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DOCTORS, DRUGS AND DRUG PROMOTION*

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THE DEVELOPMENT and introduction of new therapeutic agents has followed a roughly exponential course over the past century, and as an inevitable result of such a process, the number of new agents introduced annually has now overwhelmed the average practising physician. This would be true even if only new chemical compounds were involved, and the problem is multiplied many times by mixtures and combinations. Each of these has its own trade name and tends to develop a vague but independent identity to which it rarely is entitled. The pharmaceutical industry has been responsible for the development and manufacture of many drugs which represent major therapeutic advances. Indeed, the advent of "wonder drugs" has tended to delude both the medical profession and the public into believing that any new product represents a modern miracle. Unfortunately, relatively few new products contribute substantially to medical progress.

Rapid introduction of large numbers of new agents and combinations, and frequent delays in the publication of full information regarding their properties and effects, have combined to produce a situation in which even the full-time pharmacologist is hard pressed to keep abreast of developments. For the busy practitioner the situation has become impossible, and a majority no longer attempt personally to evaluate the data on new agents even when it is available. There is an increasing tendency to try new agents simply on the basis of drug-house literature. The volume of this material has expanded tremendously since the end of the war. It ranges from a few words on a blotter to elaborate, profusely illustrated booklets, and includes thousands of pages annually in the standard medical journals. Because it has come to play a major role in disseminating information on new drugs, the material prepared and distributed by pharmaceutical manufacturers must be carefully evaluated, and evaluated as advertising.

It is clear that the medical profession plays a major role in determining types and volume of drug advertising. In the hard-headed world of business, the type of promotion employed is determined by the response obtained. Journal advertising, direct mailing, free samples, business gifts such as pens or notebooks and various forms of entertainment all have been shown to increase sales. Obviously, if any of these forms of promotion were not heeded by the profession, it would soon disappear. However, it appears that the physician, ostensibly endowed with scientific scepticism, is as susceptible to the huckster's art as is the general public. "Ethical" medical advertisements employ more technical terms than are used by the white-coated television "doctor" extolling the latest mouthwash, but the approach employed in most medical advertising is identical.

Occasional brochures produced by some manufacturers contain relatively complete and reliable surveys of available information regarding an agent or preparation. These may contain considerable valuable material, but they are more difficult and time-consuming to read and require considerably more thought on the part of the physician than do the shorter, gaudier bits of advertising. Consequently, they frequently are neglected by the profession. This has been recognized by advertising departments, and such "full coverage" brochures usually are sent only to a short, selected list of physicians.

A type of "prestige" advertising requires special mention. Pharmaceutical manufacturers frequently put out booklets on specific disease entities or sponsor closed-circuit television programs which are primarily educational in nature. Some of these are excellent in content and presentation and provide a real service. However, they must be distinguished sharply from promotional material. The fact that a booklet contains an informative and reliable article on liver disease does not mean that the advertisements enclosed in the same cover also are reliable.

All promotional material, irrespective of its form or source, must be evaluated with a full appreciation of the role of advertising and of advertising personnel in the contemporary pharmaceutical industry. In the advertising business it is freely recognized that a major purpose, if not the major purpose, of advertising is to create a demand where no real need exists. This clearly is a factor in much drug advertising. New preparations which effectively fill a real need require little promotion. The first sulfonamides, penicillin, cortisone and more recently chlorothiazide needed no advertising to create a demand. Most of the promotional material is not prepared by, or even seen before publication by medical personnel. It is prepared by highly specialized promotional departments, which in many instances represent the effective controlling influence in a pharmaceutical organization. These departments have available extensive analyses of all drug sales from which they evaluate sales trends and determine marketing policy.

The chemistry of medicinal compounds has advanced to the point where it generally is possible for a group of good chemists to produce on request a compound closely related to a known drug which has comparable activity and avoids patent infringement. This "me-too" agent usually does not have important advantages over its predecessor, and indeed may be somewhat inferior. It is necessary

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only that it be different and that it have comparable activity. The advertising department will "discover" and establish its superiority. A mixture may be even more easily and rapidly prepared to meet sales requirements. If the components previously have been cleared for sale, very little information regarding its therapeutic or toxic properties is required prior to marketing. Given adequate promotion, such a mixture can be highly profitable. Polypharmacy of this type represents a large step back towards the complex Latin prescriptions of a century ago, with the added disadvantage that the drug house rather than the physician determines the composition. These multiple-drug preparations expose patients to an increased number of toxic reactions, particularly of the sensitivity type. Multiple vitamin preparations containing folic acid are examples of mixtures which do serious harm, in this case by promoting neurological damage when given to persons with an unsuspected pernicious anæmia. Drug houses and physicians bear equal guilt in the use of such mixtures.

Certain therapeutic areas have become so large and lucrative that major drug houses rarely can afford to ignore them. A new product does not have to have any well-established advantages to take over 5 or 10% of the sales volume in many fields, and inasmuch as a number of types of therapeutic agents now have annual North American sales in excess of $50,000,000, it obviously is unnecessary for a company to await the development of a really superior product before entering the competition. This is particularly true because the subjective nature of responses and/or the chronicity of many disease processes which have attracted recent attention (atherosclerosis, rheumatoid arthritis, allergic reactions, mental disease, etc.) are such as to make it impossible to draw definitive conclusions regarding therapeutic efficacy until a drug has been in use for years. It is clear that substantial profits frequently can be realized from even a very inadequate product long before any clear evaluation of effectiveness is possible.

The above considerations emphasize the necessity of carefully scrutinizing promotional material. Unfortunately, there is no simple and reliable formula for sorting useful information from that which is useless or misleading. However, certain factors warrant special attention.

A major consideration in the adoption of any new product is toxicity. It is axiomatic that every drug has some toxicity, and the common promotional statement that a given product has "low toxicity" or has not produced this or that specific type of toxic reaction is of limited significance. It is much more important to know the types of toxicity which may occur. Advertisements rarely carry this information. Detail men may be asked for and sometimes are helpful in obtaining the desired data. However, this very useful information frequently is not included in the routine promotional material which they receive, and it may take them some time to obtain it. A related problem is presented by advertisements which include a considerable discussion of toxic reactions, but fail to mention those which may be of major concern. Current advertisements for new adrenal steroids are illustrative. They uniformly refer to decreased salt retention as an advantage, but say nothing about suppression of pituitary-adrenal function or decreased resistance to infection—major hazards in the use of any agent of this type. In the absence of definitive information, it usually is correct to assume that the new agent is at least as dangerous as its predecessors with respect to the unmentioned properties.

One always must be sceptical of claims regarding the low toxicity of new drugs. Reports of toxicity are slow to appear. This is accentuated by the current tendency to administer multiple agents simultaneously, which often makes it difficult to be sure which is responsible for a given reaction. In addition, reactions which involve induced sensitivity are not prominent until an agent has had a considerable period of widespread use. Chloramphenicol provides an example of a common pattern of toxicity reports. No clear cases of bone marrow damage due to this drug were reported for several years after its introduction. Finally, a few definite cases were reported, followed by a considerable number of reports, which brought about a sharp reduction in its use. More recently, this antibiotic has again been employed more extensively, but without a parallel increase in reports of toxicity. However, the paucity of published reports of toxic reactions cannot be taken as reliable evidence that the drug has changed or even that physicians have become more adept in its use. It may be simply an expression of the well-known fact that observers are disinclined to publish reports of additional cases of a well-known toxic reaction.

A favourite advertising statement which must be interpreted with caution is that a new drug or preparation is "more potent" than its predecessors. Unfortunately, the term "potency" appears to have developed almost mystic connotations of effectiveness, of ability to do things which a less potent drug cannot accomplish. In advertisements it is meant to suggest therapeutic superiority where the manufacturer cannot make this claim directly. "Potency" has no such implications. It simply refers to the dose required to produce a given response. Except where previous preparations were too bulky to be easily administered, potency *per se* is of little significance. A recent advertisement for a new steroid stated that it had "enhanced potency without corresponding increase in side reactions in therapeutic doses". The enhanced potency means simply that the therapeutic doses are reduced, and this statement should properly read "same therapeutic effects, same toxic reactions". One suspects that this is not the connotation intended, or how the statement actually was read by the majority of recipients.

Advertisements which make frequent references to published studies pose special problems. They are definitely superior to those without references because they do provide the physician with a basis for checking on the statements made. However, the presence of references does not guarantee the validity of generalizations made from them. A thorough check for reliability requires access to reasonable library facilities and considerable work. However, simple attention to the journals quoted may provide considerable information. Anyone even moderately acquainted with the medical literature is aware of the fact that studies published in some journals provide much more reliable information on the average than do those published in others. Indeed, some journals have become so uncritical of the material which they publish that they are regularly utilized for the publication of "studies" which are purely promotional. A good journal does not necessarily assure good work, but it considerably increases the chances of reliability.

Selection of references is an obvious method of obtaining unjustifiably favourable opinions, as is the quotation of phrases or sentences out of context. The former is the more difficult to detect and may not be obvious except to one thoroughly familiar with the literature on the subject in question. In evaluating papers quoted in drug promotion, it is very important to note doses and dosage schedules. For example, the full significance of a recent promotional effort, which provided references to both efficacy and lack of toxicity, was not apparent until it was noted that the doses used in studies quoted to demonstrate lack of toxicity were considerably lower than those used to substantiate efficacy.

Clues to the real significance of the references quoted may sometimes be found in the advertisement itself. One advertisement extolling the merits of a new nitrite "coronary dilator" contained essentially the following points, each with references. (1) Many clinical observations have demonstrated nitroglycerin to be the most consistently useful agent in angina pectoris. (2) An agent with comparable activity but with a longer duration of action would represent a real advance in the treatment of this condition. (3) Our nitrite has a considerably longer vasodilator action than does nitroglycerin. Therefore, it is the agent of choice in the treatment of angina pectoris. The first two points were documented by references to well-known authorities, the third by an obscure publication showing that the drug in question produced a somewhat more prolonged hypotension in anæsthetized cats. Although a casual glance at the list of references would indicate substantial authoritative backing for the claim that the new agent represented a major advance in the therapy of angina pectoris, more careful scrutiny of the references presented failed to reveal any evidence that the drug in question had ever been found to be of value in this condition, or that any of the authorities quoted to substantiate the first two points had tested or even heard of it.

Advertisements quoting what appear to be relatively reliable reports of clinical improvement resulting from the administration of a given preparation still require careful scrutiny, coupled with a clear appreciation of the natural history of the disease process in question. Favourable responses to therapy in cases of acute peptic ulcer are illustrative. It is well known that this is a cyclic disease in which the patient most commonly consults his physician during a relapse. Most will improve without therapy, and improvement can be hastened somewhat by almost any type of treatment including simple rest, mild sedation, any one of several diets, antacids, "antispasmodics" or just careful attention and concern on the part of the physician. Obviously, under these circumstances, the simple observation that 23 of 25 patients improved on a given preparation means little. Data on improvement from an acute exacerbation of this disease are meaningful only if carefully compared with the improvement induced by some standard treatment under controlled, "double-blind" conditions. A more difficult problem in the management of patients with peptic ulcer is the prevention of recurrences, and any drug which could prevent recurrences would represent a real therapeutic advance. However, this critical point is almost never mentioned in advertisements. This is not due to failure of advertisers to recognize the importance of this aspect of the disease, but to the inability of their product to do anything about it. In the absence of information regarding recurrences, one can safely conclude that the new preparation does not alter them, and therefore has no major advantages over any one of a great number of older and usually much cheaper forms of therapy.

The interpretation of advertisements for mixtures presents special problems. One of the first questions to ask is whether the combination is really logical. The advertiser frequently counts on the physician's failing to look below the surface in this regard. Adrenal steroids are well known to produce or reactivate peptic ulcers and it is superficially logical to combine them with an antacid. However, with the usual therapeutic regimens, the increase in acidity and the decrease in resistance to erosion induced by the steroids is essentially continuous, and in any case, the maximum effect of a given dose is exerted several hours after oral administration, long after any antacid administered with it has left the stomach. These considerations make it obvious that combination of steroid and antacid in the same tablet will be of little value and may actually be very dangerous in leading to a false sense of security.

One clue to the real value of a drug may be obtained by noting the combinations which receive major attention in advertisements. It is well known that mild sedation is useful in the management of patients with peptic ulcer. Phenobarbital is a

valuable drug for this purpose and the mild "tranquillizers" have been utilized as a more expensive method of obtaining the same effect. When a manufacturer pushes his "antispasmodic" or "antisecretory" compound in combination with phenobarbital or a "tranquillizer", it suggests that he does not have much confidence in the efficacy of his "primary" agent, and the prescribing physician may well treat it with even greater scepticism. Drug combinations frequently are justified on the basis of convenience to the physician and patient. However, in the final analysis, their major contributions are to preclude independent evaluation of the effects of the constituents and adjustments of the relative dosages to meet the needs of specific patients.

A minimum and absolute requirement in the utilization of a mixture is to know what it contains. To stress this point may appear to insult the practising physician, but experience has shown such caution to be necessary. A casual local survey during the past year revealed the following: (1) A majority of physicians utilizing a "new" and effectively advertised analgesic did not know that it is simply the standard APC (acetylsalicylic acid, phenacetin and caffeine) plus a little barbiturate. (2) Several physicians did not know the composition of the mixed electrolyte solutions they ordered by a simple number or letter designation. As a result, we have seen two recent patients with post-traumatic oliguria receiving potassium-containing solutions. Both died of potassium intoxication before renal function was reestablished. (3) A mixture of antimalarials and a steroid was administered for a dermatological condition without any appreciation of the amount of steroid in the mixture, and consequently without any provision for gradual withdrawal to allow recovery of suppressed endogenous pituitary-adrenal function. These examples, without further comment, should adequately emphasize the absolute necessity of knowing the exact composition of any mixture employed.

The above discussion may paint a rather bleak and hopeless picture of the essential impossibility of the busy practitioner adequately evaluating the drugs and drug advertising to which he is exposed. It would not be honest and accurate to leave any other impression. The advertising pressures and the multitude of new agents and combinations which do not represent real advances in therapy have combined to produce a situation with which the practitioner cannot cope satisfactorily. The drug houses themselves should take the lead in reversing the current trend by introducing new therapeutic agents and mixtures only when these provide advantages of considerable magnitude over anything previously available, and by making their advertisements less promotional and more informative. A major step in this direction would be to give their medical and research departments more control over advertising policy and content. Many of these departments contain well-qualified men who currently are embarrassed by some of the products and advertising claims of their own companies, which they may refuse to defend in conversations with their professional colleagues. However, much of the responsibility rests on the medical profession, whose obligation to the public requires active protest against current promotional practices. This can be expressed in many ways, but, in the long run, the most effective protest is refusal to prescribe agents for which real advantages have not been proved and on which complete information is not provided. For the present, the practitioner can considerably improve his utilization of new drugs, or at least minimize his mistakes, by developing a high degree of scepticism. This can be actively expressed along the following lines.

1. Be slow to accept any new agent. In dealing with new drugs it is particularly important to remember the principle—"First, do no harm." Very few new drugs represent major advances in therapy, and those which do will quickly show their real value. You will do your patients little harm by delaying the acceptance of new agents, and you may save them from dangerous side effects, from unjustified reliance on new drug therapy to the exclusion of more reliable, if less spectacular measures, and if nothing else, from the unnecessary expenditure of considerable sums of money. New drugs are never cheap.

2. If you do wish to consider the early use of new agents, select one at a time, carefully evaluate all of the available data on it, and reject its use unless there is clear evidence that it represents a real therapeutic advance. Thorough investigation of a few agents will always prove to be more profitable than cursory examination of many. It is desirable to select products for investigation from among those for which the manufacturer has provided relatively complete bibliographies. This simplifies the task, provides some selection on the basis that full information is more apt to be provided for those products in which the manufacturer himself has confidence, and finally, in the long run, such selection may induce manufacturers to provide more adequate information on their products.

3. Be particularly sceptical of mixtures, of new dosage forms and of compounds closely related to established agents. There is still much truth in the concept that how you use a drug is more important than what drug you use. Proper use requires personal familiarity with both therapeutic and toxic responses, which rarely is possible if one switches preparations at frequent intervals.

4. Finally, and most important, consciously maintain your prerogatives as a physician to decide on the basis of your own training, reading and experience what drugs to administer, and in what forms and dosages. It is appalling to note the extent to which drug houses and patients now determine therapeutic practices. Neither is qualified for this

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role. Certainly the mother is not qualified to decide whether her child should receive an antibiotic for his sore throat, and the drug manufacturer is no more competent to decide, through a fixed-ratio mixture, the relative doses of two or more drugs to be administered to a given patient.

Drug advertisements and detail men can be useful sources of information in the harassing process of keeping up with new developments in drug therapy. However, if one does not have the time, the facilities or the inclination personally to evaluate their wares, less harm will be done if they are ignored completely. Remember that advertising is advertising.

UNDERGRADUATE, POSTGRADUATE AND GRADUATE MEDICAL EDUCATION IN CANADA

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AN ATTEMPT to deal in detail with medical education in Canada at all levels as indicated by the comprehensive title above would be beyond the capacity of any one individual, and would occupy most of the space in the educational number of the Journal.

A definition of terms may serve a purpose. By undergraduate education, one implies the content of teaching in the faculty of medicine of a Canadian university leading to a degree in medicine. This degree in most Canadian universities is a doctorate of medicine.

The term postgraduate education applies to short courses of training given by universities, hospitals, or other medical organizations to those who have a degree in medicine and are in practice.

Graduate medical education is usually construed to mean a more prolonged course of continuous training in a university basic science department, hospital, or clinic. The minimum period of graduate training is one year in most instances.

There are 12 universities in Canada in which the complete course of undergraduate medical education is carried out. The current number of the Journal gives brief information on the undergraduate course offered in each of these Canadian universities. The requirements for admission vary somewhat. However, all of the universities require a period of college or university training of two to four full years, during which certain standards must be met, before the student is considered eligible for admission to the faculty of medicine. During this so-called pre-medical training, certain subjects such as physics, inorganic and organic chemistry and zoology, among others, must be included.

After acceptance into a university faculty of medicine, the student spends either four or five years in training before he qualifies for a degree in medicine. In the universities which require five years of training, the fifth year is given over to practical training in an affiliated teaching hospital. This final year in universities with a five-year undergraduate program is credited to the student as a junior intern year, which is a requirement in all Canadian provinces for licensure to practise medicine. In the cases of the universities with a four-year program, the year of junior internship is taken after graduation.

The prospective student should enquire from the dean of the faculty of medicine of the university in which he is interested, for details of admission requirements and the date set for making application for admission.

In the case of students who have pursued a part of their undergraduate medical training outside Canada and wish to be considered for admission with advanced standing, a request should be made to the dean of the medical faculty in which they are interested. Such requests should be accompanied by a transcript of the student's record. One need hardly add that such a student must have a fluent knowledge of the language used in the university to which he applies.

Most faculties of medicine in Canadian universities, or medical schools as they are sometimes called, have accepted the philosophy that the period of undergraduate training is aimed at giving the student a basic training in medicine. It would be impossible during a four-year or five-year period for a student to acquire a comprehensive knowledge of medicine. He is not trained or directed towards becoming a specialist in basic science in a special clinical field, or as a general practitioner. It is hoped that when he has earned a degree and is no longer a medical student, he will become a student of medicine during a period of graduate and postgraduate training, and indeed throughout his professional life.

During the first year of graduate training, commonly known as the junior internship in a hospital approved by the Canadian Medical Association, the student widens his interest and comes into closer relationship with the sick. During this year the student usually makes a decision whether he wishes to pursue further graduate training with

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