Rochester; Alvin P. Shapiro, U. of Pittsburgh; William R. Wilson, U. of Iowa.
2. This report has been examined and is endorsed by the Council and the Clinical Pharmacology Committee of the American Society for Pharmacology and Experimental Therapeutics.

Aging

The biological aspects of aging were discussed at a symposium held at the Salk Institute for Biological Studies, San Diego, California, 4–6 November 1965. Speakers included gerontologists from the United States and England.

Maynard Smith (University of Sussex, England) provided a general introduction to theories of aging. In his opinion it was unlikely that there was any such thing as *the* aging process but only a series of aging processes which natural selection would tend to synchronize even if the causes were physiologically independent. He emphasized the impossibility of deciding