

The Problem of Evaluating New Drugs

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THE PRESENT RAPID developments in drug therapy pose a serious problem for the busy practitioner—young or old. The older veterinarian may recall with some nostalgia how his training in therapeutics involved a comparatively few “tried and true” drugs with which he entered his practice. New drugs appearing at relatively infrequent intervals were added to his armamentarium and he had time to evaluate them for himself more or less at leisure. These were then added to his “Materia Medica” or discarded. Recent advances in all phases of medical sciences began to add many new words to his professional vocabulary and his interpretation of new drug activities had to be evaluated in terms of vitamins, endocrines, chemotherapy, antibiotics and a host of other developments based on a more intimate knowledge of the intricate nature of physiological mechanisms. In the light of this newer knowledge, synthetic drugs are now almost tailor-made for specific clinical entities while some of the old stand-bys have undergone refinement with increasing potency. Newer vogues in medication, particularly the increased use of parenteral drug administration,

have also added to the problem. The experienced clinician can sympathize with the recent graduate and the student who must face the same problems in drug evaluation with very limited experience to draw upon. An added harassment, particularly to the already overcrowded student, has been the adoption of the metric system in dosage computations as “official” in the United States Pharmacopeia and the National Formulary. Since the apothecary system is still widely used, conversions between the metric and apothecary systems must be learned.

The establishment of ethical drug houses with competent research and clinical facilities, producing new drugs with high standards of uniformity and quality is another facet in this changing picture. The decreasing use of extemporaneous prescriptions and the increasing use of compounded drug preparations is also evident. In using the former, the practitioner must know the related activities of the components, while in the latter these factors are presumably evaluated for him. Many preparations are now on the market that differ only in minor variations of the formula but are sold under different trade name. Indeed, many drugs differ in name only! This is true even of some of the official drugs, where the names seem to be official only from one edition to another.

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For example, the proprietary "Demerol" was once officially listed as Isonopicaine and then changed to Meperidine. The "unit" of digitalis has undergone several revisions in standardization from cats to frogs to pigeons. To have significance, the digitalis unit must be qualified to the edition of the USP.

Finally, there is an increasing interest and knowledge on the part of clients in new therapeutic advances from drug house advertisements and in articles in the popular press. Information from these sources may provide difficulties to the busy veterinarian particularly in the ready availability of some of these potent drugs to the laity, or sometimes almost on insistence by the client to use some of the new but clinically unproven drugs. From newspaper accounts clients are more aware of the publicized anticipated benefits than they are of the potential hazards which are inherent in all potent drugs. Experiences with the antibiotics may serve as a case in point without further comment. The practitioner is anxious to pass on the benefits of new therapeutic advances to his clients, but must be assured in his own mind that these new drugs will actually produce the benefits attributed to them without being too hazardous or creating new problems. It is obvious that the practitioner cannot place under clinical trials the many new drugs that appear almost daily so he must place reliance upon the reports of the work of others and interpret their finding in the light of his own experience and therapeutic wants.

There are several sources of information on new drugs. It might be pointed out here that really "new" drugs represent only a small fraction of the many preparations put out as new drugs each year. Most therapeutic innovations are old friends easily recognized by reading the label beyond the proprietary name. In the normal course of development leading to the marketing of a new product, "preliminary" reports and some fundamental studies are first reported in the journals of basic sciences. The exceptions to this are usually those drugs developed by drug

manufacturers in their own experimental laboratories. As business firms they are rightfully protecting their investments. Further, many compounds with academic research backgrounds have been developed into useful drugs by these firms. Studies are made on the mechanisms of action; the determination of therapeutic levels, toxicities and on a number of clinical trials, after which the drug is evaluated by the Food and Drug Administration. It may then be marketed with or without restriction according to the ruling of this federal agency. The results of the clinical trials and other data are then published in a scientific journal or through advertisements of the manufacturer. After the drug becomes rather widely distributed, other reports may be published on the therapeutic usefulness and clinical experiences with the drug under field conditions. Controlled laboratory and clinical studies establish the validity of a new drug, and field experiences establish its practical usefulness.

A comparatively recent embellishment of reports on new drugs, and biological data in general, has been the inclusion of a statistical analysis of the experimental or controlled clinical results. This sanctification of results has largely replaced the "average" which is more a measure of direction than degree. Some animals may show no response to an "average" dose, while for others this dose may be toxic.

The primary purpose of significance studies obtained through statistical analysis is to point out the probabilities of events which can occur under a given set of circumstances. These methods have been formalized in many ways, such as the determination of normal probability, law of alternative probabilities, permutations and combinations, binomial law, the law of small probability (Poisson's law) and many others. An important point which is overlooked all too frequently is that statistical proof is offered to support conclusions obtained in experimental work and not necessarily to justify them. Much so-called scientific "proof" offered in a statistical form may prove to be a pitfall.

For example, a pollster random sampling in a railroad station might find that 60 percent of the people there are going on a trip. By repeated observation and statistical analysis he may be able to draw valid conclusions and predictions on travel habits. He would not, of course, be justified in concluding that 60 percent of the population travels. In other words, statistics have to be coupled with a certain amount of horse-sense in evaluating data. It is not the purpose here to discuss statistical methods but it should be recognized that significance studies of data by competent analysts have contributed much in the evaluation of new drugs particularly in posology and toxicology.

Although many individuals are not versed in the intricacies of statistical development, they should have some guideposts for evaluating the various reports they receive. A practitioner does not necessarily have to be a statistician in order to gain knowledge from a statistical interpretation any more than a car driver has to be a mechanical engineer. As stated previously, most new drugs are actually modifications of drugs with established clinical usefulness altered in form, vehicle or combined with other drugs. Evaluation may be made beyond the claims for the drug on the basis of personal experience with the parent compound and what alterations can contribute to improving the product. Reports on drugs with which the reader has limited or no experience and which therefore have to be evaluated on the basis of the report fall into one of three categories:

First, there is the type of report containing generalized unsupported claims for a product, liberal in terminology and short on facts, characteristic of too many types of advertising. The terms "scientifically proven," "laboratory tested," "used by thousands" are examples of generalizations which are actually meaningless without elaboration or substantiation. It is possible for someone to exploit a drug as "laboratory tested" and actually be able to verify the statement. Indeed, it may have been laboratory tested and found ineffective or even toxic! In other words,

such statements contain important omissions. If there is merit in products promoted in this manner at least sources of evidence to support the statements should be mentioned so that the reader may be able to obtain further information if he so desires. Testimonials and letters of recommendations from consumers may also be included in this category. Since they are expressions of opinion only, they are not worth much, particularly since complaints are so carefully excluded.

Second, there is the type of report which contains the essential elements of a valid report but is incomplete. Every researcher recognizes that two factors must be included in every investigation. These are controlled conditions for replication of experiments and a sufficient number of trials for drawing the necessary conclusions. The incompleteness of reports in this category may result either in insufficient numbers of cases to draw conclusions, or failure to report the total number of tests. For example, a report on blood levels of a given drug has no significance if studies are made on only two animals, particularly if they show wide variation. If at four hours the blood level of the drug is 25 milligrams per 100 cubic centimeters in one animal, and 5 milligrams per 100 cubic centimeters in the other, a conclusion cannot validly be drawn by interpolation that the average blood level for this drug is the average of the two results. One may presume that a third test might fall in between the two levels, but has no more assurance of that than the probability of getting a 100 milligram blood level. The smallest sample which may validly be treated statistically is six tests under the same conditions. This does not mean, however, that by mathematical manipulation one can justify his conclusions. It means only that on the basis of the results obtained, one may expect that in another series of tests, the probabilities of obtaining the same results as found in the first six tests may be quite accurately predicted. In the example of the blood levels referred to above, the drug levels could vary between 5 and 25 milligrams per 100 cc. or they could vary between 5 and 7 four out of

five times and have one result quite outside this range. Statistics will tell the individual how often in further trials he can expect a recurrence of these phenomenon. As a "rule of thumb" a variation of plus or minus 20 percent is considered as being within "normal" range. Also, it has been established that if a test is repeated 30 times (considered statistically as a large sample) that 90 percent of error due to chance is eliminated. In other words, that in repeating a biological test 30 times, one can predict, within the range of results obtained previously, that the anticipated results will fall within that range at least 90 percent of the time. The other shortcoming of this category is the failure to report control studies, or to state the total number of cases on which the conclusions in the report are based. For example, a statement that "25 patients were successfully treated with our drug after other drugs had failed" even if instances are cited, is significant only when this includes a summary of the total number treated and that the conditions were similar in all situations. Successful treatment of 25 out of 25 is excellent, but what if these successful treatments represented 25 out of a thousand? In summary, results should be interpreted in the light of the conditions under which the tests were conducted, the total number of trials and include the failures as well as the successes in the tests. There are no perfect drugs as yet, and the practitioner has the right to know what his chances of success with a given product should be.

Third, there is the type of report which contains all the necessary information from which the veterinarian may evaluate the drug for himself.

He is not being "sold" anything. Complete information is presented and the conclusions are drawn by the reader. These are the types of reports which appear in professional journals and in some of the literature supplied by reputable drug houses and represent a professional approach to an important problem. Any practitioner who uncritically tries a drug "to see if it is any good" is hardly in a position to criticize the layman who tries

a proprietary remedy on the same basis before calling the veterinarian.

LINKS OF REMEMBRANCE

A hungry dog once wandered
 Into a butcher store;
 The butcher threw some sausage
 To the dog upon the floor.
 The butcher said, "Now eat it."
 The dog said, "I decline,
 For in that link of sausage is
 That 'Ole Gal of Mine.'"

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