DRUGS ON THE MARKET*

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THE first essential in appraising a drug, personally or by proxy, is to judge the possibility of bias, which takes so many forms. The crudest form, financial interest, is almost necessarily present in the case of statements of drug firms. It may be crude indeed, in which case, it generally may be spotted by all but intellectual infants. But it can be assumed that even the best-intentioned firms are not blind to the interests of their stockholders, and are so hopeful of making a "strike" that they are likely to err on the optimistic side, once they are committed to marketing a drug. This does not necessarily disqualify their evidence, but it instinctively should enjoin extra caution in appraising their estimate, especially that of the salesmen who are quite apt to go somewhat further than the firm itself.

"Controls" are the one method by which an honest investigator can eliminate personal bias, conscious, unconscious or accidental. But when are controls "adequate" in kind and in degree? The answer is, "that depends." It varies for each case. As to kind, they must be such that they cannot be modified at the whim of the investigator. That means usually a "blind" test, such as comparison with a placebo or an established drug with the conditions set down in advance, so that the investigator is left no discretion, once the series is started; for instance, alternate admissions receive the drug to be tested, the other the placebo. Of course, patients must be comparable, but as no 2 patients are alike, this may not be a simple situation. It may be necessary to "stratify" them into grades, perhaps by the degree or duration of the disease, alternating the patients in a given stratum.

The question of adequacy of the controls depends on the natural variability of the "blind" placebo series, and may require the aid of a statistician. The statistician can work only with the data submitted to him, and may not be able to judge whether these data are good or bad. The responsibility, therefore, depends upon the competence and good faith of the investigator. Statistical analysis can go no higher than its factual source—and sometimes not that far.

Drug manufacturers are under const nt drive for multiplication of remedies as such, even if this is mere duplication. They naturally wish to share the harvest while the sun is shining; they do not wish to seem behindhand; they feel that they must match all promi ing drugs, lest they be thought unprogressive. This drive has a good feature; it motivates research, and it brings out improvements that may be worth-while. It has its bad aspects, in that it

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wastes effort, not only on the part of the manufacturers, but of the physicians who are urged to try new and unproved drugs, worthless though they may be. The good and the bad in multiplication are delicately balanced, but the interests of the manufacturers incline to stress multiplicity, while those of the physician and the public favor simplification—the elimination of superfluous duplications and equivalents. Barbiturates are an example of the benefits, for while manufacturing enterprise has resulted in many superfluous duplications, it has also brought out distinctive differences that are practically useful. The antihistamine drugs and the sex hormones, on the other hand, are instances where multiplication has resulted chiefly in confusion and wasted effort. The situation can be greatly simplified by adhering to certain criteria to insure the essential objectives that make a new drug worth-while, namely, its advantage over the current drugs, rather than the superficial differences which are a trap for the unwary.

These criteria have been summarized in a Report of the Council on Pharmacy and Chemistry:

(1) **Potency:** In a new drug asserted to be more potent, the difference should be material. A gain of potency, even of 100 per cent, signifies little if the same ends are secured simply by increasing the dosage of the weaker drug, unless it also means a relative decrease in undesirable side actions, material reduction in cost, or some similar benefit.

(2) **Lesser toxicity**: This has a practical meaning only if the margin of safety—the ratio of therapeutic dose to the dangerous dose—is materially greater. No advantage is gained, for instance, if the toxic dose is ten times that of the old drug and the therapeutic dose of the new drug is also ten times higher. Likewise, a gain of 10 or even 50 per cent in the fatal dose is of no material advantage if the toxic dose of the old drug is so far from the therapeutic dose that the toxic level would never be attained in practice. Nor is anything gained if the additional margin of safety of the new drug is only 10 or 20 per cent greater than that of the old drug, unless the therapeutic and toxic doses are approximate.

(3) **Freedom from side actions** is generally only relative, and has no practical significance unless sufficient in kind or in degree to be pertinent.

(4) **Cost** may well be relevant, especially with the more expensive drugs. Unfortunately, the newer drug, more often than not, has little effect on material economies.

Another confusing problem of multiplication is the duplication of names for identical products, imposed by the imperative financial necessities of the drug firms. A firm that develops a really new drug generally makes a large investment in research and promotion expenses. If it is to fulfill its obligations to its stockholders, it must regain the expenditure, plus a substantial profit, as well as the outlay on experimentation with substances that prove ineffective after they are marketed or never reach the market. To meet this inescapable fact, the firm tries to protect itself against the competition of those who would reap the harvest without having financed the experiments. This protection

is furnished by patents and especially by trademarks, for patents expire in 17 years after which anyone is permitted to produce and market the product, but trademarks endure. A trademark signifies a distinctive name or device that identifies the product of that particular firm. To further establish this identity there must also be a common name which may be employed by manufacturers after the patent expires, a name in actual use some time before the expiration. The originating firm introduces this common or generic name, preferably at the time its trademarked brand name is introduced, in addition to the chemical name, which usually is complicated. We have at least three names initially. The chemical name is supplied by the chemists. The firm, understandably, stresses the brand name, which is short and easily read, pronounced, written and remembered. This involves some ingenuity, for there are already so many names on the trademark list that it is difficult to find one that does not conflict. Moreover, the Council on Pharmacy and Chemistry will not accept a trademark that suggests therapeutic use, because it often is or becomes misleading. The Council urges that the generic names suggest the chemical structure, although it is not always feasible to do this and still provide a name practical for prescriptions.

The name must not misrepresent the chemical structure. The manufacturer naturally tries to accustom the physician to the use of its brand name, but too much emphasis must not be placed upon this, lest the courts assume it to be the common name and cancel the trademark, as in the case of Cellophane. They are, therefore, obliged to carry water on both shoulders—a heavy bucket for their brand name on the right, and a little tin cup for the generic name on the left shoulder. The physician is strongly impelled to use the brand name, which is so prominently displayed; he would do better to use the generic name in his thinking and in his writing. When the patent expires, and competing and generally cheaper brands become available, these cannot be sold under the original trademark name. The United States Pharmacopeia and National Formulary do not recognize brand names when the product becomes official, but use the generic name, now usually the one originally adopted by the Council on Pharmacy and Chemistry. The United States Pharmacopeia does not mention adrenalin or novocain, for example, but epinephrine and procaine. When a physician states that he injected adrenalin or novocain, he infers that he used these particular brands, which suggests, absurdly, that our suprarenal glands manufacture epinephrine by courtesy of Parke Davis and Company.

Let us assume that the patent on a good drug expires, and other manufacturers are free to make it, but not under the original brand name. They could do so under the unrestricted generic name, but infrequently do. While this was the original objective of the Council on Pharmacy and Chemistry, manufacturers were uncooperative, and perversely sold the product under new brand names of their own because it was good business financially. A manufacturer will not sell much nowadays, unless he advertises; if he advertises only under the generic name, his competitors will also reap the profits. Therefore he aims to protect himself by trademarking a brand name of his own.

Lest the Council lose all control over his product, it seemed the lesser evil to permit additional brand names—until a substance became official in the United States Pharmacopeia or National Formulary. That sets a time limit, at least, on multiplication, and the physician can always avoid confusion by becoming accustomed to the use of the generic name, which covers all brands.

There is the dilemma: on the one hand, a personal investigation of the original literature, which requires experience, special skill, critical judgment and much time; on the other hand, the shortcut offered by the manufacturers, easy, smooth, and beset with bias. The perplexed physician needs help in the appraisal of new drugs, but it must be honest, unbiased, well-informed, and critical. Fortunately, this help is easily available.

There is, in the first place, the United States Pharmacopeia. There was a time, within my experience, when it was the confessed policy of the United States Pharmacopeia to accept anything extensively prescribed, making extent of use the sole criterion of merit. This policy gave no consideration to whether the use was based on adequate criteria or merely on vogue, superficial impressions that had never been critically tested. Moreover, it did not contain the newer drugs, only those which had aged for at least 10 years. Thus the United States Pharmacopeia was of no great help in the selection of drugs. All this has now been changed; the selection is made by the medical members of the Revision Committee, on the basis of informed advice when there is any question. Therefore a drug which is now in the United States Pharmacopeia is fairly certain to be worth-while. The publication is to be revised every 5 years instead of 10, so that it will include all but the most recent important drugs. Other signs of progress include the emphasis on English instead of obsolete Latin titles, and the preference of the metric over the common system in weights and measures. These changes are most encouraging to those of us who solicited them through some decades. The next United States Pharmacopeia convention will be held in May, 1950, and it is hoped that medical organizations will show their appreciation and interest by sending delegates. The National Formulary has also been greatly improved, but is less critical. One limitation of both books from the standpoint of the physician is that they give no information whatever about actions, or whether the drugs are valuable for a given purpose. Aid with the newer drugs is the special field of the Council on Pharmacy and Chemistry, which has operated continuously and successfully for more than 43 years. It consists of 17 members, appointed by the Trustees of the American Medical Association, from nominations presented by the Council. Members are selected for their general reputation of high ideals and practical wisdom, combined with outstanding knowledge and experience in their special field. They serve for long terms, generally as long as they are able and willing to give the time that this work requires. Technical questions outside of the experience of the regular members are referred to the special consultants. The Council has a full-salaried executive secretary, Dr. Austin Smith, and under him several carefully chosen full-time professional and clerical staff assistants. The well-staffed and equipped Chemical Laboratory of the American Medical Association is in close relation with

the Council on Foods and Nutrition, Physical Therapy and other departments. When a new drug appears on the market, the headquarters staff gathers all pertinent information from the manufacturers and from other sources. This is presented to the referee, who prepares a comprehensive critical report as to the properties of the drug, its actions and uses, and whether the claims made for it are fully justified by the evidence. The Council then votes whether it should be accepted, rejected, or should await further investigation. If it is accepted, a careful description is published in the Council columns of the Journal of the American Medical Association, and reprinted in the annual New and Nonofficial Remedies. If further evidence is necessary, the manufacturers are given opportunity to supply it. If the drug seems of sufficient importance, an interim status report is published in the Journal.

Acceptance may be taken as assurance of the drug's value and its purpose in the light of existing knowledge. It does not indicate that it is the best drug for any purpose, for that varies with conditions, but it does give reliable and unbiased information from which the physician can determine upon consulting the annual New and Nonofficial Remedies, how it best suits his particular need. If the drug is recent he may refer to the current issues of the Journal of the American Medical Association. If he does not find it there, he may write to the Council at the American Medical Association in Chicago, and he will receive the available information. Meanwhile, he may save himself time, trouble and disappointment by asking the salesman whether his drug has been accepted by the Council. If it has not been accepted, it usually means that adequate evidence is not yet obtainable. The Council on Pharmacy and Chemistry demands that the manufacturers supply such information with good evidence for their claims. If this requires extensive cooperative clinical investigation, and if it appears of sufficient importance, the Council may arrange research through its Therapeutic Trials Committee. The most important project engaged upon at the present time is the evaluation of the field of sex hormones in the treatment of malignant tumors.

To summarize, you may protect yourselves from being victimized by "Drugs on the Market" in the bad sense, and secure the full benefit of "Drugs on the Market" in the best sense, by adhering to the following principles:

1. Restrict your prescribing to the smallest number of drugs sufficient for your needs.

2. Do not "try" a new drug unless you have a good reason.

3. Scrutinize carefully before you add needlessly to the drugs with which you are already familiar.

4. Insist that a new drug has been thoroughly studied before you try it.

Do not make up your mind, and especially do not give scope to your tongue or pen, unless and until your conclusions can stand up before critical judges. Until then, cultivate the priceless quality of personal reticence. The publication of a few false judgments that could have been avoided may blast a professional reputation, sometimes beyond repair. There is more risk of harm in talking too much than too little.