

## Special Article

### *Clinical Pharmacology and the Anesthesiologist*

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THE RECENT "REDISCOVERY" of clinical pharmacology must sound strange to many anesthesiologists who have thought of themselves as practitioners of pharmacology and, thus, clinical pharmacologists by definition. What then, they ask, makes someone a clinical pharmacologist?

The answer is, of course, that there is no consensus on the definition of a clinical pharmacologist. Some have said that any clinical investigator who learns "enough pharmacology" can function as a clinical pharmacologist.<sup>1</sup> In the view of others, he should have dual training: in pharmacology and in a clinical specialty,<sup>2</sup> in our case, anesthesiology. Certainly, good reasons have been advanced to support these views, and few proponents claim exclusiveness. I should like to emphasize another point of view. For reasons I will develop, I submit that clinical pharmacology is best done as a collaboration between pharmacologist and clinical investigators.

Pharmacology and anesthesiology (or any other clinical specialty) each more than fully fills a man's scientific capacity. Thus, it follows that you lose pharmacological capability when you train someone to be both a pharmacologist and a clinical physician-investigator. Examples of happy and productive combinations of dual training notwithstanding, the basic fact is that the man who expends part of his effort in acquiring a second training will take this part away from his first discipline. Some, nevertheless, contend that it is necessary to combine two disciplines in order to cover the essential area of contact between the two. This argument has validity, but not to the point of exclusiveness. The middle ground between two disciplines can be cov-

ered just as well, and perhaps better, by two individuals each of whom has only one primary area of training but does have sufficient understanding to speak the other's language and to understand the possibilities and the limitations of the other's field. In this case, even unusual talents and capabilities in each of the two fields can be pooled for maximal productivity of the combination. Concerning the pharmacologist on the team, his usefulness to his clinical partner is directly proportional to how good he is as a pharmacologist. As stated, all anesthesiologists are pharmacologists, so for a pharmacologist to be of value to an anesthesiologist he must really be good, in pharmacology, not in anesthesiology.

There are secondary benefits of this approach. When one person combines two disciplines, he still is only one person. If a pharmacologist can collaborate with one anesthesiologist, he can also collaborate with a second, and a third, clinical specialist. Since we do not have sufficient clinical pharmacologists, this seems desirable, especially in view of the fact that most clinical pharmacologists are concentrated in internal medicine (table 1). There are some clinical specialties—anesthesiology is fortunately not one of them—which could not attract clinical pharmacologists at all if the pharmacologist had to make a commitment for a lifetime. Yet, obviously, not only internal medicine needs clinical pharmacology.

Another highly desirable benefit is that the investigative team consists of a minimum of two. This is a safety measure for the patient—subject and a comfort to the investigators. The clinical member of the team carries primary responsibility for the patient's welfare, and will keep this responsibility in mind more easily than if he were physician-investigator in one person. In our team the clinical member has absolute veto power during an ex-

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periment, which he can use if he feels that the interests of the patient are not sufficiently considered.

I often hear the argument that this team approach is difficult or impossible in practice: that a clinical pharmacologist has to "control" clinical management of patients to secure the working conditions he needs. I have not found this the case. Management of many patients in a modern hospital is not the province of one man, even though only one has final responsibility. Optimal management of many patients requires true collaboration of several specialists. Collaborative clinical pharmacology, therefore, is nothing more than the application of a sound principle of modern medical care.

Finally, I have often heard that the clinical pharmacologist needs "competence" in order to be considered seriously by his clinical collaborators.<sup>2</sup> Anyone lacking clinical "credentials" will not be acceptable to the clinical physician even if the physician is accustomed to working in a team. My experience does not support this. Surely, the investigator who has no concept of clinical realities or of the basic difference between animal and clinical research will soon find himself out of step with his clinical collaborators, not because of lack of clinical "status" but because of his lack of understanding.

The special aspect of the collaborative approach to clinical pharmacology is not the lack of clinical training as such, but results rather from the need of one investigator to convince his colleagues that what he wants to do is indeed worth doing. Presumably, he need not do this if he has "patient control" (although he must account to a vigilant human studies committee in the institution). This may be a hindrance or an advantage, depending upon one's point of view. I can conceive of situations in which the need for an investigator to justify his research plan to his colleagues may be a disadvantage. However, in the vast majority of instances it is a very good principle indeed that requires the investigator to state his case in a manner understood by competent and informed colleagues. Remember, this is not a laboratory investigation, where even a poorly designed experiment will do little harm, but a study of a human sub-

TABLE 1. Training Programs in Clinical Pharmacology According to Clinical Specialties

| Specialty                  | Number of Programs |
|----------------------------|--------------------|
| Medicine                   | 35                 |
| Pediatrics                 | 8                  |
| Anesthesia                 | 6                  |
| Psychiatry                 | 4                  |
| Neurology and neurosurgery | 3                  |
| Obstetrics-gynecology      | 2                  |
| Surgery                    | 1                  |

\* From information supplied by the American Society for Pharmacology and Experimental Therapeutics; status as of December 1, 1970. The total of these programs adds up to more than the units actually existing because several units cover several clinical specialties.

ject, which usually carries a risk and should not be undertaken lightly.

There is one general point one may make about the clinical pharmacologist: he should be a broadly trained pharmacologist. The object of study of clinical pharmacology is always the whole patient, in whom direct and indirect drug effects and interactions of many different "systems" (circulation, respiration, nervous and endocrine systems, genetic, metabolic and behavioral) are to be expected and must be looked for. To do this, one must know as much as possible about what to look for, and that takes the broadest training in pharmacology imaginable. This is why not everyone who uses drugs in clinical investigations can be called a clinical pharmacologist.

What kind of work should the anesthesiologist and pharmacologist do together? We can divide our needs into two easily recognizable groups: work on presently used drugs, and work on new drugs. Better, perhaps, we can distinguish: a) work designed to learn new facts about a drug or combination of drugs, whether old or new; b) work in which a drug serves as an important tool for obtaining new information primarily non-pharmacological in nature, *e.g.*, physiological, biochemical, clinical; c) work designed simply to assess presently used drugs and treatment schedules in a reliable way.

Not much needs to be said about the first type of investigation. Here, the collaborative approach is obviously advantageous. When

a drug is new, phase I and phase II studies should only be done in close collaboration with a pharmacologist familiar with the data of preliminary animal studies. We are far from being able to predict all actions in man by extrapolation from observations in animals. But perhaps it needs emphasizing that we can predict many effects in man quite well, and that it is the exceptions for which we must be alert.<sup>3</sup>

Initial investigations with new drugs should be as broadly designed as possible. In spite of the fact that such studies are initiated with a definite hypothesis, usually the question "does drug X do what we expected on the basis of animal observations and with what toxicities," the first clinical use of any new drug is as open an experimental situation as you can find. We have many examples in which therapeutic or toxic effects not predicted from animal observations were revealed only when a new drug was administered to man. Perhaps the pharmacologist will discover the novel effects because of his greater familiarity with the pharmacology of the class of substances to which the new drug belongs, or it may be the clinician who notices the unusual and unexpected because of his greater clinical experience.

The second type of involvement of the clinical pharmacologist is also easily understood. The investigator who plans to use a drug as a tool should familiarize himself with the whole pharmacology of the drug. To obtain this information directly from a "practitioner" is easier and often better than to obtain it from the literature, since publications usually tell only part of the story. Also, even though anesthesiologists as a group may be by far the most informed about such matters, there are still general pharmacological principles which are not always appreciated in clinical practice. Let me use as an example the clinical use of propranolol. This beta-adrenergic blocking agent is a competitive antagonist. When tested against an applied agonist such as norepinephrine or isoproterenol, it will only shift the dose-response curve to the right, without decreasing the maximum effect attainable. When, however, the agent is used to block response to sympathetic nerve activation—and this is almost

always the clinical situation—we see that the maximum response attainable in response to nerve activation is greatly depressed even with doses of propranolol which shift the response to directly applied agonist only moderately.<sup>4</sup> Thus, in the clinical situation, propranolol behaves as if it were an unsurmountable antagonist. Furthermore, since the duration of action of a dose of propranolol which completely blocks all responses to nerve stimulation is relatively brief and the dose-response relationship is steep, we probably do not achieve a steady-state partial or complete block with clinical dose schedules, but rather a see-saw from full block to zero block between doses. This is simply extrapolation from animal experiments. Supporting clinical evidence would be difficult to establish and, so far as I know, has not been reported. Yet, it is clear that such considerations are very important for the clinical use of the drug.

It is timely, perhaps, to say something about the third type of clinical investigation. For a long time pharmacologists, statisticians, and clinical physicians have been deploring the lack of reliable, statistically sound, clinical data on many drugs (e.g., drug efficacy study of NRC/NSF). The call for "sound" evidence is easily understood even by individuals not medically trained, such as lawmakers and journalists. Perhaps the time has come to emphasize the limitations of this type of work before we commit our resources too deeply in this direction. This type of information does not come cheaply, either in direct expenditures or in terms of investment of scientific manpower. And once we have embarked on these programs, we are committed for relatively long periods. We had better know what we can reasonably expect and what we cannot expect as return for this investment.

It seems an obvious thing to call for a large-scale, multi-center, joint study when we are confronted with questions which on simple statistical grounds are beyond the reach of single investigators, teams, or institutions. There are notable examples of highly successful applications, such as the V.A. study of drug treatment of tuberculosis. Yet, other efforts have not yielded worthwhile results. What did we really learn from the National

Halothane Study? Only that halothane has no higher overall anesthetic mortality and morbidity than other agents. This is valuable information, but the study did not end the fear of hepatic damage and has not contributed much to the safety of anesthesia. Additional information accumulated since, concerning the mechanism(s) of the hepatic damage produced by halothane, may ultimately lead to the identification and exclusion of patients with high-risk factors, and may be much more productive in improving the safety of anesthesia. We have also learned that there are considerable differences in anesthetic mortality rates among different institutions. Perhaps this is also valuable information. It alerts us to the fact that the statistical evaluation of an agent such as a general anesthetic inevitably includes the skill of the "user," as well as other factors such as the quality of supporting services (nursing, pharmacy, laboratories).<sup>5</sup> Although great efforts are made to insure randomization of the patient populations under study, equal efforts are not always made to randomize the influence of the "quality of delivery."

The importance of such factors differs predictably. General anesthetics are used clinically in the steep part of their dose-response curves. Small changes in concentrations cause large changes in responses, both desired and toxic. Thus, careful regulation of administration becomes an important factor. Antituberculous drugs, on the other hand, have a much larger therapeutic ratio, and results obtained with them are much less affected by the skills of different users. Combining therapeutic results from different hospitals did not entail a disadvantage.

These factors should be understood and taken into account in the planning of studies with drugs such as general anesthetics. Epidemiologic comparisons of different agents should not obscure the possibility that improved training of physicians in the use of such drugs may be the most important factor in their clinical safety.

When Beecher and Todd<sup>6</sup> found a higher mortality associated with the use of neuromuscular blockers, that observation could have led to the disappearance of those agents. Fortunately, this did not happen, and the safety

of neuromuscular blockers was improved when their use was better understood and experience increased. Today, few anesthesiologists would want to omit these drugs from their therapeutic armamentarium.

Let me make my point more clearly by presenting a hypothetical study of digitalis that could have been done at some point in the past.

We could imagine that at one time in the past a statistical study had been set up to decide the value of digitalis therapy. The questions would have been: How many patients are improved by digitalis given in accordance with the then-available best therapeutic regimen, and how many patients are harmed by the same regimen? One could have used an objective criterion for evaluation: the mortality rates of two patient populations treated randomly with placebo or digitalis. I suspect that such a study, had it been undertaken only 40 years ago, could have resulted in the banning of digitalis. Toxicity of any effective schedule of medication would have been formidable; and therapeutic efficacy would have been low had the main concern been to avoid toxicity. We recognize today that the most important factor in the clinical use of a potent drug with a small therapeutic ratio such as digitalis is the knowledge, experience, and diligence of the physician. The hypothetical study described would have done little to provide information which would have improved the safety of digitalis use.

Let me carry the hypothetical case still further. Suppose we had carried out such a study at the time when the cardiac action of digitalis was not firmly established and the indication might have been the presence of edema, regardless of origin. In this case the non-cardiac-edema patients would have been subjected to the toxicity without having a chance for a therapeutic effect. The statistical results would have been weighted against digitalis by inclusion of a group in which efficacy could not be expected. Fortunately, the example could have been possible only a long time ago, but perhaps we have analogous situations today. There are still many "symptoms" which may be consequent to various defects but are treated by the same drug. Our diagnostic capability does not permit us

to differentiate among the different defects. We still have difficulty diagnosing myasthenia gravis with certainty in all cases, and there is suspicion that an identical functional defect in neuromuscular transmission may have different pathogenetic causes. What about angina pectoris? Vascular lesions cannot be demonstrated by coronary angiography in a certain percentage of patients who have clinical symptoms of coronary vascular insufficiency. However, we are evaluating drugs like propranolol in treating the symptoms of angina. Perhaps propranolol is 100 percent effective for one type of coronary insufficiency and not effective for another. We have good reason to believe also that the undesirable effects of propranolol are quite different in different patients, and are greatly affected by the mode of administration or the training of the "user." At this time, more may be accomplished by careful observation of single patients in efforts to work out the indications and contraindications and methods of administration for propranolol (or any other beta-adrenergic blocking agent) in angina pectoris than can be expected from a statistical assessment of its efficacy and toxicity by multiclinic trial.

The lessons are clear: first, the epidemiologic evaluation of drug therapy is affected by the training of the users. We may then properly ask whether it is better to use funds for such assessment or for improving training of physicians in the use of drugs. In cases where potent drugs with low therapeutic ratios are involved, the second alternative may be preferable. There is ample room for improvement of training in the use of drugs, as has been pointed out by many observers.<sup>2</sup>

The second conclusion is a plea to our regulatory agencies not to hinder advancement of knowledge by restricting the use of drugs on the basis of statistical evidence of low efficacy and high toxicity in such cases as described above. Often the state of our knowledge does not provide a sound basis for statistical study, for example, because we cannot assess the uniformity of a patient population. Ineffective drugs and drugs with unacceptable risk/benefit ratios, especially when better therapy is available, should be removed. However, decisions concerning drug therapy

should not be made on statistical grounds only, but should consider the total relevant information available. Recently, Feller<sup>8</sup> emphatically deplored the misuse of statistics in basic biological sciences. He points out that the main goal of basic science is the discovery of new facts, and that statistics are often used inappropriately in this context. Clinical pharmacology also has the discovery of new facts as one of its goals, perhaps the most important one. The evaluation and assessment of existing therapy is only one aspect of medical research, and it can be argued, as Shannon did recently,<sup>9</sup> that the advancement of our knowledge as a whole is still the most important consideration in medical research and carries the greatest long-term promise.

In addition, I urge that the teaching of clinical pharmacology be given more emphasis than in the past.<sup>2-7</sup> Anesthesiologists have always had far better-than-average training in pharmacology, whether it be called clinical or otherwise, but the need is for even more, because anesthesiology is also the specialty in which the most potent and the most toxic drugs are the most widely used.

## References

1. Dowling HF: Medicines for Man, the Development, Regulation and Use of Prescription Drugs. New York, Alfred A. Knopf, 1970
2. Lasagna L: Clinical pharmacology: Present status and future development. *Science* 152: 388-391, 1966
3. Wolstenholme G, Porter R (editor): Drug Responses in Man. A Ciba Foundation Volume. Boston, Little, Brown and Company, 1967
4. Flacke JW, Bendixen HH, Osgood PF: Block of cardiac nerve action by propranolol. *Fed Proc* 27:351, 1968
5. Gaddum GH: A perspective on pharmacology, Drugs in Our Society. Edited by P Talalay. Baltimore, The Johns Hopkins Press, 1964
6. Beecher HK, Todd DP: A Study of Deaths Associated with Anesthesia and Surgery. Springfield, Ill., Charles C Thomas, 1954
7. Carr EA: A short course in clinical pharmacology. *Clin Pharmacol Ther* 11:455-459, 1970
8. Feller W: Are life scientists overawed by statistics. *Scientific Res* 4:24-30, 1969
9. Shannon JA: Medical research: Some aspects that warrant public understanding. *New Eng J Med* 284:75-80, 1971