Research, regulation and development of new pharmaceuticals: past, present and future Part II

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Drug Combinations

Another thorny area is that of drug combinations. Academic experts tend to denigrate such mixtures; practitioners tend to use them to a considerable degree. The main arguments *against* combinations are:

1. Fixed ratio forces a dosage of one or more ingredients that is ineffective or excessive.
2. Needless ingredients increase the "price" of the combination, either from the standpoint of dollar cost or from drug sensitization and drug toxicity.
3. Combinations encourage sloppy diagnosis and therapy since there is less need to be precise and since the drugs may mask disease processes.
4. Many mixtures are indefensible pharmacologically and appear to be irrational polypharmacy perpetuated by poor medical practice.

The main arguments *for* combinations are:

1. Flexibility of dosage is less important than is generally implied by the experts, since precise bioassay in patients is not often easy of accomplishment.
2. While some fixed ratios are bad, others are perfectly satisfactory for many patients. Indeed there is something to be said for a ratio that has been subjected to careful scrutiny as opposed to the multiple ratios possible when doctors prescribe individual drugs to be taken simultaneously by their patients, or write their own prescription for drug combinations. (Can one guess at the chaos that would occur if doctors were free to choose their own ratios of estrogen-progestogen contraceptives?)
3. A drug combination increases convenience for the patient and can decrease cost, nursing time, and medication errors. Would anyone wish to suggest, for instance, that all multivitamin preparations be banned so as to insure that vitamins be dispensed individually, or that intravenous solutions such as Ringer's lactate not be given as such, but the individual ingredients administered separately via different flasks, or that oral contraceptives be taken in two tablets instead of one?
4. Precise diagnosis is often impossible in actual practice, especially in outpatient situations, and "covering one's bets" with a mixture may be good practice in such a case. A common example is the administration of multiple antibiotics to a patient suffering from sepsis of obscure etiology, a practice condoned by most first-rate hospitals.

There are several additional points to be considered in regard to fixed-ratio combinations:

1. The administration of drugs in combination will never be more effective than getting the same drugs into a patient by giving them individually. Therefore, convenience *must* be a consideration if combinations are to be approved under any circumstances.
2. If it is claimed that two drugs, such as antibiotics, combined in one mixture are actually superior in performance to either antibiotic given alone, trials should be required to demonstrate the validity of this claim and to indicate that the toxic price being paid for the combination is not so great as to outweigh the therapeutic benefits.
3. If the claim for a mixture is only that the ingredients are additive, perhaps especially if these ingredients are fundamentally dissimilar in character (as, for example, a coronary vasodilator plus a sedative, or an anti-anxiety drug plus an antispasmodic), one should be able to accept clinical data on the performances of the *individual* drugs coupled with bio-

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availability studies (and possibly a small amount of clinical data to rule out toxic potentiation). There is evidence that the FDA has acted on this basis in the past. Since 1967, at least 11 pentaerythritol tetranitrate and phenobarbital mixtures were approved by the FDA. (The most recent approval came in March, 1971.) It is difficult to believe that these NDAs were supported by data other than the kind just referred to.

4. If the situation is one where diagnosis is unclear or impossible, one may wish to accept the concept of an "umbrella" combination. This principle is espoused, for instance, by some expert ophthalmologists, who approve topical ophthalmic mixtures containing a corticosteroid and an antibiotic, in view of the difficulties in deciding whether inflamed eyes are infected, responding allergically to some stimulus, or both. In such situations, it may be good medical practice to tolerate the possible "waste" of one or another ingredient in the mixture.
5. The inappropriate use, in some patients, of combinations that are used validly in other patients is without question undesirable. Proper education of the physician, perhaps supplemented by monitoring of his performance, might minimize such misuse. If this is impossible, then society must make a decision as to whether the benefits from having a specific mixture available are greater than the disadvantages that come from its occasional or frequent misuse, or *vice versa*.

Manpower Needs

An FDA publication [11] has described in the following words those individuals who should perform the early evaluation of drugs:

"Q. Who should carry out the early phases of a clinical investigation?

"A. Investigators thoroughly conversant with the action of drugs should conduct the earlier phases. . ."

In these stipulations lies the possibility for a bottleneck in the evaluation of compounds. There is no question but that if these terms are rigidly applied there are not enough clinical pharmacologists in the country to do all the work that is required of them. No one has ever satisfactorily defined what a "generalist" clinical pharmacologist is, but there are large numbers of individuals who would not qualify as such but who are nevertheless capable of performing one or another of the tasks required in drug evaluation by reason of their expertise in certain special areas. If one broadens the definition to include such persons (who might be experts only in drug metabolism, or in the clinical aspects of a given entity under consideration), then the supply of investigators is probably *not* a severely limiting factor.

Experience within the Veterans Administration system and in other cooperative trials planned and executed in this country and abroad shows that physicians other than highly experienced, specially skilled clinical pharmacologists can collect reliable data. The amount of past experience required is probably inversely proportional to the tightness of design of the protocol and the ease with which it can be adhered to scrupulously and compulsively. It is in the less formal, "uncontrolled" aspects of the early evaluation of drugs that a considerable amount of background and experience is important in delineating the presence or absence of interesting activity that should be further pursued at a controlled trial level.

Facilities

One of the interesting developments of the past two decades has been the gradual evolution of excellent facilities for early evaluation of compounds under the auspices of industrial sponsors. The earliest unit of this sort was put up by the Eli Lilly Company in Indianapolis, and in more recent years this approach has been mimicked to a certain degree by a number of other firms. In some instances, these facilities are at prisons and allow only for the early evaluation of compounds in healthy prisoner volunteers, but in other cases units are available in hospitals where studies can be done on outpatients or inpatients, or on healthy volunteers, to provide data on a compound at almost any level of its development.

Such units, properly used, can save time and money for the sponsor. Negative reports on

compounds that look promising in animals are, paradoxically enough, at least as likely to come from the company's own efforts as from those of non-industrial investigators. The opportunity for legal trouble or damaged reputation if ethical or scientific improprieties occur is at least as great in this situation as when the compound is studied outside of the immediate control of the industrial sponsor. In addition, the usual academic or professional investigator is quite happy in most instances to have the earliest work done by someone else, since he is less likely to find himself involved in the study of a drug that has no utility or produces serious or unpredicted toxicity.

In academic institutions or private hospitals, there is much less commitment to clinical pharmacologic facilities. A few such clinical pharmacology groups have significant amounts of space and local support, but this is the exception rather than the rule.

Financial Support

In the past, clinical pharmacologists and other clinical investigators frequently obtained their support from National Institutes of Health (NIH) grants for training or research. The current atmosphere in Washington is such that for the foreseeable future it would be naive to expect sustained levels of support. In fact, at a time when the needs for clinical pharmacology and the evaluation of drugs in man are greater than ever, the support of such activities at the federal level is diminishing.

Should there be direct federal involvement in drug development? It has been suggested, for example, that a national drug testing center be built in Bethesda or some similar locale, with facilities and personnel for studying drugs at all levels of their development. It is difficult to envision such an enterprise being housed under one roof or attracting an adequate number of topnotch investigators, but the proposal keeps surfacing from time to time. The FDA has initiated contracts with academic institutions to have certain kinds of testing done. Such approaches will provide useful information to the FDA, but it is as undesirable to have decisions about drugs made solely on the basis of FDA contract-supported research as to have such decisions made solely on the basis of research carried out by drug house employees.

Industrial companies are usually generous in supporting research by non-industrial investigators on a *quid pro quo* basis. With certain exceptions,* however, drug firms are usually less willing to provide support on a "no-strings" basis to help groups get started or to sustain their general activities. It is crucial for the development of clinical pharmacology units to have such support available on a continuing basis from either federal or industrial sources. To rely completely on project-oriented grants would hamper the proper development of such units.

At the academic level, support for clinical pharmacology often remains at the level of lip-service. Some deans of medical schools and professors of clinical and basic science departments have been wholehearted in their support, but in many schools one finds little concept of what clinical pharmacology is or could be. The academic contribution has also been limited by the tendency of academicians to look down their noses at participation in new drug development (although they are usually happy to utilize exciting new drugs when someone else develops them).

Even with support at a much higher level than is available at present, it is difficult to envision all of the public's needs being met by academic clinical pharmacologists. Progress will require the work of individuals who are competent clinicians and accurate observers, but who may not have had specialized training in clinical pharmacology. Such clinicians have contributed, and will continue to contribute, significantly to the whole process of drug development.

Certification

From time to time, it is suggested that some certification process should be adopted to

**Some industrial concerns have set up philanthropic foundations, some of which have given support to clinical pharmacology. The Burroughs-Wellcome Foundation, the Pharmaceutical Manufacturers Association Foundation, the Smith Kline and French Foundation, the CIBA Foundation, the Schering Foundation, and the Sandoz Foundation are all examples of this highly laudable philosophy.*

identify those clinicians capable of expert participation in drug development. Certification can be a desirable process, but it need not be. One has only to look at the unfortunate influence that certification has had on certain educational systems to show that the process can be stultifying and deadening, excluding original and creative talent that lacks "credentials." Thus one should look hard and long at the problems of certification in a specific area before deciding that such certification is desirable.

In the field of clinical pharmacology, there are many barriers to a sensible, equitable system of certification. The field is extremely broad, and it is difficult to imagine what an examination would cover that was intended to test one's abilities as a "general" clinical pharmacologist. Some clinical pharmacologists are experts at controlled trials; others are amateurs at the game. Some are expert statisticians; others are not. Some are experienced in drug metabolism; others do not know their way around a laboratory.

In addition, the clinical backgrounds of such pharmacologists can vary tremendously. Many are internists, but some are anesthesiologists, neuropsychiatrists, or pediatricians. No one has yet suggested, to my knowledge, a board certification process that would make sense in terms of requirements, testing, and post-certification monitoring.

In the absence of such plans, it would seem desirable to postpone any attempts to certify clinical pharmacologists. Such certification would stigmatize those who have not bothered to be so certified or who could not be by the proposed scheme.

There is, however, a need for a more adequate description of those training programs in clinical pharmacology now available throughout the country. Although the American Society for Pharmacology and Experimental Therapeutics does serve as a clearing house for information of this sort, a full description of such opportunities, including those available in the drug industry, is not available. Furthermore, a mere listing of program directors and institutions is not adequate. A moderately detailed description of the training program at each institution and past performance in regard to training fellows would be of considerable help to the young physician who is contemplating a career in clinical pharmacology and wants help in picking a spot. One or another of the various organizations in the country concerned with pharmacology or clinical pharmacology could address itself to this purpose with good effect.

Economic Problems

An analysis of the rate of introduction of new pharmaceutical products in the United States reveals a substantial decrease over the last 15 years. For "duplicate single products" and combination products, the data show that a declining rate was in evidence by the late 1950s, antedating the 1962 amendments to the Food and Drug Law. For new chemical entities, the fall has occurred primarily since 1962.

Why these changes? One possibility — and the alternative explanations to be listed are not mutually exclusive — is that the fantastic output of the pharmaceutical industry preempted many additional contributions by tackling successfully the "easier" development problems, and that post-"Golden Age" research is necessarily less productive because the nuts left to crack are tougher ones.

A second explanation is that the new regulations and new FDA philosophy have generated such delays in evaluating and approving drugs that the number of successful candidates introduced per year has necessarily shrunk. Mere delays would eventually result in yearly approval rates similar to the old rates; there is no evidence that this "catch-up" is occurring. As far back as September 12, 1963, at a hearing held before the Subcommittee on Public Health and Welfare of the Committee on Interstate and Foreign Commerce, Congressman Paul Rogers pointed out that there were a good many NDAs that had been filed anywhere from one to five or six years previously.

Bloom [9] has analyzed the available data and concluded that while there has been almost total stifling of new drug approval in a field like the cardiovascular-pulmonary one, in some other areas the decline has been less remarkable, eg, in antibiotics and the tranquilizer-psychostimulant category. In the area of cancer chemotherapy, there has ac-

tually been no decline. Why? Are our techniques for screening drugs or evaluating them better in these fields? Are FDA requirements more lax or flexible in an area like cancer chemotherapy? Can the personal bias of FDA monitors possibly affect the course of events so dramatically?

Clymer [12] has surveyed the economic impact of the new climate of drug development and regulation. He states that in 1968 it actually cost $1,342,000 to develop a new biological, and a bit more for a single chemical agent. Clymer believes that it now takes five to seven years and $2.5 to $4.0 million to market one product. For each such product, he estimates that 6 to 10 additional products would "abort along the development path." Making certain assumptions, he calculates that it costs $10.5 million for each successful product, exclusive of the research originally necessary to generate the new compound.

Mund,[13] in a separate analysis, has looked at the research and development costs of the drug industry and concludes that whereas it used to take $1.5 million or so to produce a new single entity, it now takes $15 million.

Mansfield, [14] examining the actual cost and time required in the 1950s and early 1960s for one major drug firm to develop a new chemical entity, found that the average cost was $534,000 during that period, and the total average development time 25 months. With a figure of 37 per cent successes, the cost of development came to somewhat over one million dollars. He notes that an acceptance of Clymer's data would indicate a sixfold increase in the cost of a successful project, a threefold increase in the length of time required for the project, and a halving of the probability of a given project being successful, with a tenfold increase in total costs per successful new entity. Mansfield further points out that only one half of this increase would have been expected by extrapolating the trends of the fifties and early sixties.

One FDA officer has suggested guidelines for evaluating a new hypolipidemic agent. It has been estimated that such a workup would cost $2.25 million. Such an estimate does not include the many additional millions required to prove that "successful" manipulation of blood lipids would indeed favorably affect the course of vascular disease. One wonders to what extent further research in such an area will be pursued.

In the field of population control, Djerassi [15] has calculated that a male antifertility agent would require 12 to 20 years and over $6 million to develop, while a luteolytic or abortifacient would take 17 to 18 years and over $18 million. He is understandably lugubrious about the incentive for industry to develop new methods of birth control.

Certain savings in the cost of drug development could be achieved without serious harm to the public. One way would be the expediting of data presentation and data evaluation at the NDA level (see *Expediting NDAs*). Another approach would be to restrict preclinical toxicity testing to those species and tests, and to a duration of testing, shown empirically to detect the great bulk of predictable toxicity. No testing program will ever pick up *all* toxicity risks, so that the question becomes: what general and specific guidelines for toxicity testing can be elaborated that will do an adequate job at the least expense of time, money, and personnel? The answer to this question should be determined on the basis of experience, and not theory or bias or habit alone. It is unfortunate that attempts to pool past data within the industry have been so fragmentary and incomplete.

A similar approach could apply to the number of clinical observations that will provide the data required to make reasonably accurate projections about the safety and efficacy of a new drug. If 500 or 1,000 cases in a given therapeutic area will quite regularly provide *most* of the data required, and further observations only add "more of the same," is it responsible to demand 5,000, 10,000, or 25,000 cases for marketing? Again, however, one cannot find empiric analyses of real-life experiences to see what general rules of study could be elaborated, and at what point the law of diminishing returns begins to manifest itself.

"Unprofitable" Drugs

What do these increased costs and complexities forbode for the development of "unprofitable" drugs? It is unlikely that companies will devote significant budgets to a purposeful search for drugs for rare diseases. As one drug

house executive wrote to me recently: "As long as the American pharmaceutical industry remains a profit-making enterprise, it must consider such figures in the light of the possible return from a successful drug development. The greater the expense, the more restrictive our programs have to become, focusing on only the very large markets and completely ignoring smaller areas of medical significance that may need close attention. More and more frequently we are forced to discard ideas because the cost of the development, if successful, would never allow a return on the investment."

Will a serendipitous discovery of such a drug as a sort of "fallout" from ongoing research programs also fall by the wayside if the process of pursuing such an agent to ultimate NDA approval is excessively lengthy and costly? If so, how should society handle this situation? Do we need a "double standard" of requirements for ordinary drugs and for drugs intended to be used only for patients with an extremely rare or deadly disease? Should companies be allowed tax or other incentives for participating in such "unprofitable" drug development? Should the NIH or some other governmental agency become responsible for such regulatory orphans?

Lessons from Other Countries

Procedures for approving drugs for marketing in other lands differ in a variety of respects from those prevalent in the United States. In Sweden, the registration time runs 12 to 24 months for new substances, and 5 to 10 months for known substances. In Switzerland, local trials are not compulsory, but are becoming more important as a determinant of approval. A minimum of two groups of 50 cases is required. Japan has a very detailed set of requirements, with the evidence required varying somewhat depending on whether the compound is a single drug or a mixture, and whether it is a new one or merely a changed dose or indication. The minimum number of patients studied varies from 40 to "more than 150."

It may be helpful to examine the difference in speed of marketing of compounds introduced both in the U.S. and abroad. Such a survey for the years 1965 to 1969 shows that 82 new single chemical entities were marketed in this country during that period. For 43 of these, introductory dates in at least one foreign country were available.

France showed an average lead time of one year, ie, the products were introduced on the average one year sooner than in the U.S. Six were introduced in the same year in both countries; three, one year earlier in France; two, two years earlier; two, three years earlier; three, four years earlier; one, seven years earlier; and one, nine years earlier in France. Six were introduced one year after the United States date; and three, two years later.

Seven products were introduced in the same year in Germany and the United States, seven were introduced a year later in Germany than in the United States, and 10 were introduced one to eight years earlier in Germany. The average lead time was 1.6 years for Germany. England displayed a similar picture, except that the average lead time was even greater, ie, 2.1 years.

These products included such drugs as clofibrate, propranolol, cloxacillin and dicloxacillin, allopurinol, azathioprine, deferroxamine, amantadine, dextrothyroxine, carbamazepine, furosemide, ethambutol, methotrimeprazine, amitriptyline, cephaloridine, haloperidol, fentanyl, indomethacin, ethacrynic acid, clomiphene, methacycline, mefenamic acid, doxycycline, doxepin, procarbazine, thiothixene, methaqualone, tolnaftate, hydroxyurea, lincomycin, tybamate, oxazepam, and chlorphentermine.

While such an analysis tells nothing of the degree to which United States regulatory procedures are "protecting" the American public from "poor" drugs introduced abroad but denied access to our market, it does show a considerable lag in United States approval of useful compounds, and to that extent an inferior public performance. In 1963, the American Medical Association went so far as to endorse the drug metronidazole (Flagyl) as a uniquely effective trichomonicidal drug to dramatize the fact that the NDA had been languishing for two years at the FDA. A look at some important and unique drugs in use in the United Kingdom but not in the United States shows important treatments (such as salbutamol, orciprenaline, or

trimethoprim-sulfa combinations) being denied to the American citizen. Other compounds (such as lidocaine for the treatment of cardiac arrhythmias) have been given by American physicians for years at the risk of malpractice suits, while waiting for FDA approval of indications long accepted by clinicians everywhere.

Are the above data cause for concern? Is there adequate international agreement about the amount and nature of evidence considered optimal for approval of new drugs? Is there needless duplication of pharmacological evaluation in animals? Of preclinical toxicity testing? Of human testing? At what levels can changes be made to achieve savings for the people of the world in both money and health? Would an analysis of foreign "errors" suggest any changes that could be instituted abroad? Are our *procedures* better for keeping excessively toxic drugs off the market, or is the United States public merely protected by time, ie, by the greater likelihood that unpredicted toxicity will be discovered in some country or other as experience accumulates? Is the negative side of the ledger so far as United States practices are concerned such as to outbalance any advantages in the American process?

FDA Regulatory Powers

A key industrial-FDA relationship has been and will continue to be the matter of regulations promulgated by the FDA to implement powers granted to it by the legislative process. There is no question about the legality of such regulatory activity, or the need for regulations. Where there *is* controversy, however, is in regard to the limits of authority and the details of the regulations. For instance, on the supervision of drug advertising, exception has been taken to the scope of the FDA regulations.

In 1963, FDA issued regulations which included the requirement that advertising should provide a "fair balance" in regard to information on effectiveness, side effects, and contraindications. Industrial spokesmen have complained that it is impossible to know in advance what constitutes "fair balance," since one may construe this requirement as demanding a balance between information on effectiveness and on lack of effectiveness, a balance between information on safety and on limitations of safety, a balance between information on effectiveness and on side effects and contraindications, or possibly some permutation of these data. These spokesmen claim that the result is a control over advertising that is extreme and bears no relation to that authorized by Congress. This complex area assuredly needs thoughtful, comprehensive attention, not a "legalistic" treatment that looks on drug advertising as primarily a matter of law, and only secondarily (if at all) as a matter of science or medicine.

Similarly, in regard to the problem of volunteer consent, there are some who believe that the FDA has gone beyond the intent of the original Kefauver-Harris amendments. Nor has the question of appeal mechanisms and negotiation in regard to the entire FDA regulatory process been satisfactorily worked out. Cavers, in a perceptive review,[11] has compared the problems of the Atomic Energy Commission and those of the FDA. His observations are worthy of wide attention, and deserve reading in the original. Here are his closing remarks:

> "...On the one hand, we have to allow the government experts and their expert advisers enough freedom from legal formalities and restraints in reaching their judgments that good men can be attracted to this task. Experts in official posts will usually yield to contrary judgments of the best men in their guild, but their morale will ebb if their own processes and judgments are often overridden by what seem to them unscientific processes and nonscientific considerations. On the other hand, sooner or later the public will reject expert judgments on which hang the safety of many people unless at least some of these judgments can be and are validated by public processes, however unscientific. One way to provide public validation is resort on occasion to a public hearing before a tribunal manned by knowledgeable people of demonstrated independence whose conclusions can be rejected by the final decision-makers in the agency only on the basis of reasoned opinions, themselves subject to public appraisal.
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> "If this or some comparable check is not available, if the staff's work is done and reviewed in secret, the agency, its staff and its processes will all risk becoming the object of suspicion, perhaps not from the public at large but from a relatively small but concerned and

articulate group of independent experts and laymen. If this or some comparable check is not available, if the staff's work is done and reviewed in secret, the agency, its staff and its processes will all risk becoming the object of suspicion, perhaps not from the public at large but from a relatively small but concerned and articulate group of independent experts and laymen. If there is no effective way for these critics to take part in the process of decision or to evaluate the judgments it yields, they will exploit whatever agency errors hindsight has laid bare and turn to political processes. The most available of these are appeals to congressional committees and to the citizenry at large, ranging from indignant letters to the editor to the hair-raising best-seller. Secrecy is not likely long to survive these assaults, nor will public and professional confidence in the agency. (A possible response by the agency might be to 'avoid future trouble by always refusing clearance' or to use 'the official escape of saying that there is inadequate data.' Austern, *Drug Regulation and the Public Health*, 19 Food, Drug Cosm. L. J. 259, 270 [1964]. This too would destroy confidence, although, for a time, in a different quarter.)"

Expediting NDAs

The technical process involved in handling NDAs could stand improvement. Both industry and the FDA have reason to desire a procedure that is as efficient as possible and includes a minimum of delays. One step in this direction is to pinpoint exactly what it is that is required of a sponsor in the way of information in order to expedite the job of review by the FDA monitor.

Another step in this direction might be the guidelines now being put together by industrial and other scientists in cooperation with the FDA. Properly drafted, they could help considerably in allowing a sponsor to make plans in regard to what and how much experimentation is needed for a new drug to be approved. Such guidelines will not be easy to draw up, since they must walk the thin line between being too general on the one hand and too specific and restrictive on the other. Nevertheless, past success with guidelines for preclinical research allows at least temporary optimism. Any clinical guidelines so drafted should be considered as tentative, and modified as needed.

Another interesting suggestion by the FDA has been the idea of more conferences between their personnel and sponsors during the various phases of drug evaluation and prior to the filing of an NDA.

It is now optional in NDA filings to present an expanded summary. It would seem highly desirable to make this usage invariable and mandatory. If so, it should be done with an understanding that such summaries will be accepted as valid. The summaries should be honest portrayals of the quantity and quality of data being presented on clinical trials, for instance, and could be validated by spot-checking sections of the application for accuracy. If such a procedure is to be truly effective, clear directions should be drawn up as to how the summaries are to be written so that they will be most useful to the NDA monitor. Companies, for their part, should readily accept the legal and moral responsibility that is implicit in the idea of an expanded summary, since the entire content of an NDA, including the summary, must even now be true and complete, under penalty of law.

How much preclinical and clinical data is "enough" evidence is something that should be dealt with in both philosophical and realistic terms. At the moment, it is hard to see much science involved in the decisions made. Numbers of patients are arbitrarily pulled out of a hat by either sponsor or FDA monitor. In my opinion, several properly controlled trials, if in agreement, are sufficient to establish that a drug has clinical utility. After this point, the accumulation of further data may flesh out the skeleton just described and provide some useful information in regard to those side effects that are seen with frequency, but beyond that I doubt that much is generally achieved. Side effects that are truly rare will certainly not be picked up short of many thousands of cases.

The recent experience with levo-dopa (L-dopa) is an interesting example of an approach that might well make good sense for other drugs. L-dopa has been a dramatic advance in the management of Parkinson's disease. Neurologists who worked with the drug were convinced that regardless of its known hazards or the possibility of unforeseen future dif-

ficulties, the compound was too important not to make it generally available. As a result, two NDAs were approved relatively swiftly, but the drug has been marketed with the understanding that experience with it will be carefully assessed so that if unforeseen major problems arise, the decision can be rapidly reversed.

This combination of a moderate amount of impressive clinical experience, coupled with early approval and effective post-marketing monitoring, could be a pattern for the future. It requires, however, post-marketing monitoring of higher quality than has prevailed in the past. For years, physicians have voluntarily filed anecdotal reports of untoward effects with journals, detail men, industrial medical departments, the FDA, or the AMA Registry of Adverse Reactions. These data have been of some use, but they do not represent the careful sort of delineation of efficacy and toxicity that could be achieved with a painstaking epidmiologic assessment of the use of a new drug. Research is needed to develop techniques that would accomplish the desired goals. In addition to monitoring, the results of such data collection would have to be fed into an educational framework capable of alerting the physician to any nuances in diagnosis, therapy, and toxicity derived from these studies.

Outside Advisers and the FDA

In the more complex and more flexible decision-making that one hopes the FDA can pursue in the future, advisers from outside the government will have an important role to play. The FDA alleges that it makes extensive use of consultants. Whether it does or not is difficult to say, because these consultations are not open to public scrutiny. Nevertheless, it is important to increase the amount of regular liaison between those FDA officials responsible for approving, rejecting, or repealing the approval for a new drug, and academic experts and the medical profession at large. Advice on these matters should not be sought from merely one group of partisans, or indeed only from so-called "experts." It is common to denigrate the ordinary practitioner's use of drugs, but important contributions to therapy have been made by such individuals, and it is arrogant to assume that practitioners cannot be accurate observers or do not learn from their experience. Recent years have seen bitter controversies between the experts and the men in practice over how drugs are used, and which drugs should be preferred, controversies that have not usually been resolved on the basis of scientific evidence.

In this regard, one should remember the admonition of Harold Laski:

> *"Expertise*, it may be argued, sacrifices the insight of common sense to intensity of the experience. It breeds an inability to accept new views from the very depth of its preoccupation with its own conclusions. It too often fails to see round its subject. It sees its results out of perspective by making them the centre of relevance to which all other results must be related. Too often, also, it lacks humility; and this breeds in its possessors a failure in proportion which makes them fail to see the obvious which is before their very noses. It has also a certain caste-spirit about it, so that experts tend to neglect all evidence which does not come from those who belong to their own ranks. Above all, perhaps, and this most urgently where human problems are concerned, the expert fails to see that every judgment he makes not purely factual in nature brings with it a scheme of values which has no special validity about it. He tends to confuse the importance of his facts with the importance of what he proposes to do about them."[13]

Relative Efficacy

From time to time the suggestion is made that the approval of new drugs should take into account the matter of relative efficacy. Indeed, it might be said that when a new drug is introduced, it will be best used if the physician knows where it stands in the hierarchy of drugs available to treat a symptom or disease. In this sense, comparative performance both in terms of efficacy and toxicity are highly important for a judicious choice among medicaments available. FDA has had a perverse and paradoxical philosophy here; it wants comparative data for approval, dislikes "me-too drugs," but has usually prohibited comparative claims favorable to the drug being promoted.

On the other hand, it is easy to be misled into the stand that a drug must be "better" than already available drugs in order for it to be marketed.[19] Is novobiocin "better" than penicillin? Certainly it has a much narrower antibacterial spectrum, and greater hepatotoxicity, but for a few resistant

organisms it will do a job that penicillin will not. Is a new drug that cures 20 per cent of patients "better" or "worse" than a compound that helps 90 per cent of the same population but cures nobody? On what yardstick does one compare such different side effects as osteoporosis and agranulocycosis, or increased susceptibility to infection *versus* peptic ulcer? Can we do without drugs that are no better *on the average* than those already available, but which may be useful in the event that a person happens not to respond well to the standard drug or has a toxic reaction from it? (Antiepileptics are a good example of this need.) The legislative history of the Kefauver-Harris amendments clearly indicates that Congress intended a drug to be marketed if a respectable body of informed medical opinion testifies to the utility of the compound, even if the opinion be a minority one.

Large-Scale Trials

Another problem area is provided by drugs that produce easily measurable effects on endpoints that are not those in which the patient and the clinician are really interested, but whose impact on the variables of real concern is assessable only with great difficulty. For instance, various drugs are known to lower blood cholesterol levels, but no one can be certain that these compounds do in fact prevent degenerative vascular disease, which is the real reason why one administers them to patients with high blood cholesterol levels. Experience in the field of cancer suggests that compounds that temporarily shrink tumor size or the number of tumor nodules do not necessarily increase life span. In the field of hypertension, on the other hand, drugs that lower blood pressure have indeed been shown to cause a diminution in vascular episodes and a prolongation of life. The recent cooperative study on hypoglycemic drugs has brought into question the safety of oral agents for lowering blood sugar. This study has been both praised and criticized, and while the final answer as to the utility of such compounds is not yet known, the results have at the very least raised the spectre of inappropriate endpoints misleading manufacturer, patients, and physicians.

Such endpoints have usually been chosen because they are easier to measure than the ones of prime concern. If the results of current studies of oral hypoglycemic agents or cholesterol-lowering drugs put these compounds into discredit, we may see an overall decision to refuse approval to any compound that has not been shown to achieve the prime goal of therapy. To prove that a drug prevents heart attacks is a formidable task. Cooperative studies are required, involving many clinics and millions of dollars. Such studies are unlikely to be funded by individual sponsors, so that government underwriting will probably be imperative. Because of the expense of such studies, it is unlikely that society will pay for many of them, and there is always considerable hazard in making decisions on the basis of a single study, no matter how well designed and conducted. We may see the drying up of research in areas such as cholesterol-lowering drugs because of such difficulties and the subsequent absence of informational feedback to the scientists involved in synthesizing and studying such drugs in the laboratory. It could be argued that refusing approval to a drug until theory has been checked out by practice is desirable. Yet if society had been forced to await the outcome of large-scale trials documenting the benefit of antihypertensive drugs, many thousands of patients, denied these agents, would have died awaiting their approval.

Pre-1962 Drugs

What of pre-1962 drugs? The FDA has taken the position that such medicaments (and perhaps even over-the-counter remedies) should be judged by the same standards as those applied today in the approval of new drugs. Will society really be better off if controlled clinical trials are demanded of all pre-1962 drugs? May the expense and time involved in such efforts coupled with the diversion of investigators away from research on new drugs possibly harm the public more than it will benefit it? Should decisions about any given drug or combination not be made on the basis of the total amount of information available, including preclinical data, controlled clinical trials, and so-called "uncontrolled" experience with the compound? There is no doubt that errors have been made by the

profession in the past in regard to the merits of drugs, and commercial success or general acceptance by the medical profession is not a *necessary* indicator of adequate performance, but neither should it be assumed that such information is totally useless. (It is paradoxical that the same people who consider practitioners to be totally unreliable observers are insistent that those same doctors have the right to flexibilize their dosage of individual drugs —presumably on the basis of their clinical observations!)

A. Bradford Hill is often considered the father of the modern controlled therapeutic trial. It is therefore of considerable interest that he has said: "Given the right attitude of mind there is more than one way in which we can study therapeutic efficacy. Any belief that the controlled trial is the only way would mean, not that the pendulum had swung too far, but that it had come right off its hook." [20]

It is suggested that a conference on this problem should be held, involving the experts who participated in the National Academy of Sciences-National Research Council review of pre-1962 compounds for the FDA, plus representatives of industry, the medical profession, and the FDA, for the purpose of discussing the original review and the resultant implementation of the experts' judgments. Certainly some of the original NAS-NRC experts are dismayed by what is being done in the name of their report.

Pressures on the FDA

In its functioning, the FDA has been hampered by pressures from Congress, the public, the drug industry, the medical profession, and the academicians. A public regulatory agency must maintain a sensitivity to the needs of the public, as well as to the needs of those regulated. It cannot operate in arrogant isolation. On the other hand, it must be sufficiently free from outside attack to perform its functions, and to operate on the basis of scientific and social judgments, rather than in response to political pressures or expediency. It is to be hoped that the quality of performance of the FDA will in time generate the sort of stature and respect that is required for the agency to achieve the latitude to function, free of excessive interference.

Final Remarks

Most people would accept the fundamental validity of the role of a regulatory agency in modern medicine. The public needs a friend in court to act as a buffer between the drug industry and the sick patient or the prescribing physician. Such scrutiny, properly executed, is vital to the protection of the public's interests.

But one can criticize the concept that a drug regulatory agency will perform best if it delays as long as possible the introduction of new drugs on the market or removes drugs from the market on the basis of unjustified political pressures, whim, or caprice. *The FDA should, rather, act in such a way as to maximize public benefit.* For a long time, physicians have been fond of quoting the Hippocratic admonition, "*primum non nocere.*" This advice may have made sense centuries ago when there were few effective drugs, so that the least one could do was to not injure one's patient. But today, with the drugs available to the modern physician, there is the opportunity for tremendous good as well as for great harm. The goal therefore is no longer "*primum non nocere*" but rather how to treat the patient in such a way as to maximize the possibilities for benefit and minimize the chances for harm. With such a philosophy operant, matters of economics and incentive would also be weighed in the balance along with scientific and medical considerations. It may be politically expedient, for the short haul, to disregard the health of the United States drug industry, but its destruction would be a gigantic tragedy —and not just for its shareholders. Those who are fond of pointing to the "simpler" therapeutic cupboards of Scandinavia or Russia might ponder the lack of pharmaceutical creativity in those countries.

We must also remember the individual nature of drug selection and use. No matter what judgments are made in regard to the marketing of a compound, ultimately an *individual* doctor will have to select an *individual* drug or combination for an *individual* patient. In so doing, there will be opportunity for errors in diagnosis or in choice of agents. Judgments will have to be made about relative benefits and relative risks. At times these will be made in conjunction with the patient or other doctors; at other times by

the physician alone. It is impossible to regulate from a central agency such individual use of drugs. *It is unimportant whether such central regulation of individual prescribing might be desirable or not, because it is quite simply impossible.* What society must demand, therefore, is the best possible performance from physicians. This will require not only the acquisition of reliable data upon which to make the original decisions concerning marketing of drugs, but also the collection of valid data post-marketing, the effective communication of old and new information about drugs to the practicing doctor, and evidence of the doctor's competence to prescribe. Since laws and regulations alone cannot achieve these goals, we had best bestir ourselves and seek other means.

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