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The Pharmaceutical Revolution: Its Impact on Science and Society

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During the last few decades there has been an extraordinary acceleration in the discovery, development, and delivery of chemicals used in the diagnosis, prevention, and treatment of human disease. This pharmaceutical revolution has affected our scientific and social structure in profound ways, and will almost certainly continue to have such effects in the foreseeable future. It is my purpose in this article to describe first some general problems that have arisen, and then to treat, in greater detail, the areas of biopharmaceutics and standards of drug quality to indicate some specific ways in which technological advances have affected industrial, professional, and regulatory groups, as well as the public.

The Implicit Science and Technology

The pertinent scientific and technological advances constituting the pharmaceutical revolution may be thought of in three main subgroupings. The first is our expanding knowledge of disease processes—their causes, the pathogenetic mechanisms, and the details of the physiologic, psychologic, or biochemical disorders that constitute disease. This knowledge has permitted pharmacologic attack on human illness to be made at a variety of levels, from the etiologic to the symptomatic. The second is our expanding knowledge of drug action—of both the desirable and undesirable effects of drugs; of their action in man as well as in animals; and, at the level of the whole organism, of their effects on specific organs, cells, and subcellular processes. Finally, there is the complex of expanding facilities and resources for drug screening, production, distribution, and promotion. Increased potential in this area has been evident primarily in the industrial sector, but by no means exclusively, since there are significant resources available within the government and academic sectors. For example, in the field of cancer chemotherapy, there are the federal Cancer Chemotherapy National Service Center and organizations such as the Sloan-Kettering and Southern Research Institutes.

Expected Benefits and Expected Harm

These substantial advances have, not surprisingly, raised hopes within all segments of society. A revolution in pharmaceuticals should conceivably produce increased health and comfort, a greater life span, better medical care, and a gain to the economy through decreases in lost time for the national work force. Such benefits have certainly accrued in considerable measure, even if they have not been enjoyed to an equal degree by all subgroups of the population.

The pharmaceutical revolution, while yielding significant benefits, has also generated its share of problems. The production of potent new drugs has given the physician the power not only to modify disease processes for the benefit of his patients but also to produce new and serious side effects, as individual drugs cause unwanted toxicity or interact with other drugs or with foods to do pharmacologic mischief (*1*). Paradoxically, medical care has in some ways been impaired by the availability of new medicaments, in terms both of overtreatment of patients and of confusion regarding the diagnosis of disease because of the temptation to treat symptoms without having determined their cause. The manufacture, legal and illicit, of powerful psychotropic drugs has led to drug abuse and addiction. Advances in drug development have generated the false hope that most of our disease problems can be handled by drugs, and that applied research in pharmacology is all that is required to meet these needs, whereas in fact a fully effective attack on the major health problems facing the public requires not only new basic information concerning such diseases as atherosclerosis, cancer, arthritis, and schizophrenia but preventive measures as well as, or instead of, therapeutic maneuvers.

The burgeoning research on drugs has led to impingements on clinical investigation as the public's anxieties have been kindled by the revelation of unethical behavior on the part of clinical investigators in the search for new drugs (*2*). Industry has also experienced added restrictions on the free enterprise system, as public discussion of questionable practices within the industry has evoked laws and regulations designed to regulate the activity of pharmaceutical firms and to monitor their performance more closely in many steps of the development process, up to and including marketing and promotion (*3*).

The search for better drugs has posed a moral dilemma in forcing a choice between the goals of society and the good of the individual, as potential present risks and gains for specific patients or risks for healthy volunteers are weighed against the chance of future advantages for society as a whole (*4*). Industry has found itself in a similar dilemma as drug development

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has become increasingly more complex and expensive because of regulatory pressures (*5*). As a result, there is even less incentive than there was formerly for industry to develop new drugs for rare diseases whose incidence is so low as to preclude repayment of the expense involved in the development and distribution of such drugs. This has in turn raised the question of whether governmental agencies should become involved in the development, marketing, and distribution of drugs to fill this need, a possibility with broad implications for the pharmaceutical industry as well as for the government. A separate issue has been the conflict between industry's desire for profits (partly needed for further research) and the public's desire for low-cost drugs. Finally, the pharmaceutical revolution has contributed in some degree to the population explosion, as death has been postponed for individuals at various age levels, with increasing debate about the quality of life (as opposed to its length), the patient's right to die (as well as to live), and so on.

New Social Organizations

The problems described above have contributed to the elaboration of new social organizations to meet new needs. The modern pharmaceutical industry in the United States has mushroomed in the last three decades (*6*). To complement this development, modern advertising of medical products has also grown at a fantastic rate, in a dual attempt to bring the fruits of research and development to the attention of doctors and to their patients and to reap financial gain for the manufacturers (and the advertising industry). Regulatory agencies at the federal and international levels have evolved, with responsibilities regarding the approval of drugs for marketing and the monitoring of drug toxicity and drug abuse. Individuals and groups in increasing numbers within the industrial, hospital, academic, and governmental sectors are studying drugs in man. Not only has a tremendous establishment developed for drug research at the animal laboratory level, and at the level of human studies, but new organizations and new administrative formats have been required for purposes of data gathering and collating.

Concern about the ethics of clinical trials has resulted in the establishment of protocol review mechanisms within hospitals; this action has been either voluntary or imposed from without through regulations promulgated by the National Institutes of Health or the Food and Drug Administration for recipients of federal research support or investigators of new drugs. New mechanisms have been elaborated for planning and conducting mass national or international clinical trials, with numerous investigators and clinics collaborating so that definitive data might be accumulated within a reasonable period.

Changes in decision making have also occurred. One example is the passage of the 1962 Kefauver-Harris amendments to the Federal Food, Drug and Cosmetic Act of 1938, giving the Food and Drug Administration (FDA) authority to evaluate claims for the efficacy of a new drug as well as the evidence concerning its safety. The recent National Academy of Sciences review of drugs marketed before 1962 has brought the academic community into action on a large scale as advisers to the Food and Drug Administration, in response to a request from the regulatory agency for help in deciding whether drugs already marketed should be removed from sale or whether the manufacturers should be required to modify their advertising claims. And, as I discuss in detail below, the development of biopharmaceutics has raised many issues in regard to what constitutes appropriate quality control and what the requirements for the quality of marketed drugs should be.

There have been several moves toward involving patients in medical decision making. The FDA regulations on new drug research suggest such involvement at least in regard to compounds under investigation, and several bills introduced in state legislatures have proposed that involvement of patients may also be appropriate in regard to decisions on drugs now being marketed. For example, the FDA regulations interpreting the manner in which patient consent shall be obtained describe in considerable detail the nature of the information to be supplied to a potential subject about the compound under investigation, about alternative forms of therapy available, about risks, and so on, before consent (usually written) is obtained. In Maryland, several bills have been introduced in regard to chloramphenicol that would have required informing the patient as to the warnings now contained in the package insert and the patient's written consent before this standard drug could be administered to him.

Implications and Predictions

The progress that has been made in drug development has underscored the need for improving the continuing education of physicians. It is difficult enough to prepare a doctor for practice while he is going through his medical school and house-staff training; it is even more difficult to keep him apprised of new information once he is practicing his profession. Hand in hand with the education of the physician there must be attempts to educate the public and its elected and appointed representatives in regard to the broad picture of drug development. Such problems as self-medication, pressures on physicians to prescribe certain drugs, the economics of drug production and delivery, the risks of excessive regulatory control, the need for continued support of research and training, and the need for insuring an adequate supply of appropriate medicaments to the public are topics that deserve continued attention.

It seems likely that national and international networks for collecting and collating data on the efficacy and toxicity of drugs will be further developed. The need for information about drugs transcends national boundaries, and there can be no tolerance of delays in introducing useful compounds or in recognizing serious drug toxicity which result from failure of physicians and agencies of different countries to share information.

Two research areas in particular deserve high priority: (i) the definition of reasonably precise probabilities for the efficacy and toxicity of alternative treatments available for a given condition; and (ii) computer-based correlations of patient characteristics and drug response so that the doctor will be able to tailor drug treatment to the needs of the individual patient with a predictability of response that is not attainable today.

An ongoing review of the ethical values and of procedural mechanisms for assessing the ethics of scientific judgments in pharmacology is required. On the one hand, society cannot afford

to have its moral fabric destroyed in a search—even a successful one—for new drugs; on the other hand, we cannot afford to be so bound down by ethical stereotypes or outmoded moral admonishments that society suffers from a frustration or paralysis of its creative skills.

It is conceivable that new formal mechanisms will be invoked to monitor the competence of the medical profession in regard to the use of drugs. It is probable that governmental regulation of diagnostic and therapeutic devices will increase in the near future; perhaps surgical procedures will be similarly regulated. What new international structures will be contrived to satisfy pharmaceutical needs remains highly conjectural. Countries vary greatly in their medical needs, according to their geography, local diseases, economics, and other factors. The developed countries could help substantially in planning the most desirable systems of drug supply for emerging countries. A poor, newly formed nation without industry might import only a few staple drugs for a period of years, expanding the list with time and eventually manufacturing an increasing number of drugs as funds, equipment, and personnel became available. Research on the development of new drugs could almost certainly be postponed for a long time without detriment to the emerging country.

Biopharmaceutical Technology and Standards of Drug Quality

The history of pharmacotherapeutics reveals three recurrent causes of trouble in regard to monitoring the quality of medicinal drugs: ignorance, ineptitude, and fraud (*7*). Throughout most of recorded history, the latter two causes have received the greatest attention. There appears to be a crude inverse relation between the extent of reliable pharmacologic data available in any given era and the degree of satisfaction, on the part of scientists, with pharmaceutical standards. The evolution of acceptable criteria for the purity and quality of drugs has of necessity been bound to the sophistication of laboratory science, but it has also been hampered by delay in applying classic concepts of experimental control to clinical trials. It is only with the advent of the era of modern drugs, in the last three decades, that the scientific community has begun to realize the unsatisfactory state of our modern pharmacotherapeutic knowledge, and to suspect the limitations of "standard" laboratory control techniques long accepted by regulatory agencies, the academic community, and the drug industry.

At least as far back as the 4th century B.C. one can find concern about the adulteration of drugs. Theophrastus wrote in the *Enquiry Into Plants* that the quality of medicines was related to the geographical origin of the plant source; the variety, age, and portion of the plant used; and the method of harvesting, preservation, and storage. He refers only once to a specific problem: balsam of Mecca was said to be seldom procurable in a pure state, in which it might be worth double its weight in silver. Theophrastus did not, however, provide a means of distinguishing between the pure balsam and the "mixed gum."

In his famous *Materia Medica*, the 1st-century Greek physician Dioscorides mentioned 40 examples of adulteration among 1000 or more drug entries. For 30 of these he gave specific methods of detection, although most of the methods were of necessity "organoleptic," relying on one or more sensory perceptions such as taste or odor. For eight others, qualitative descriptions of the pure substances were provided, and were presumably considered adequate for telling the true from the adulterated sample. Some physicochemical methods were also used, but it is not clear how accurate they were. Balsam, for example, was to be applied to a piece of wool; with pure balsam, the cloth was said to show no stains after it was washed. Pure balsam was also supposed to diffuse easily in water or milk, and not to float, like oil, on the surface. Drugs were held in a flame, then the degree and ease of flammability, the color of the flame, and the color and odor of the smoke were determined. Pure frankincense was said to be readily flammable, to have a pleasant sweet smell, and to give off clear, airy smoke. The solubility of compounds was also utilized for purposes of identification.

Pliny the Elder, a contemporary of Doiscorides, also relied heavily on organoleptic tests, but he mentioned in his writings a larger proportion of physicochemical techniques. His works are marked by an indignant distaste for the "fraudulent propensities of man [which] are apt to corrupt and falsify everything." Critical of his colleagues, he was even more caustic about the "*seplasiarii*," or "druggists," whose fraudulent and adulterated ready-made plasters and salves were prescribed by physicians. Galen also distrusted the drug merchants, calling them "roguish dealers of petty wares," but recognized that they, in turn, were victimized by the "*rhizotomoi*" (root-gatherers) and by those middlemen who brought the crude medicaments to the druggists.

In medieval Islam, the preparers of medicines functioned in privately owned shops which were government-supervised. Manuals existed to guide the police officer in charge of markets in testing the genuineness of goods and the accuracy of weights and measures. A special assistant, or *amīn*, was appointed to supervise the drug dealers. This official made frequent inspections, personally supervised the preparation of some compounds, and extracted an oath from the druggists to the effect that no further admixture would take place after such compounds left the *amīn*'s presence. In one Arabic treatise, the inspectors were exhorted to fill the pharmacists with the fear of God, to lecture and threaten them with corporal punishment, and to examine their drugs weekly.

The idea for the first official pharmacopeia [at least the first in the Western World (*8*)], is said to have originated in Florence, where the *Nuovo Receptario* was published in 1498. Its full title is translated as "New Formulary Compiled by the Most Renowned College of the Distinguished Doctors of the Arts and Medicine of the Magnificent City of Florence." The preface states that the book was compiled by physicians "at the request of the executive officers of the guild of apothecaries," a profession which was then a patrician one, whose members were important in Italian political and social life. The *Receptario* was based entirely on the Greco-Arabic drug therapy of the time. It was not a critical reappraisal, but was intended simply to codify standard concepts, provide for uniformity, and furnish pharmacists with a practical and handy book for daily use. Originally written in vernacular Italian, in 1518 it became available in a Latin translation to the entire Western World.

The first work in English to discuss a means for detecting adulteration in drugs was the 1690 *Medicina Hydrostatica: or Hydrostaticks applied to the*

Materia Medica, by Robert Boyle, the founder of modern chemistry. The method was the measurement of specific gravity, a relatively precise tool but one which was of limited use at the time because the *materia medica* was largely botanical.

A number of writers began to urge general reforms. J. E. Gilibert wrote *L'Anarchie médicinale* in 1776, in which he described how drugs which had been already adulterated in their countries of origin, and had deteriorated in transit, underwent further harmful change at the hands of nonpharmacist dealers: "certain articles quadruple in mass on leaving Marseilles. There is sold, for example, one hundred times more cinchona than America could furnish. . . ."

An 18th-century master apothecary of Brussels, J. B. A. Vanden Sande, advised some sort of governmental control, limitation in the number of pharmacists, compulsory qualifications and examination of pharmacists, regular systematic tours of inspection by qualified agents, price schedules, central stores, standard weights and measures, and supervised pharmaceutical education. He also discounted the value of accepted tests of purity for certain vegetable drugs, despite their virtually unquestioned status for almost two centuries. Unfortunately, the state of science and technology still lagged behind the public needs; analytic chemistry had to mature, and scientific instruments had to be developed and refined, before drugs could be analyzed with a precision not attainable with the unaided senses.

These scientific needs were met during the 19th century. The analytical balance, the microscope, and refractometers became commercially available in models of good quality. Colorimetry, spectroscopy, and analytical techniques based on specific gravity, melting points, viscosity, and surface tension all began to be widely applied in Europe toward the end of the 19th century. Inorganic and organic qualitative and quantitative analysis also developed during this period.

Biological testing lagged behind. Despite the fact that digitalis-like drugs and ergot preparations seemed to require a quantification of potency that was impossible to achieve with techniques other than bioassay, there was resistance to such testing. The opposition was based in part on the great variability in such assays; but there was also concern because the facilities required for bioassay were not likely to be available in community pharmacies, and it was feared (quite correctly, it turned out) that the manufacture of galenicals would fall more and more into the hands of large-scale drug manufacturers and wholesalers. Not until the 20th century did bioassay achieve the status of inclusion in the official compendiums of Great Britain and the United States.

With the rise of the modern drug industry and the development of automated tableting, capsuling, and packaging, the new science of "biopharmaceutics" developed (*9*). The word first appeared in print in 1961, when John Wagner, an industrial pharmacist, defined biopharmaceutics as "the study of the influence of formulation on the therapeutic activity of a drug product; alternatively, it may be defined as the study of the relationship of the physical and chemical properties of the drug and its dosage forms to the biological effects observed following the administration of the drug in its various dosage forms" (*10*). In the last decade it has become recognized, for example, that the "inert" excipients in a capsule, the coating of a tablet, or the particle size of a preparation can greatly affect the biologic potency of a given drug.

The leadership in this new discipline has come from the field of pharmacy, not from that of pharmacology. It is pharmaceutical scientists who are primarily responsible for the laboratory drug standards that have been elaborated to determine the effectiveness and safety of drugs, standards set forth in official compendiums such as the *National Formulary* (*NF*), the *United States Pharmacopeia* (*USP*), the *British Pharmacopoeia* (*BP*), and others.

In regard to effectiveness, modern compendiums provide (i) assays intended to ensure that the tablet or other dosage form is not subpotent (that is, does not contain less of the drug than it is supposed to) and has not deteriorated or lost part of its activity (by volatilization, for example); (ii) identification tests to detect mixups or mislabeling; (iii) content-uniformity tests for tablets; and (iv) disintegration time limits for tablets.

In regard to safety, assays are available which are intended to ensure that tablets are not superpotent (do not contain more of the drug than they are supposed to), are not mislabeled, are not contaminated by foreign steroids (*11*), and do not contain general toxic impurities (such as arsenic and lead) or specific toxic impurities (such as chloroacetanilide in phenacetin, or 5-nitro-2-furfuraldazine in nitrofurazone). In addition, there are sterility and pyrogen tests to detect harmful microorganisms in parenterals; specifications for the glass or plastic containers in which drugs are packaged; and packaging and storage requirements to prevent the drug from being exposed to environmental conditions that would cause it to deteriorate.

The first official distintegration time limits for tablets appeared only 18 years ago, with the publication of *NF IX* and *USP XIV*. The disintegration time was supposed to be an indicator of the availability of a drug for absorption into the body. The time limits specified in the monographs on tablets have undergone drastic revisions over the years. For over half of the tablets admitted from *NF XI* to *NF XII*, for example, the disintegration times had been reduced, in most cases by at least 50 percent, presumably as the result of theoretical considerations, improved manufacturing techniques, and clinical evidence that such changes were required to prevent poor therapeutic performance. When properly applied, disintegration times certainly provide a useful index of quality control; nevertheless, the concept has come under vigorous attack because disintegration time is not necessarily related to absorption. As Levy has put it, one could make a tablet out of crushed glass particles that would disintegrate promptly, but the contents would never be absorbed.

What is clearly needed is some reliable test to measure "physiological availability," and much effort during the past few years has gone into the study of in vitro dissolution rates with the goal of predicting the absorption rate in man. It is generally believed that disintegration tests are adequate for predicting absorption of drugs having solubilities greater than 1 percent over the physiological *p*H range of 1 to 8; it is presumably the relatively insoluble drugs that present the main problem (*12*). The reason for focusing on the dissolution process is that frequently this appears to be the rate-limiting step; once the drug is dissolved in gastrointestinal fluids, absorption is ordinarily very rapid.

There is also recent evidence to suggest that polymorphism and crystal

structure are importantly related to the absorption of certain drugs, but official compendiums do not at present provide standards for these properties. Apparently this deficiency is due to the fact that the drug industry is not as yet "tooled up" to use x-ray diffraction or optical crystallography to provide a routine assessment. Nevertheless, in the future (possibly in *NF XIII*) the *NF* will probably stipulate specifications for crystalline structure for drugs in which polymorphism plays an important role in the physiological availability of the compound. Such drugs include chloramphenicol, griseofulvin, prednisolone, novobiocin, sulfathiazole, sulfisoxazole, and tolbutamide.

Another important source of confusion in regard to therapeutic performance is the varying efficacy of salt and ester forms. The particular chemical form in which a drug is given can importantly affect its solubility, absorption, efficacy, or toxicity, although pharmacologists and physicians often seem to act as if it cannot. In a good deal of the pharmacologic and clinical literature, for example, it is common to refer to the drug as the base or acid (such as phenobarbital) even when the salt (such as sodium phenobarbital) or ester is actually used, regardless of the striking evidence on record that the chemical form can dramatically alter the speed of onset and peak effect, as gauged by measured blood concentrations or by biologic effect (*13*). Polymyxin B and E (colistin) were for years thought by many to be very different in their toxic potential, whereas most of the difference was due to the fact that one drug was commonly administered in the form of the sulfate and one as the methanesulfonate; when the same salts of the two antibiotics are compared, these pharmacologic relatives look remarkably similar, both therapeutically and toxicologically. Erythromycin produces hepatotoxicity when given in the form of the estolate, for example, but not when given as the stearate.

An especially thorny issue is the prediction of in vivo performance of timed-release dosage forms or "enteric-coated" delayed action preparations. A spate of papers has suggested that such formulations are often less predictable in their effects than standard dosage forms; a recent supplement to *NF XII* provides a new procedure for in vitro testing of timed-release forms, although at present there are no officially approved preparations that require its use. Indeed, the technique is apparently not designed as a substitute for in vivo studies and clinical evaluation.

While this minor revolution in biopharmaceutics has been going on, a major revolution has occurred in clinical drug evaluation. The ancient uncontrolled trial, the anecdotal report, and the "clinical testimonial" lost favor as it became evident that the unpredictable course of many diseases and complaints, and the biases and expectations—both positive and negative—of patients and doctors made reliable quantification of therapeutic benefit and toxic potential difficult in the absence of formal experimental controls.

While the Book of Daniel contains an account of a clinical trial that contained controls, and James Lind studied the effects of various treatments on scurvy in a reasonably modern manner in the mid-18th century, the widespread use of controls in biology dates from the 19th century, and their use in therapeutics, from the 20th century (*14*). The therapeutic controlled trial has developed on the foundation laid by the growth of modern statistics. As the science of statistics shifted from the historic recordings of things past to sampling techniques, the concept of degrees of freedom, the null hypothesis, fiducial limits and levels of confidence, and methods for assessing differences between groups, the tools became available for comparing measurements and for projecting such comparisons, on the basis of probability theory, to members of the population other than those actually studied.

The addition of this experimental rigor to the clinical evaluation of drugs added a new dimension to the standardization and control of medicaments. The preoccupation of older compendiums with precise tests for the purity of drugs that were in fact useless in practice was replaced by a more rational emphasis on drugs of proven merit. No longer do pharmacists have to concern themselves with the scrupulous formulation of unicorn horn, pepper, asafetida, or hydrocyanic acid. It is unfair, however, to suggest that this weeding out of useless remedies was entirely due to the advent of properly controlled clinical trials; a good deal was accomplished simply by the discovery and introduction of drugs that obviously and dramatically "worked" better than the hoary nostrums they replaced. Thus, for a long time the clinical assessment of drugs lagged behind the ability of the competent chemist and pharmacist to guarantee the purity of a drug product.

Racing ahead of scientific know-how, on the other hand, has been social pressure for control of drug quality. It was not, for instance, until after the passage of regulatory drug legislation in Britain in the 19th century that science and technology began to be systematically applied to the detection of adulteration, that individuals began to qualify themselves for such specialized work, and that the necessity for setting or improving drug standards became recognized. (The 1875 Act set no guides for administering the law.) It was not until the muckraking efforts of American journalists in the United States ultimately led to the Pure Food and Drugs Act of 1906 that general official or scientific concern with the quality of nostrums and patent remedies was stimulated. (In both countries, the legislation was greeted with horror and gloomy predictions by many drug manufacturers.)

In the United States, legislative and economic pressures have indirectly begun to force public dialogue about the criteria for so-called "generic drugs." Ordinarily, a new drug which is patentable can be sold exclusively by its manufacturer for a period of 17 years. After this period, although the trade or brand name remains the property of the original manufacturer, the drug can be marketed by other manufacturers under its chemical name or its generic name. While the price of drugs is a complex matter beyond the scope of this article, theoretically, at least, savings for individuals, hospitals, governmental agencies, Medicare and Medicaid programs, and others should be achievable through competitive bidding and the prescribing of generic preparations. Accordingly, in 1968 senators R. Long and J. Montoya each introduced bills in the United States Senate which would make the federal payment of drug bills in certain health programs more or less contingent on prescription by generic name. A bill with similar intent was introduced by Delegate W. Orlinsky in the Maryland legislature in the same year. The two Senate bills were not passed; the Maryland bill was passed but was vetoed by Governor Agnew. In 1969, Orlinsky submitted a revised bill, which is now law. (It is of interest to note that in 1841 the eminent Jacob Bell, editor of

the *Pharmaceutical Journal*, wrote that "one of the chief sources of the evil [adulterated drugs] consists in the demand for *cheap medicines*, and the imperfect acquaintance which the public possess of the tendency of this prejudice.")

In years past, such a move to popularize prescription by generic name would have been expected to elicit strong support from many quarters, although the ethical-drug industry (not the smaller generic-drug manufacturers) has always opposed such prescription. Not only does the industry have an economic stake in the continued popularity of drugs marketed by trade name but large manufacturers could point quite honestly to their more extensive and expensive quality-control programs. Up until the last few years, such arguments were confusing to many not directly involved in biopharmaceutical research. There might be a problem regarding the unscrupulous or incompetent manufacturer whose drugs do not meet *USP* standards, but what quality-control measures *beyond* those required by the *USP* were needed to insure adequate drug performance? If *USP* standards were not sufficiently high, why *have* such standards? Does not the very concept of "standard" imply the criterion of performance (*15*)?

Sad to say, it appears that the earlier naive reliance of the profession, and indeed the industry, on both "big-firm" quality control and older standards seems to have been misplaced. There have been many reports of errors in manufacturing practice, both by large companies and by small ones. One large firm marketed a tetracycline that degraded, under certain shelf conditions, to a toxic product; another recalled some shipments of a tranquilizer-antispasmodic combination because the mixture contained too much anticholinergic drug; still another large and respected firm was found to have been using for years an enteric coating that produced capricious absorption of drugs; an epidemic of precocious puberty was traced to contamination of isoniazid with estrogen in the plant of a small generic-drug manufacturer; many large firms were found guilty of mislabeling and of penicillin contamination of other drugs manufactured in the same plant as the penicillin (*16*); and so on and on.

The most dramatic instance occured in 1968 when nine brands of chloramphenicol were taken off the market (*17*). Here was a particularly shocking affair. By law, all antibiotics have to be batch-tested by the FDA. Yet nine brands, having met all in vitro criteria, were found, on testing in healthy volunteers, to be inferior to (and less predictable than) the originally marketed Parke-Davis brand. How serious and widespread was this problem? How many other drugs generally available were in fact defective in performance?

The question facing the federal regulatory agencies, the drug industry, the medical profession, and the public thus became: What data shall be deemed adequate justification for allowing a generic-drug manufacturer to place his drug on the market? In the case of chloramphenicol the problem was at least superficially simple: not only did the brands deemed unsatisfactory apparently take longer to achieve peak concentrations of antibiotic in the plasma but these peaks were lower and highly variable, with some subjects absorbing so little drug that none was detectable in the plasma.

But what should the *general* guidelines be? How high a peak concentration is "high enough" for a drug? How fast is "fast enough" for absorption? How variable can it be? Is a "peak and valley" drug better than a "plateau" one? (It might, for example, be better in the case of an antibiotic, but not in that of an antiepileptic medication.)

Rationally, one would ask that the behavior of the drug in the body, and its concentration in biological fluids, be such as to allow one to predict a satisfactory clinical response. Unfortunately, this information is not readily available for most drugs. For treating some infections, for instance, a relatively constant concentration of drug at the site of disease may be crucial. For others, intermittent treatment, with discontinuous concentrations, is adequate. In the use of some drugs, plasma concentrations correlate well with clinical response; with other drugs (such as quinacrine for malaria) the response correlates better with total dose than with plasma concentrations. "Hit-and-run" drugs that are rapidly excreted but have lasting effects on the body obviously will not show tidy relations between blood level and response. With some drugs, the breakdown of the original product into active or toxic metabolites poses the question of *what* one shall measure. It is also conceivable that the original chemical activity produces the desired effect and that a metabolite produces the major toxic effect, or that cell receptors are differentially susceptible to blood levels of drug or metabolites.

Should a manufacturer's version of a particular generic drug be shown, prior to approval, to work well *clinically?* (It should be pointed out that no one has presented evidence that the chloramphenicol brands taken off the market performed poorly in patients.) If so, who will do this rather unexciting work? Is it ethical to try an unproven version of a generic drug in a patient with a serious disease? (There is some precedent for this in the old procedures for standardizing injections of crude liver which required testing in a patient with pernicious anemia in relapse.)

Can we rely on new *in vitro* tests, such as those that measure dissolution rate? These are at the moment promising, but hardly proven indicators, and there are many unanswered questions. At what *p*H should these studies be made? At what temperature? With how large a beaker? At what rate of stirring?

Must we at least demand biological performance, with respect to absorption, that mimics closely (how closely?) the performance of the original drug (for which supporting clinical data would ordinarily have been available prior to FDA approval)? If so, shall this work be done in animals? If so, in what species? In man? If so, in healthy volunteers, in sick patients, or in both? Of what age? Under what conditions of diet? In bed patients or ambulatory patients? Should the tests be single-dose studies, or multiple-dose "equilibrium" studies?

At present, it is evident that no one has the answer to these questions. It is just as evident that decisions must be made pro tempore with as much wisdom as possible. In theory, what is needed is a series of studies correlating in vitro tests (old and new), in vivo fluid and tissue concentration studies (it is assumed that the drug can be measured by *some* technique), and clinical trials. At the very least, studies must encompass two of these levels of attack, otherwise we will never achieve the desired goal of picking the simplest technique that works. In vitro tests would be the cheapest, simplest, and

safest; clinical trials, the most bothersome; in vivo drug absorption studies fit somewhere between the other two.

Everyone now admits that "chemical equivalency" does not necessarily guarantee "therapeutic equivalency." Nevertheless, there is as yet only a handful of instances where drugs that met *USP* and *NF* standards proved therapeutically ineffective. There are almost certainly more examples, if we look for them. (The military, who do their own testing and have their own standards, are reported to have rejected a high percentage of products submitted by competitive bidders.) It is unreasonable to insist that the first drug version on the market be the only one in use. Indeed, one industrial expert, A. E. Slesser of Smith, Kline and French Laboratories, has asserted that the main trouble lies in failure to adhere to *USP* or *NF* criteria, not with the criteria themselves. Feldmann has alleged (*18*): "Where there is chemical as well as physical equivalency, then one can expect to have therapeutic equivalency." At the very least, the public deserves to have drugs that meet the current standards, *whatever* they may be—a label saying "*USP*" or "*NF*" should guarantee that the drug inside the package has indeed been shown to meet *USP* or *NF* standards. This requires FDA surveillance, inspection, and testing; at present these are admittedly inadequate and incomplete.

The order of priority for experimental testing of generic drugs has to be determined. It would seem desirable to start with drugs (i) that have solubility characteristics suggesting erratic absorption, (ii) that have to be given frequently during the day (and thus seem to depend on maintenance of blood concentration for effect), and (iii) that are life-saving (drugs such as anticoagulants, corticosteroids, penicillin, digitalis, quinidine, and so on).

For the moment, legislation aimed at mandatory prescription of drugs by generic name is probably best kept in abeyance. Such laws, in the absence of new information, cannot be wisely or safely administered. Nor are they likely to speed the accumulation of data that will allow for better quality-control standards. (Since many popular drugs are not available under their generic names, it is also possible that the bureaucratic red tape required to implement such laws would cost more than the putative savings.)

It is also evident that those responsible for quality control of drugs will have to keep revising standards in the light of new scientific and technological information. Present *USP* monographs, for example, specify measurements of drug content that do not generally identify important capsule-to-capsule or tablet-to-tablet variation in performance; the limits on particulate contamination of parental solutions seem grossly inadequate; and so on. The future of drug quality control seems destined to provide one of the most interesting areas for studying the impact of technological knowledge on the total social picture of health care.

References and Notes

1. L. Lasagna, *Perspect. Biol. Med.* **7**, 457 (1964).
2. "Ethical aspects of experimentation with human subjects," *Daedalus* **98** (Spring 1969).
3. L. Lasagna, *The Doctors' Dilemmas* (Harper, New York, 1962), chaps. 8 and 10.
4. ———, *J. Chronic Dis.* **16**, 955 (1963).
5. It has been estimated that it takes from 4 to 8 years and several million dollars, on the average, to bring a drug to market in 1969.
6. In 1939 drug sales in the United States were about $300 million at manufacturers' price levels. By 1957 the figure had increased sevenfold, and the total has been rising steadily since then.
7. For those interested in consulting original papers and additional literature on this problem, there are two excellent sources of references. One is E. W. Stieb and G. Sonnedecker, *Drug Adulteration: Detection and Control in Nineteenth-Century Britain* (Univ. of Wisconsin Press, Madison, 1966); it contains over 100 pages of "notes," which really constitute an annotated bibliography. The other is *Readings in Pharmacy*, Paul A. Doyle, Ed. (Interscience, New York, 1962); on pages 118 to 122 there is a section entitled "Additional readings" which contains over 100 references on the history of pharmacy.
8. The Chinese "Pen-ts'ao ching," attributed to Shen-nung, antedates the birth of Christ.
9. In regard to biopharmaceutics, see G. Levy, in *Prescription Pharmacy* (Lippincott, Philadelphia, 1963), chap. 2; Levy is not only the first person ever to have an academic laboratory and title in pharmaceutics but also the most prolific worker and writer in the field.
10. In his paper, [*J. Pharm. Sci.* **50**, 359 (1961)] Wagner refers to Gerhard Levy (personal communication) when stating that the word *biopharmaceutics* "was recently coined." Levy and Eino Nelson have been largely responsible for attracting the attention of American scientists to this field.
11. The assay for contaminating materials is limited generally to "expected" impurities.
12. This general principle is certainly not invariably true; for example tetracycline hydrochloride, which is highly soluble, may dissolve slowly, depending on particle size and diluents.
13. L. C. Epstein and L. Lasagna, *J. Pharmacol. Exp. Ther.* **164**, 433 (1968).
14. L. Lasagna, in *Drugs in Our Society*, P. Talalay, Ed. (Johns Hopkins Univ. Press, Baltimore, Md., 1964).
15. In fact, obviously senseless *USP* standards have been under attack for years; examples include those for the assay of thyroid preparations and digitalis glycosides.
16. The safest cure for this, technologically, seems to be the manufacture of penicillin in a separate plant.
17. Some of these brands have been subsequently reapproved, presumably because the manufacturers supplied new evidence as to the quality of their products.
18. E. G. Feldmann, *Amer. J. Hosp. Pharm.* **25**, 110 (1968). This of course begs the question, since it does not define "chemical and physical equivalency."

19. This article was written as the result of participation in a discussion group led by Seymour Kety and supported by the Harvard University Program in Technology and Society.