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Mass Drug Catastrophes and the Roles of Science and Technology

Walter Modell

Drug disaster—qua drugs—attracted little attention until very recently despite the fact that no drug catastrophes of modern times compare even remotely with those of the past, probably because we have come to expect only good from drugs.

The roles of science and technology in the causation, control, and prevention of poisoning from the new drugs can best be developed against the background of the history of mass poisoning and drug catastrophe. A logical, meaningful definition of "drug" is essential to such an examination if one is to establish the relative importance of different kinds of mass poisonings and chemical catastrophes. In a purely biologic sense and as the pharmacologist views it, any substance that by its chemical nature alters structure or function in the living organism is a drug. Drug action is therefore a general biologic phenomenon; usefulness in disease and adverse effect are merely results of pharmacologic action. Pharmacologic effects are exerted by foods, vitamins, hormones, microbial metabolites, plants, snake venoms, stings, products of decay, air pollutants, pesticides, minerals, synthetic chemicals, virtually all foreign materials (very few are completely inert), and many materials normally in the body.

Early man knew much more about poisons than about drugs with therapeutic value (*1*). Even later, although Hippocrates saw little use for drugs in therapy, when they wanted to dispose of Socrates, the Greeks had an herb for it. Toxicology paved the way to pharmacology. If the surgeon can be said to have been fathered by the barber, then the modern pharmacotherapist is the direct descendant of the Borgias. It seems only yesterday (perhaps it was less than 30 years ago) that strychnine was an important drug in every physician's pharmacopoeia; today it is archaic, not because it is poisonous but because it has no demonstrable medical use.

The ancients knew nothing of modern approaches, nor did they have the understanding that can turn poisons, like curare, into agents of therapeutic value. They learned by accident alone, and, their methods of observation being limited, the effects that were first attributed to drugs were more likely to be adverse than therapeutic. Man learned early that the wild parsnip caused quick death, and bites of certain snakes, a more lingering one; that the sting of certain insects caused local or even serious systemic reactions; that certain fish were not "seafood"; and that toadstools were not for eating. He knew of fishberries, strychnine, hemlock, and curare. Cleopatra's testing of the poison of her asp on her slaves before she applied it to herself is typical of the pharmacological experiments of the time (*1*).

Poisoning, accidental and deliberate, was well known in peace and war. The environment had a full complement of potent poisons with which man had to learn to deal, along with wind, water, heat, cold, and famine, in order to survive. Poisoning from strange foods and foods from strangers' kitchens was a common danger for the wealthy and those in power; the food taster or tester was the equivalent of the "informed" subject of a modern acute experiment in clinical pharmacology. Even as late as the 17th century there was more exact knowledge of and concern with poisons than with medicinal effects of drugs.

Today, poisoning is uncommon; the physician no longer tends to think of it in making a differential diagnosis involving even the most bizarre symptoms. Poisoning, innocent or homici-

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dal, is more often first suspected by the medical examiner; only the suicide who leaves a written message gets a quick diagnosis. Today we are shocked when poisoning is reported—especially so when it comes from the use of a new drug; we have recently come to expect only good from drugs.

Pharmacologic effects of plants other than quick death were identified as due to drugs when they were as patent as diarrhea, diuresis, or emesis, and drugs were early used for these purposes in medicine. Effects on sensation, behavior, and gait were also relatively easy to discern but, except for analgesia, their usefulness in disease was not clearly identified, while effects on internal homeostatic mechanisms, which might be therapeutically useful, were much too subtle to be recognized —much less put to use.

It is natural, however, that, of the drugs that did not kill promptly or disturb unduly, those with pleasurable effects—gin, opium, coca, tobacco, coffee, peyote, hashish—were used by ancient man for their pleasurable effects alone. By the very nature of the reasons that led to their choice, these were habit-forming and addicting; thus nonmedical use of drugs in early history laid the foundation for what is still one of man's most important social problems and, beyond dispute, the most important of the mass adverse effects of drugs—addiction. Although the continued use of many drugs may lead to addiction in the sense that adaptation, tolerance, and the withdrawal reaction may develop (adrenal insufficiency after cortisone, hyperglycemia after insulin, and such; as a rare curiosity, even habituation to sodium bicarbonate in those attracted by the eructations it induces, with serious acidosis on withdrawal), habituation and addiction pose serious social problems only with drugs that affect the central nervous system.

Alcohol, in one form or another, is used the world over just for fun as well as in religious, ritual, social, and even political celebration; but it is used because it acts like, and in fact is, a drug. It is one of the oldest drugs deliberately used for a currently accepted pharmacologic action.

Alcohol must have been accidentally produced long before man evolved, and he used it before history was recorded (*2*). With time, many fermented beverages, mead, wines, beers, ales, ciders, and so on, were achieved. Because fermentation stops when the concentration of alcohol reaches about 12 to 14 percent, no stronger alcoholic beverages were known before the distillation process was developed during the 9th century. Acute, fatal alcohol poisoning must have been rare before that time because of the enormous quantities of fermented liquor necessary to accomplish this feat. The possibility of fatal poisoning by alcohol is not known by laymen today even though death after a drinking contest is not a rarity. Distillation provided not only stronger drink but also a quicker kick; it was not until this facet was added to its poisonous properties that alcohol became a serious problem in the Western World.

The physical effects of chronic alcoholism, which is usually complicated by the effects on the peripheral and central nervous systems and the liver of concomitant reduction of intake of food and vitamins, were not accepted by all physicians until the early 20th century, although we know that the effects were common after spirits became widely used in Europe.

Alcohol is a drug that is strongly entrenched in our culture. Although the antitobacco group make a similar claim for their candidate, alcohol has probably caused more disease than any other drug in man's history. It is a major cause of social disability: there are at least 2,500,000 socially useless alcoholics in this country and about as many more whose productivity is curtailed by alcohol; it accounts for countless broken homes, broken marriages, serious automobile accidents, and other tragedies—and much of our crime. It is also pleasurable, habit-forming, and addictive and causes physical disease, psychosis, and death. Although used as a universal remedy in medicine until recently, we now know that it has no important therapeutic actions; it is a mild, prompt sedative and a poor antiseptic; it is not, as is so widely assumed, a stimulant at all.

Montezuma's Revenge does not compare with what might be called Pocahontas's Revenge, for it was the Red Man who introduced the invaders from the Old World to tobacco. The effects of tobacco on the central nervous system that the smoker seeks (causing definite changes in the electroencephalogram, with sensations that the smoker cannot describe) are presumed to be caused by nicotine; the ill effects, by tars. It is probable that the sites and rates of absorption differ with the different methods by which tobacco is used.

Nicotine is one of the very potent natural poisons; it is rapidly absorbed through the skin, on which a few drops may be fatal. But pure nicotine was not extracted from tobacco leaf until long after smoking was established as an acceptable habit; it is so potent and so quickly fatal that man has never been able to use it on himself for pleasure. It is used as an insecticide, however, and before World War II more tobacco was consumed in the manufacture of nicotine insecticides than for smoking. Now the situation is reversed; we use other poisons for the insects and reserve the tobacco for ourselves.

The cigarette is more attractive to many than the cigar or pipe (the forms used by the American Indian) because it leads to inhalation of higher concentrations of vapor into the lungs, a site of almost instantaneous absorption. The tremendous increase in tobacco smoking during the last decade almost entirely reflects increase in the use of cigarettes and is probably related to the intensity of effect of the drug. Unfortunately the hot smoke of the cigarette contains tars as well as nicotine; even hard-sell advertisements for filter cigarettes do not claim separation. Careful studies indicate that the smoking of pipes or cigars and the chewing or sniffing of tobacco do not cause cancer of the lung, which relates statistically to cigarette smoking alone (about 40,000 deaths annually in the United States). It is also held by many that tobacco causes heart and vascular diseases (*3*).

Were tobacco introduced as a new drug would our society, with this information at hand, accept or reject it? Would we permit a known carcinogenic agent to be used for anything but the treatment of cancer?

Opium was used before history was recorded. In the Orient, where it is still used in the natural form in the old traditional way, it is not considered as antisocial as it is in Western cultures, and drives against its use have been largely unsuccessful; there it is not as much associated with crimes of violence as it is here. While opium came to Europe perhaps 2000 years before Christ (*4*) and was long used in medicine as well as for other purposes, it was only after the extraction of morphine (1805) and the invention of the hypodermic syringe (1834), which made possible more rapid and

more intense effects, that addiction became a substantial problem in the West. Although opium abuse (see De Quincy) was long established in Europe, it did not become an important addiction in this country until about 100 years ago.

Acetylation of morphine to make heroin (1890), a much more potent drug, vastly aggravated the problem. At the turn of the century it was estimated (however crudely) that there were 1 million narcotic addicts in this country; measures, including the Harrison Narcotic Act, were initially effective in reducing this number, but now the morphine (in fact heroin) habit is spreading again.

Crime committed in the pursuit of morphine constitutes a very large proportion of all crime in New York City (*5*). The death rate of addicts is much higher than of the general population, accounting in part for their lower average age; in part it reflects accidental overdosage. Those able to get the drug freely (having money, chronic illness, or special connections) do not seem to suffer in any way from the habit however long it continues. A large hospital study bears out the contention that longstanding addiction to morphine has no deleterious physical or mental effects and, except for the unproductive periods of reverie, no social detriments (*4*). Crime is a means of getting narcotics to satisfy the habit; it does not result from pharmacologic action of the drug.

Coca leaves have been chewed by many South American Indians for centuries for its central stimulant action, often to help them work at high altitudes or while undernourished. Importation of the leaf did not lead to chewing in Europe. However, when extraction of pure cocaine from the leaf made possible intense and rapid effects, the cocaine habit rapidly developed. Freud, the first physician to procure pure cocaine, tried it, liked it, used it for his depressions, recommended it, and was, by his writings and teachings, largely responsible for the rapid spread of the habit at the turn of the century. He was publicly denounced at a medical meeting as the cause of the "third scourge of mankind"—the first scientist to be blamed for a major drug disaster (*6*).

Although habit-forming, cocaine is not tenaciously so, and, since it is not physiologically addictive, strong personalities like Freud and Sherlock Holmes had no trouble in controlling the habit. The Harrison Narcotic Act was far more effective in limiting the use of cocaine than of morphine or heroin. Cocaine acts as a potent and sometimes unpredictable central stimulant, and rash and violent behavior have been attributed directly to its action; it is clearly antisocial. It is also highly toxic and, because of irregular and sometimes unanticipatedly rapid absorption, occasionally fatal (*7*).

Hashish, marihuana, bhang, pot, and a multitude of other names are used to describe cannabis and its preparations. This hallucinogenic drug was in use before history was recorded, and since one variety or another of cannabis will grow almost anywhere in the world, with little or no work required for its husbandry and little art for effective preparation, it is not surprising that the drug is easily available and widely used.

Cannabis is habit-forming but not addictive; the habit is not difficult to break. A chronic effect on the brain is suspected. In the Middle East and North Africa where the drug (in the form of hashish) is used by many in large amounts from childhood onward, the population of mental hospitals has a much higher proportion of chronic users of hashish than does the general population; there is then suggestive evidence of chronic mental effects. Chronic users there are largely socially useless (*8*).

About 25 years ago the purified principle of cannabis, tetrahydrocanabinol, was isolated, but it is so difficult to extract, while simple preparations are so effective, that it has not entered into illicit traffic; only a few humans are known to have used it (in experiments) (*9*).

Mescaline (peyote) is a psychedelic drug that has long been used by North American Indians and is now used in the Native American Church (Indian) in religious rites. The ritual standardized and limited all aspects of use, including dosage; adverse effects were not noted.

In modern times, drugs with similar or closely related effects on the brain, psylocibin, LSD (lysergic acid diethylamide), and amphetamine (Benzedrine), have been used experimentally without serious adverse reactions. Lysergic acid diethylamide is far more potent than any psychedelic drug previously known, far more potent in fact than any other drug acting on the brain (*10*). Preliminary conditioning, ritual, and "set and setting" assist the psychedelic drug in developing particular effects with the low dosage used in religious rites and experiments, whereas the layman, usually a "loner" taking the drug without psychological "props," takes a much larger dose in order to experience effect. Since LSD has gotten out of the hands of the authorized experimenter (and mescaline, out of the hands of the Native American Church), indiscriminate, uncontrolled use at excessive dosage of, and serious reactions to, these drugs are common (*11*).

With the coffee break a union requirement for some workers, it may be a surprise that tea (which usually contains even less caffeine per cup than coffee) came in for some grave appraisal in the early 18th century when the habit began to establish itself in England. Acrimonious and, since they failed to stop it, now amusing literary polemics on the physical dangers and values of tea to body, mind, and soul were rampant before Samuel Johnson and other tea addicts won.

Caffeine and closely related xanthines are not now considered causes of serious drug adversity. The xanthines are widely distributed in nature and many cultures have found xanthine beverages to their liking. In ours, the central stimulant action is felt by all who use it at breakfast, luncheon, coffee breaks, dinner, and other odd times. Caffeine is a habituating drug and, since caffeine withdrawal causes in many people headache and general letdown that are relieved by drinking coffee, it also satisfies the definition of pharmacologic addiction. It is not a serious addiction, however, and "cold turkey" treatment is no great trial for the "addict."

Caffeine causes insomnia and restlessness, which can be overcome by proper timing and dosage. Caffeine also stimulates the secretion of gastric juices, which fact may be good for digestion (and logically calls for coffee or tea before a meal rather than after) but is bad for ulcers—actual, incipient, or even healed. For those wishing to experience the cerebral effects of caffeine, there seems to be no other medical reason why this drug cannot be taken ad libitum. Here, then, is a drug that causes pleasurable central stimulation and waste of time during working hours, a habituating and addicting drug that is now sanctioned by an established position in every meal of the day. Were this mild central stimulant a new drug, would its characteristics be considered desirable, ac-

ceptable, or adverse? Would its unrestricted use be permitted? Would Dr. Johnson win again? (*12*).

By far the most important mass drug poisonings, in the usual meaning of poisoning, were the sporadic epidemics during the Middle Ages of St. Anthony's Fire [caused by rye rot (ergot)] whose consequences were more horrible than those of leprosy (*1, 13*). The syndrome was characterized by pain, abortion, loss of fingertips, and psychosis (perhaps due to LSD, which is a congener of ergotamine, the active principle of ergot, and very easily derived from it). The epidemics diminished sharply when the cause was recognized, and disappeared at the turn of this century.

Therapeutic agents in use during the Middle Ages also caused mass poisoning (*1*). Mercury induced reactions in a large proportion of patients who took it, a steady stream of saliva and loss of teeth being among the less consequential ill effects; permanent damage to the kidneys was more substantial. But the therapeutic value of mercury in treatment of syphilis was presumed to justify its use, for in the widespread epidemics of the 16th century the acute form of syphilis apparently was far more virulent than now. Although mercury was only palliative, it was the only effective antisyphilitic drug that medicine had to offer, and the hazards were accepted as justifiable in the treatment of a serious disease. Hence mercurialism is not ordinarily cited as an example of mass drug disaster; it was expected!

Few records were kept during the early searches for new drugs, and no systematic attempts were made to bring out their potential for adversity. Withering's reports show toxic effects from digitalis in about 15 percent of his patients.

While most of the drugs of disaster were first used without help from Science, their use was often under better control before technologic improvements stimulated it—improvements such as distillation of alcohol, extraction of morphine from opium and of cocaine from coca leaf, invention of the hypodermic syringe, acetylation of morphine to heroin, modification of the cigar to the cigarette—by making it possible to obtain more intense and more rapid effects than with the cruder products.

One should note that except for mercury, which was used despite recognition of its hazards and the accidents, all the great drug catastrophes were caused by drugs affecting the central nervous system. None resulted from medical usage; all resulted from deliberate nonmedical use by the layman or accidental exposure to poison. Some drugs are still with us as major social problems but are rarely recognized for what they are; all dwarf the horrible thalidomide disaster. These may be fairly compared with the catastrophes that have occurred during the continual trial in man of vast numbers of new synthetics and newly isolated chemicals of nature in recent years.

Modern drugs acting on the central nervous system, with important adverse effects, have displaced some old drugs having similar effects; they have not enlarged the base of drug disaster. Meperidine (Demerol), which was introduced about 30 years ago, has become an outstanding cause of accidental therapeutic addiction; coincidentally, the rate of accidental therapeutic addiction to morphine has declined. Lysergic acid diethylamide is not a new type of drug but one of the ancient family of psychedelic drugs (only the word psychedelic is new).

Addiction to barbiturates is often substituted for alcoholism because their effect on the central nervous system is rather similar to that of alcohol. Barbiturates are habit-forming and addicting, but they do have advantages over alcohol: they have no odor, they are lighter to carry and easier to hide, and they can be easily taken surreptitiously. They also disturb the appetite less (having no significant caloric value) and so do not result in the nutritional deficiences that often complicate chronic alcoholism and cause serious physical disease. The extent of addiction to barbiturates is unknown, but it is certainly a large problem. Whether the total problem has been extended, along with the substitution of barbiturates for alcohol, is unknown. But there is another important question: Which type of addiction is preferable?

Compare the following with the disastrous toxic effects associated with the mere palliation of syphilis with mercury. Chloramphenicol has a rate of serious reaction of perhaps 1:50,000, but its unique curative action in typhoid fever alone justifies its continued availability. If it is used when it is not really needed, any adversity derives not from the drug but from the prescriber. Penicillin causes 300 to 400 deaths annually from allergic reaction. The cure of many acute infections so far outweighs the danger of allergic reaction, in a population in which perhaps 10 percent are sensitive, that its continued use is clearly justified. The tetracyclines cause disturbances in bone formation, but they cure far too many infections for this fault to be a reason for any restriction other than proper prescription. Highly toxic drugs are regularly used in cancer chemotherapy, but the dangers are known and carefully weighed. Other modern drugs also have substantial benefits as well as clear dangers that are recognized and limited by control; that is much more than can be said for the old drugs, most of which had almost nothing but adversity to offer—an unhappy conclusion that led Oliver Wendell Holmes to recommend that all drugs but opium be jettisoned. There have been very few serious drug problems during the 20th century.

About 10 years ago a suspicion, after smoldering for perhaps 50 years, led to acrimonious controversy: Was phenacetin, a drug about 75 years old and used for that period the world over in a variety of remedies, and sold without prescription in large amounts for the relief of everyday aches and pains and headaches, the cause of sporadic cases of serious kidney disease? This complication had been reported only in connection with continued massive dosage of phenacetin analgesics over many years. Thus it was 65 years before the question was raised, and it is still uncertain whether the association is a causal one. In any case, phenacetin is a drug prescribed for himself by the layman, and at least in the United States the kidney complication is uncommon.

During the last years of prohibition in the United States there was an outbreak of serious, irreversible, toxic peripheral neuritis in the South; it was known as the jakes. The cases were numerous and countless in the sense that the number is unknown. The cause was traced by a pharmacologist detective to contamination of fluid extract of ginger with tri-*o*-cresylphosphate; once this was done, the jakes promptly disappeared.

In the 1930's "Elixir of sulfanilamide" was marketed and sold widely because it was a palatable solution of the first of the new wonder drugs. The concoction was sold without anyone troubling to find out whether man or animal could tolerate the solvent (ethylene glycol), which also served as the

vehicle for the flavoring; the "elixir" was acceptable for infants who could not swallow tablets. After about 100 deaths in infants, it was demonstrated that ethylene glycol is a potent renal poison in animals. It was possible to stop the sale of this preparation not because it was lethal but only because it was mislabeled: it was not a true elixir since it did not contain alcohol. This episode led to amendments of the Food and Drug Act that for the first time required tests on animals for toxicity before drugs could be sold commercially.

About 20 years ago lithium chloride was introduced as a substitute for salt for persons on salt-restricted diets. It was most successful because, unlike all other substitutes, it tasted like salt; it was in fact ten times as salty as salt. Because heart disease requiring salt restriction is exceedingly common, a great deal of lithium chloride was taken. It was not, however, sold as a drug but as a food in food shops; thus were circumvented the requirements for toxicity testing. About 500 cases of disturbance of the central nervous system were quickly recorded, and similar effects were soon shown to occur in animals. The drug was then officially designated a drug and removed from the market. Whether or not the government designates a chemical a drug clearly determines who may be poisoned by it without restriction.

In recent years triparanol (MER/29) was introduced on the drug market after meeting the requirements of the Food and Drug Administration. The drug hindered the synthesis of cholesterol and was presumed, therefore, to be useful in the prevention and treatment of arteriosclerosis. It caused a variety of adverse reactions in about 500 patients, ranging from baldness to impotence to cataracts, before it was withdrawn. Similar effects, however, had been noted in experimental animals.

Thalidomide caused what was probably the greatest drug catastrophe of our time; about 5000 cases of phocomelia are attributed to it. Yet the horror may well have been greater but for modern methods of pharmacologic detection. Identification was difficult; no one thought of drugs as teratogenic; the vital statistics required for control purposes were poor; the sensitive period during gestation was brief, so that many pregnant women who took thalidomide fortunately bore normal children, thereby helping to obscure the teratogenicity of thalidomide. But there can be no question; 50 years ago the disaster would have been far greater.

The most recent experience with the screening of new drugs is very impressive when the whole picture is examined. Of all the synthetic chemicals, plant extracts, and microbial metabolites that were tested for clinical utility during 7 recent years, only 250 were found by the Food and Drug Administration acceptable for general clinical use. The research director of a pharmaceutical manufacturer recently estimated that only one of every 3000 new chemicals tested in the laboratory, for possible usefulness and danger in therapy, is finally passed by the Administration for use in clinical medicine (only 20 of the 3000 prove safe enough for testing in man) (*14*). If this estimate is projected backward, the 250 drugs accepted into commerce result from the screening of about 750,000 drugs.

Of this large number, only eight caused serious unpredicted reactions in man. With two of the eight, more extensive standard experimentation with animals would have revealed the particular dangers; as to the remaining six, we have no preliminary tests that would have revealed what was discovered after extensive trial in man. Some deaths resulted from use of these six drugs, but they were few and the drugs were promptly withdrawn from the market when the reactions were noted. As far as one can judge on the basis of these six drugs, it is possible that a more effective early alerting system may have further reduced the small number of accidents.

Our current experience clearly shows that we do not know all that should be known about drug adversity; that, although our preliminary systematic studies rule out the vast majority of unduly hazardous drugs, we do not yet know how to predict all adverse effects of drugs. Widespread experience in man is still needed to develop the full story, especially to elicit the rare events. Often the rare events in man are never seen in animals at all. For this reason a probationary period of about 3 years has been suggested, during which all physicians would be required to make special observations and to turn in reports of both good and bad unpredicted reactions to new drugs (*15*).

Experience with catastrophic reactions to drugs is that drugs that act on the central nervous system are the most frequent cause of mass disaster; that the danger of mass catastrophe becomes substantial only when the drug escapes from control by the medical profession and into the hands of the layman; and that science increases the possibilities of mass drug catastrophe by technologic advances—often very simple ones—that make possible more intense and more rapidly developing effects on the central nervous system, either increasing the effectiveness of old drugs or creating new drugs having similar effects but greater potency or more rapid action.

In terms of the potential for mass catastrophe, inherent in new drugs, that I have outlined, there are now no new drugs having unique effects on the central nervous system, but there is always the possibility of a unique action that man finds especially pleasurable; and there is a special danger because little can be learned by experimentation on animals about actions of drugs on the central nervous system of man that make for addiction. Most immediate is the still-undetermined hazard of the very potent and easily manufactured LSD, which is out of control, still available to the interested layman, and widely and indiscriminately used. The only comforting feature is that LSD is not, in the pharmacologic sense, an addictive drug; if it needs to be controlled it should not pose the same great difficulties as do narcotics.

Perhaps more important today to all of us as a source of mass drug hazard (than new chemicals introduced for therapy) are substances that are not always defined as drugs and are used in industry or agriculture—pesticides, herbicides, gasoline additives, and so on. We are chronically exposed to them because of indiscriminate contamination of our environment, and neither physician nor layman can avoid them. These should count as drug hazards (*16*).

Agreement on definition of drug and drug adversity is essential to progress and safety. We seem to be unwilling to apply definitions of drug and drug adversity that are logical and consistent with the meanings of the science of pharmacology and can be used in relation to the acceptability of new drugs in medicine, at the same time making sense of generally accepted practices with common drugs which today are more wasteful and destructive of health and life than all the new

drugs tried, used, and discarded during the last century of pharmacologic progress. What needs to be understood and incorporated into the modern definition of drug adversity is not the truism that "most drugs" or even "all drugs" are toxic (we have known this for a long time), but that all effects of drugs—good, bad, and indifferent—are examples of drug toxicity, a selective toxicity producing alterations in structure and function, which by some happy chance are useful to the sick man, or, by some misfortune, make matters worse for him (*17*).

Our new drugs are the products of a well-grounded scientific program that has led to the great positive achievements of modern therapeutics. The benefits must be weighed against the cost, which is far less than ever before; the benefits are incomparably greater. The concept that modern pharmacologic advance has left a new trail of disasters in its wake is simply untrue. What is true is that drug development has grown and expanded very rapidly, that reportage is better than ever, that observation is more acute, and that we no longer placidly accept adverse reactions of drugs. In some cases of old drug problems, matters are even becoming worse.

Unfortunately the layman views experimentation with drugs as a new, dangerous, and cold-blooded scientific pastime conceived by the Nazis, whereas in fact it is merely a safer, more public, and better controlled version of the natural, unwitting, inevitable, historic, and too-often-catastrophic drug experimentation in man that started with the witch doctor.

A great current danger is that legislation based on an inconsistent, puritanical, and illogical definition and lacking a historic view may well limit drug research and at the same time may aggravate old, and create new and serious, problems of drug adversity.

There is no aspect of drug experimentation on man that is not more ethically handled now than in the time of Hippocrates, Galen, or Withering—and now handled more safely. If a code is needed to define the ethical basis for drug research in man, it should be designed to protect man from mass disaster as well as to preserve the rights of the subjects of drug trials, and at the same time to foster progress in therapeutics. It should take into account past as well as current history—not merely thalidomide but penicillin and a host of other modern drugs—and it *must* have logic and consistency. It must recognize and weigh the accomplishments of pharmacology as well as unavoidable accidents and rare and unpredictable reactions to drugs.

If drug disasters have become less frequent, one cannot attribute the fact to legislation. All our outstanding modern achievements in pharmacotherapy preceded our new drug legislation; it is more logical to conclude that they result from the basic interest of the biomedical scientist in the health of the community and from his drive. It is a matter of medical science keeping its own house in order.

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Implant Biotelemetry and Microelectronics

Report on developments in implant telemetry, associated problems, and the potential of microelectronics

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Implant biotelemetry is a technique of biomedical instrumentation for conveying information from within the body of an unrestrained living organism to a remote location through a wireless transmission linkage. The essential blocks of such a system are shown in Fig. 1. The transducer or sensor converts the biologic parameters into electrical signals that can be processed by the conditioner. The signals are then transmitted by the radio transmitter to a remote receiver and recording or display facilities. The implanted transmitting unit, consisting of the transducer, conditioner, and radio transmitter, is located totally within the body of the organism under study. The location may be intracavitary, such as within the intestines, mouth, or bladder, or may be inside the internal as well as external surfaces of the body—subcutaneous or deep within the tissues. We now report some developments of telemetry systems to be used inside the body, after a brief review of the history and existing systems of biotelemetry.

Although radio transmission of analog signals has been known since 1844 (*1*) and frequency-modulation radio links were used to transmit pneumograms in 1948 (*2*), extensive development of biomedical telemetry techniques did not really get started until the transistor was discovered in 1948 and made

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