SPECIAL ARTICLE

The Physician’s Responsibility in the Age of Therapeutic Plenty

By Mindel C. Sheps, M.D., M.P.H., and Alvin P. Shapiro, M.D.

To the various apppellations that contemporary historians are attaching to the decade of the sixties, medicine could well add the title, the “Age of Therapeutic Plenty.” The veritable flood of samples of new drugs, of descriptive literature, and of promotional gimmicks that crosses the desk of the practicing physician each day is ample testimony of the “drug explosion” of recent years. In cardiovascular disease, for example, the advent of anticoagulant therapy and the development of potent hypotensive and oral diuretic agents have provided many new preparations, while the dozens of coronary and peripheral vasodilators, of sedatives and tranquilizers and of products intended to lower blood cholesterol further contribute to this prolific growth. Hand in hand with the increased potential for pharmacological therapy in cardiac disease has gone the development of cardiovascular surgery, which began meekly with a few simple shunts and bypasses and now is rapidly approaching the realm of the fantastic, limited not by lack of daring or dexterity, or by instrumental deficiency, but by basic immunologic phenomena, which themselves are seemingly not immutable. As a result, not only does the lay press glow with therapeutic enthusiasm, but even the professional literature abounds with information of hopeful portent.

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Effects of the Drug Explosion

Confronted by this apparently endless display of therapeutic wealth, the cardiologist trained in the tradition of digitalis, nitroglycerin, and therapeutic humility sometimes must find himself confused and wonder where therapeutic enthusiasm ends and therapeutic hypomania begins. For to the critically minded physician, there is cause for bewilderment. For example, after 15 years of anticoagulant therapy, argument concerning its efficacy still exists. Hypotensive drugs hailed 5 years ago are discarded as newer and seemingly more potent ones are introduced with the same fanfare. Although the role of the level of serum cholesterol in atherosclerosis remains a moot question, dietary and other measures to lower this level are widely urged. Through various media, the physician is adjured to tranquilize and to reassure, or, alternatively, to exercise and motivate his cardiac patient, while particularly disturbing to him are the occasions when treatment of one symptom results in a new set of side effects requiring additional medications. Yet, despite the increase in available therapy, effects on mortality are not impressive. We might have expected that the new drugs would produce improvement in mortality statistics for cardiovascular disease. It may be considered disturbing that we fail to find such improvements. Indeed, although the death rates from rheumatic and hypertensive heart disease declined slightly during the decade from 1949 to 1958, the age-specific mortality rates from arteriosclerotic heart disease during this period increased by at least 5 per cent in
every age group over the age of 25 among men and did not decrease in most age groups among women.1 2

Furthermore, the adoption of new treatments has been accompanied by the development of therapeutically induced syndromes, which have aptly been named "Diseases of Medical Progress."3 4 The reports of the National Office of Vital Statistics contain another reminder of the harm that therapeutic efforts sometimes bring. Table 1 shows the number of deaths occurring in the years 1949 to 1958 that were certified by the attending physician as due primarily to the causes euphemistically labeled as "therapeutic misadventure." This group of categories, which was first introduced in 1949, is not used "for primary death classification if the condition for which the treatment was given is known" (i.e., if the condition is stated on the death certificate).5 In all likelihood, therefore, the rather sizable numbers shown in the table underestimate the total number of deaths that actually resulted from therapeutic misadventure. In particular the deaths assigned to misadventure in administration of drugs or biological agents are likely to be an underestimate, because this category specifically excludes not only accidental overdose and a wrong drug given in error but also allergic reactions to drugs. Furthermore, it does not include deaths ascribed, without mention of drugs, to conditions such as agranulocytosis, aplastic anemia, and purpura, which may result from drug therapy. Yet in most of these years more deaths have been assigned to misadventure in the therapeutic administration of pharmaceutical agents than to misadventure from either anesthesia or transfusion and infusion. Fewer patients of course are exposed annually to anesthesia or to transfusions and infusions than to drugs and biological preparations, and the average risk accordingly is less with pharmaceutical therapy. Nevertheless, the figures in table 1 indicate that the administration of drugs and biological agents in accordance with recommended dosage carries a risk of death that is not negligible.

On the brighter side, unquestionable therapeutic progress has been made. Rheumatic heart disease is on the wane, syphilitic heart disease is a rarity, the patient with malignant hypertension is not inevitably doomed, the edema and other discomforts of the cardiac cripple can be controlled, and the patient with a coronary thrombosis is no longer shunted out of a productive existence, to mention only a few advances. The period of therapeutic frustration in cardiovascular disease when we sat by and waited for nature to provide its own remedy or follow its inevitable course lies in the past. Yet, perhaps as a reaction to this long period of frustration, the pendulum may have swung so far that now there sometimes is too much emphasis on being able

Table 1

Deaths Ascribed to Therapeutic Misadventure as Primary Cause, U. S. 1949-1958*

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<td>Therapeutic misadventure in:</td>
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<td>Surgical treatment</td>
<td>20</td>
<td>184</td>
<td>259</td>
<td>268</td>
<td>296</td>
<td>317</td>
<td>334</td>
<td>378</td>
<td>442</td>
<td>467</td>
<td>2965</td>
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<tr>
<td>Administration of drugs or biological agents</td>
<td>39</td>
<td>68</td>
<td>62</td>
<td>71</td>
<td>79</td>
<td>118</td>
<td>116</td>
<td>171</td>
<td>164</td>
<td>148</td>
<td>1035</td>
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<td>Infusion or transfusion</td>
<td>51</td>
<td>45</td>
<td>87</td>
<td>84</td>
<td>66</td>
<td>71</td>
<td>83</td>
<td>103</td>
<td>131</td>
<td>103</td>
<td>824</td>
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<tr>
<td>Anesthesia</td>
<td>43</td>
<td>76</td>
<td>73</td>
<td>57</td>
<td>60</td>
<td>58</td>
<td>64</td>
<td>74</td>
<td>78</td>
<td>82</td>
<td>665</td>
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<td>Local applications and other or unspecified</td>
<td>7</td>
<td>137</td>
<td>118</td>
<td>105</td>
<td>91</td>
<td>124</td>
<td>21</td>
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<td>37</td>
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<td>therapeutic misadventure</td>
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<td><strong>Totals</strong></td>
<td>160</td>
<td>510</td>
<td>599</td>
<td>585</td>
<td>592</td>
<td>688</td>
<td>617</td>
<td>756</td>
<td>852</td>
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the problem has been to prove that small differences in mortality and morbidity have been due to anticoagulants, in the presence of a large number of other uncontrolled variables capable of influencing the results. Since the drugs are not innocuous, such validation becomes of vital concern. At present, we find ourselves in the situation of having a widely accepted means of therapy which is of uncertain efficacy, sufficiently tempting in theory at least to obviate abandonment and yet capable of producing considerable harm. Perhaps it is not surprising that anticoagulation at "subtherapeutic" levels sometimes is a way out of the dilemma, but as Wright has indicated, whether this is protection for the physician or for his patient is a debatable question.  

It is, of course, easy to criticize in retrospect and perhaps not altogether proper to do so when one realizes that anticoagulation represented the first definitive therapy for a disease long handled only with supportive measures, but it is disturbing that the lesson of proper clinical assay has not been learned. As was recently pointed out by Sawyer et al., the same errors are being made with the thrombolytic agents, which potentially offer a more physiologic but presently an even more dangerous form of therapy than anticoagulants. These authors, who are among the pioneers in the field, state that there is no practical or theoretical justification for the current release of certain fibrinolytic agents for therapeutic use, and that "poorly controlled large scale types of clinical evaluation usually reflect only the enthusiasm of the investigator,... and rarely provide useful information for further development." But their pleas appear to be unheeded, and fibrinolytic agents are advertised extensively.

Many examples of uncontrolled claims and unsupported sanguinity can be culled from the literature concerning treatment of angina pectoris. Nitroglycerin still appears to be the most impressive drug for management of the acute pain, but the duration of its action is short and it has limited value in preventing attacks. Hence, a major effort has been made

\textit{to treat} rather than on the question of \textit{what is accomplished} by treatment.

As physicians, our basic function is the relief of suffering and the prevention of death; consequently, in therapeutic questions, not only our self-esteem but also our feelings of humanity may be arrayed against the truth. In most fields of science, we rarely admit a conclusion to be true until its opposite has been proved untrue. But in medicine we are inclined to "give the patient the benefit of the doubt" and may feel compelled to try the newest therapy, even on inadequate or inconclusive evidence. Here our logic perhaps has been set awry. The "doubt" may be that the new has unknown hazards and as such offers the most "benefit" if we remain with the natural course of the disease or persist with the older and more tested remedies. It is not therapeutic nihilism to demand proof of efficacy of a new drug, for with increased therapeutic potential have come increased therapeutic risks. To the medical risks must be added the social and economic complications that have disturbed various non-medical agencies and committees. It would seem timely, therefore, lest we undo some of the gains of our therapeutic accomplishments, to outline a few current examples of questionable practices and unjustified enthusiasms in the field of cardiovascular therapy, to consider the causes for our present state, and to suggest some remedies and safeguards for the future. For, as was aptly stated by a "Professor Bigelow of Boston" in reference to therapeutic evaluation in a nineteenth century text on Materia Medica, "it is for truth that we must earnestly seek, even when its developments do not flatter our professional pride nor attest to the infallibility of our art."  

\textbf{Some Current Problems}

The history of anticoagulant drugs demonstrates a familiar example of a situation in which experience has failed to solve a therapeutic controversy. Even in thrombophlebitis — usually considered the least debatable indication — diametrically opposing views are illustrated by different studies.  

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to develop longer-acting preparations. The xanthines have been extolled, but now are used rarely, although recently it has been argued that they must be given as an elixir to be effective, a suggestion that perhaps gladden the hearts of many patients insomuch as this method of administration assures a tidy intake of alcohol. Whether alcohol itself produces a beneficial effect by causing coronary vasodilatation or through its psychologic effects is a question which finds a parallel in the current discussions as to whether monamine oxidases actually increase coronary flow in angina pectoris or merely affect the subjective response to pain. Since the latter situation could lead a patient to ignore a warning signal to desist from activity, the issue is of vital import. Although it remains unsettled, the drugs are already in clinical use.

To judge by the volume of advertising, erythrol tetranitrate and various congeners and different dosage forms are currently the “hottest items” for coronary dilatation. In the January 1961 issue of this Journal, approximately 20 per cent of the drug advertisements were concerned with one or another form of this preparation. Yet the literature contains controversy related not only to poor experimental design in some studies, but also to inconsistencies in the types of preparation, dosage, and routes of administration used by different investigators. Angina pectoris is a disease which by definition is a subjective syndrome. The symptoms are mimicked by many other conditions; they may be unassociated with objective findings; the extent of the coronary artery pathology may not be reflected in the severity of the pain; and the episodes are influenced by emotional factors, both in their precipitation and in their relief. These considerations demand precise experimental design and rigid control measures for successful clinical assay, and yet many studies fail to take them into account. Apparently we have not learned the lessons taught by the early enthusiasms for khellin, heparin, and ligation of the internal mammary artery in angina pectoris, enthusiasms that were proved exorbitant by subsequent well-controlled analyses.

Another common practice that has affected cardiovascular therapy in a particularly virulent form is the “getting into the act” school of drug development, illustrated by the thiazide diureties. Here a drug with fairly clear-cut effects has been duplicated by at least eight congeners. Little effort has been devoted to demonstrating that the congeners are more effective than the original; indeed, the few studies aimed at this question have revealed no significant differences. Undeterred, the multiplication of products continues; again in the January 1961 issue of this Journal, an additional 12 per cent of the advertisements are for thiazide preparations.

No discussion of this type can omit the cholesterol problem. Hormones, unsaturated fats, nicotinic acid, cholesterol antagonists and inhibitors, low-calorie liquid diets, and thyroid analogues have all been employed to lower levels of cholesterol. Various food producers have gone into the drug business, while the Poultry and Egg National Board takes doleful full-page ads in the journals to protect its interests. Restrictive diets are widely advertised and televised if not prescribed, and we have become a “fat-conscious” people with changed social customs. For instance, whereas the quality of milk—and perhaps the influence of its consumer—formerly was judged by its high butterfat content, now consumption of the product with the lowest fat content is considered the mark of the provident person and the intellectually elite. All this commotion obscures the relatively circumscribed nature of the statements of responsible scientists who point out that the evidence that a reduction of blood cholesterol will lessen the incidence or retard the course of atherosclerosis is circumstantial, and that many other factors are involved. A reasonable reduction in the intake of calories and of saturated fats is recommended by these authorities but primarily as an article of faith—or, more precisely, as an “epidemiological experiment”—and not as a mandate.

The adoption of therapeutic measures and
of medical theories on the basis of poorly documented evidence or of no evidence at all is of course not a new phenomenon, nor is the frequent sequel of disillusionment which follows the revelation of side effects, complications, or ineffectiveness of yesterday's discoveries. This process is, however, out of keeping with our aspiration to make the practice of medicine a rational, scientific endeavor.

The Role of the Pharmaceutical Industry

Analyses of prescription practices show that there is an increasing tendency toward rapid acceptance of new drugs that often remain popular for only a short time. This excessive readiness to accept new products probably bears some relation to the advertising efforts of a highly organized, greatly expanded industry which is geared to the marketing of new drugs that are expected to have only a short and meteoric career. The pattern of rapid acceptance coupled with rapid obsolescence has been ascribed by one company representative not only to the "keen competitive research race" but also to "modern 'crash' promotional programs that create almost immediate acceptance and prescription demand." The general manager of another company stated: "Research and the prompt commercialization through the new product development procedure is fundamental... In the pharmaceutical and chemical industries, new products are the 'keys to the kingdom.'" As Business Week put it recently: "If you want to stay in business, the drug industry says, you'd better get a fast profit. The best way to get that return—figured on sales, rather than on investment as in most manufacturing—is to set a high price on your newest drug, the one most eagerly awaited by doctors and patients."

Thus the pharmaceutical industry, along with the beneficial drugs it has provided, undoubtedly has also stimulated premature use of diagnostic and therapeutic agents and often a wasteful and bewildering multiplication of preparations that are almost identical in their effects. For these and other reasons, many students of the problem have recommended that the legal controls exerted on the industry be strengthened considerably and that the industry itself take constructive action to change existing practices. Without denying the desirability of such measures, however, the medical profession should consider the great responsibilities borne by the physician and by organized medicine. In the rest of this paper, an attempt will be made to indicate how these responsibilities might be met.

Responsibility of the Medical Profession

The Individual Physician

A number of important problem areas are primarily amenable to physician action, regardless of controls exerted directly on manufacturers of pharmaceutical products. The physician himself, consciously or unconsciously, establishes the criteria which he applies to new and to old methods of therapy. It lies in his power to alter the existing situation by the widespread adoption of a tough-minded scientific approach to the recommendations and claims to which he is subjected. It is worth remembering that the most enticing advertisements for "ethical" preparations can have no effect without a physician's prescription. The target of promotional efforts is the physician who must serve as the medium through whom these products reach the eventual consumer, the patient. If irrational and unjustified practices exist, physicians have participated actively in their growth. A logical place to start tackling the problem, therefore, is at the point where the physician decides whether he will prescribe a medication and what preparation he will prescribe. He can insist on exercising conscientious and careful judgment after study of the published information about the chemical nature of the drugs, about their pharmacological action, and about the results of clinical trials on patients.

The difficulty of the physician's becoming and remaining well-informed about all the latest pharmaceutical agents cannot be denied. But surely the difficulty is not an acceptable excuse for prescribing powerful preparations in ignorance of their effects. In
most cases, the delay involved in waiting for reliable information before prescribing a new preparation will not rob the patient of an important benefit. As has been pointed out, it may indeed protect him from unfortunate consequences. Furthermore, as a rule we are not involved with therapeutic problems that need emergency solutions or with drugs that are really startling improvements, while much of the pressure and apparent urgency for making judgments about new therapies are not generated primarily by the patient's needs. Admittedly, it takes more effort and time to obtain reliable information about drugs than it does to follow the suggestions of the detail man and of the advertisements, circulars, and reminder pads. But the physician can make intelligent and responsible decisions only if he informs himself from professional sources. As has recently been emphasized by May,33 and as pharmaceutical manufacturers themselves have stated,34 the efforts of the drug companies are promotional and should not be mistaken for education.

Professional sources of information are available in increasing numbers and variety. The U. S. Pharmacopoeia represents the best current judgment of a large group of experts. More recent and current drugs are discussed in the Medical Letter on Drugs and Therapeutics. Critical review articles are published in a number of journals. The American Medical Association plans a considerable expansion in its efforts to inform the profession about the drugs on the market.35 In this connection, it should be emphasized that in recent years the fact that a product is listed in New and Nonofficial Drugs does not in any way signify that it has been approved by the A.M.A. Council on Drugs.36 The discussion of each particular preparation must be read to appreciate what the Council has to say about it.

To judge for himself, however, the physician must rely on careful study of the original reports of investigators. As has been emphasized repeatedly, there is considerable variation in the quality of therapeutic investigations and therefore in the credibility of their conclusions. Accordingly, the physician must first learn some of the principles of proper experimental design and adequate clinical trial in order to be able to scan an article carefully and judge it on its merits. Such principles, which are set forth in a number of recent books37-39 should offer guidance in deciding if a particular study has been performed in a proper fashion and whether it presents results and conclusions that are valid. It should be emphasized further that the medical student in the Age of Therapeutic Plenty must be prepared more specifically for his eventual responsibilities by planned programs in the principles of clinical pharmacology both in the medical schools and during hospital training. Although time-consuming and not always simple, a critical review of the available evidence is the only way the physician can avoid both the extreme of therapeutic nihilism and the peril of surrender to commercial advertisements and to patient pressures.

It may be noted that all the sources of information about drugs that have been mentioned, whether critical evaluations or original papers, are published materials. Except in the rare instances when a new drug bears definite promise of a dramatic effect in a serious condition, there is every reason for the practicing physician to wait for published evidence of efficacy. A great deal might be achieved by one practice alone, that of not prescribing a drug before the pertinent evidence is published and made available for objective review.

Organized Medicine

A number of medical journals are attempting to establish criteria for the advertisements they publish. In our opinion, medical journals should refuse to accept advertisements whose claims are not documented by published reports rather than by information "in the manufacturer's files,"33 unless the journals explicitly and prominently disclaim all responsibility for the advertising they carry. If, in addition, the editors were to adopt more rigorous criteria for the scientific validity of clinical papers, the level of medical literature and perhaps of medical practice would be considerably elevated.
THE PHYSICIAN’S RESPONSIBILITY

Another problem of distinct concern is the quality of clinical investigations, particularly of nonapproved drugs. When a pharmaceutical manufacturer makes application for release of a new product he is required to submit reports of toxicity studies on animals and of clinical trials in patients. As the situation now stands, the choice of investigator and the judgment of his qualifications, of the facilities at his disposal, and of the type of trial he wishes to make, rest entirely with the drug manufacturer. Although most reputable firms exercise due caution in this choice, particularly in the initial phases of testing a new drug, many times evaluation in the later stages of a drug’s development is performed by quite unqualified practitioners who contribute testimonials rather than data. Indeed, in some instances practitioners have actually been circularized with form letters asking them to test out a new drug. Obviously, individual physicians and investigators, along with the pharmaceutical companies, have kept a rein on practices of this sort by their own self-policing. Procedures to be followed for the trial of nonapproved drugs in hospitals have been outlined, and include professional as well as legal and ethical provisions. There is, however, a need for organized medicine as a whole to establish criteria for clinical trials.

The organized medical profession has historically assumed responsibility for setting standards for medical education, for medical licensure, and for specialty practice. The profession has taken the position that to perform major surgery for instance, a physician requires training and experience over and above that which suffices for licensure, and it has taken measures to have this position enforced. Obviously the medical profession could also establish minimum requirements that should be met by clinical investigators who perform trials, particularly of nonapproved drugs, thereby insuring adequate professional standards. Such action seems highly desirable and before long may become urgently needed.

Trials of nonapproved drugs have been emphasize for several reasons. These trials are the earliest and potentially the most hazardous; in fact they are at times essentially toxicity trials on human beings. Unlike the ease of approved drugs, it is not required that the evidence regarding their safety be reviewed outside the company. Furthermore, the unpublished reports of these trials form the basis both for the action taken by the Food and Drug Administration and for the early advertising and labeling of new drugs. The need for standards applies with only a little less force to the early trials of a new drug after release on the market. Although basic principles for a scientific approach to this question have been laid down and serious work on improving the methods of clinical trials is being done on a level consistent with that of other scientific research, a considerable part of the published literature remains of a questionable quality.

Summary and Conclusions

It is evident that the current response of the medical profession to the problems and the opportunities created by the plethora of potent new pharmacological agents is deficient in certain respects. New remedies are adopted rapidly, and apparently widely, at times in the face of poor or inadequate evidence. Many of these remedies, helpful or not, are not innocuous but produce unpleasant side effects, toxicity, and sometimes even death. The responsibility for providing rational and beneficial treatment is ultimately the responsibility of the physician. It is suggested that this responsibility would be discharged more adequately if the following measures were introduced:

1. Increased attention in the education of the physician to the principles of clinical pharmacology.

2. Refusal, on the part of individual physicians, to prescribe a preparation before they were convinced, by a critical examination of published evidence, that this product is the best available therapy for the patient.

3. The adoption, by medical journals, of more critical standards for the publication of clinical papers.

4. The requirement, on the part of the
medical journals, that advertisements for pharmaceuticals cite references to published papers that support their claims.

5. The adoption and enforcement, by organized medicine, of minimum standards to be met for the clinical trial of drugs generally and of nonapproved drugs particularly.

Individually or collectively, the members of the medical profession must accept their responsibility for therapy. Individually and collectively we face new problems and we must find new ways of dealing with them. In the short term a great deal might be accomplished if we took seriously a variant of the war-time admonition: "Is this prescription really necessary?". In the long term, we need to take the initiative to ensure that the control of therapy will remain where it belongs: in the hands of scientific, objective, and conscientious physicians.

References


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An underlying philosophy, when it can be found, is invaluable in practice, not only because it quickens and maintains interest, but because it forms a stable guide to action when experience fails, as it often will in face of the unusual, to give precise or particular direction.—SIR THOMAS LEWIS. Diseases of the Heart. New York, The MacMillan Company, 1933, p. vi.
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