THE DISEASES DRUGS CAUSE

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The last quarter-century has seen a pharmacologic revolution. Like most great revolutions, it has had a great impact for good. Like all great revolutions, it has produced grievous injury for some. Like other great revolutions, it cannot ever be completely undone, even were we to desire it. I shall not discuss the benefits of the drug explosion, but some of its harmful consequences. Therefore, this presentation will lack balance, although it may gain in emphasis. In any case, it is not, I submit, either a hysterical or an exaggerated picture which I shall draw.

In 1955 Barr pointed out that major toxic reactions and accidents occurred in 5 per cent of patients admitted to the medical service of a great hospital [1]. More recently, Schimmel has analyzed the same problems at another famous university hospital [2]. He found that roughly one patient in five suffered some iatrogenic complication, and that half of these reports could be classified as drug reactions. A popular journal dealing with clinical pharmacology and therapeutics runs a regular feature in each issue devoted to what is called, somewhat ironically, "Diseases of Medical Progress." Physicians in the United States have become accustomed to warnings from either the Food and Drug Administration or pharmaceutical firms indicating some new mischief caused by prescription drugs. The forms of toxicity responsible for such warnings have ranged from agranulocytosis to cataracts, from liver toxicity to severe hypertensive crises and fatal cerebrovascular accidents.

It is apparent not only that a problem exists but also that, despite the fairly high frequency of reported trouble from drugs, the publicized cases constitute merely the floating tip of an iceberg, with much of the difficulty

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remaining hidden beneath the surface of our awareness. This statement is in part based on the knowledge that a survey at my own institution of one hundred randomly selected charts signed out by the house staff as having shown no untoward effects from drugs revealed that 7 per cent of the patients could be unequivocally classified as having suffered drug reactions. In addition, however, my opinion is strongly affected by the abundant historical evidence to the effect that a varying length of time is required before the medical profession becomes fully aware of the trouble that a drug can cause, and that this interval can be quite long at times. It may be said without fear of error that many of the drugs now on the market have a potential for causing difficulty that is incompletely appreciated.

Let me give some substantiation to this last comment. For at least three years the gallbladder dye bunamiodyl (Orabilex) was in wide usage in our community. It seemed to be a most efficacious agent for X-ray visualization of the gallbladder and was considered to be essentially free of serious side effects. Then some members of our staff observed a patient who manifested renal failure after exposure to the drug. Inquiry quickly revealed that a considerable number of such cases had been seen elsewhere in our city and in nearby Washington and, furthermore, that one could show a reasonably high incidence of diminished renal function if one studied unselected patients undergoing X-ray examination of the gallbladder with this dye [3].

The story of phenacetin is perhaps even more instructive, in view of the extraordinarily long interval between its introduction and the realization that the compound may be capable of causing "interstitial nephritis" and papillary renal necrosis. Although the relationship between phenacetin and this insidious renal disease is by no means clear-cut, there is a large amount of circumstantial evidence incriminating the drug [4]. Another therapeutic standby, the salicylate group, was in widespread use for years before it was generally recognized as a cause of serious gastrointestinal bleeding. It is not difficult to demonstrate in man or laboratory animals that salicylates have corrosive topical effects [5] which can lead to bleeding—yet fifty years of usage elapsed before the profession became aware of this propensity. Why?

Clearly, we are in our present dilemma in part because of the very richness of the toxic spectrum produced by drugs. Some side effects, to be sure, are merely extensions of the therapeutic effects of the compound and are

not likely to be missed clinically or to fail to be predicted from animal experimentation. I refer to such things as the oversedation seen with barbiturates, the excessive cardiac depressant effect that can be caused by quinidine, the bleeding from excessive dosage of anticoagulants. There are other side effects which, while not extensions of the therapeutic effect, are nevertheless both predictable and obvious, such as the constipating effect of codeine. But much of the difficulty from drugs is subtle, unpredictable, or unsuspected, and it may be enlightening to examine the reasons why this is so.

One important difficulty stems from species differences. An example is the inability of the dog to acetylate sulfonamides. If one were to rely on a species which cannot achieve this biotransformation, obviously one could not predict that man, a species which *can* carry out this acetylation, may get into difficulty from the precipitation in the kidney or ureter of the less soluble acetylated metabolites of sulfonamides. By contrast, the dog is extraordinarily susceptible to quinine, becoming blind at plasma concentrations that are tolerated quite readily by man. The monkey is very sensitive to compounds of the meperidine class and relatively insensitive to the toxicity of isoniazid. A more interesting and potentially more important difference has come to light in recent years. I refer to the ability of rodents and other laboratory animals to increase the rate of metabolism of compounds administered to them chronically. Work by Burns and Conney [6] suggests that for at least some drugs the rate of metabolism is speeded up to such a remarkable degree that after a number of weeks it is almost as if the animal were not receiving any drug at all, the blood concentrations of drug being essentially unmeasurable. This obviously has great implications for chronic toxicity studies and for extrapolations from lower animals to man.

But there are serious difficulties in predicting toxicity in man apart from species differences. One problem is related to the sheer numbers of experimental animals required. If one wishes to detect a side effect that is produced just as frequently in animals as in man, but with an incidence of one in twenty, one will need to study at least 58 animals to be 95 per cent sure of picking up the effect, and 90 animals to be 99 per cent sure. If one is looking for a side effect that occurs only once out of a hundred times, then one has to study close to 300 animals to be 95 per cent confident of detecting the effect, and over 450 animals to be 99 per cent sure [7]. When one

considers that many important and irreversible side effects in man occur only once in many, many thousands of cases, it is obvious that predicting such trouble from animal studies cannot be done easily.

There are many examples of inadequacies in our toxicology tests, attributable at times to our ignorance and at other times to our ineptness. Owens, in a review of a number of experimental anti-cancer drugs [8], found that the prediction value of animal tests for human toxicity affecting the liver, kidney, gastrointestinal tract, or bone marrow was reasonably good, whereas for central nervous system toxicity in man the predictive value was questionable, and for skin reactions it was nil. On some occasions, however, one can go back and show that the problem is more often failure to look properly for toxic effects than inability to predict from animal data. It appears, for example, to be relatively easy to produce cataracts with triparanol (MER-29) in animals. The congenital anomalies produced by thalidomide can be mimicked, albeit with some difficulty, in rodents. The difficulties that newborns have gotten into from chloramphenicol—which can be traced to undeveloped enzymatic systems for glucuronidation of chloramphenicol in premature infants—could in fact have been predicted from the toxic effects seen in mature animals given large enough doses to achieve blood concentrations of the drug similar to those achieved in prematures with smaller doses [9].

An important category of problems arises from the complications introduced by human disease. For example, the precipitation of acute porphyric crises by the administration of barbiturates depends on the presence of an inherited metabolic fault: "toxic" porphyria *can* be produced in animals, but the situation is not at all the same as the human disease [10]. The same type of situation exists in those individuals who show increased susceptibility to succinylcholine because they are genetically endowed with atypical plasma choline esterase [11]. Patients with a latent gouty diathesis are probably more likely to develop acute gouty arthritis when on thiazide diuretics than are non-gouty individuals. Allergic persons will show certain kinds of drug reactions more frequently than will non-allergic people. The curious syndrome of fatal lactic acidosis in diabetic patients receiving phenformin (Diabenese), the oral hypoglycemic agent, may perhaps be related to special problems encountered by diabetics in handling lactates under a variety of circumstances. The precipitation of disseminated lupus erythematosus by penicillin, hydralazine, or anti-convulsant drugs seems

related to an antecedent "lupus-Anlage" [12]. The precipitation of angina pectoris by hydralazine obviously demands the presence of coronary artery disease as well as a species which can report pain.

There is one fascinating and especially tricky aspect of drug toxicity. In a number of reported studies it appears that some drugs do not so much produce a specifically high incidence of one toxic manifestation as an increased incidence of difficulty of various kinds. It does not take much prescience to be impressed by an increase in the incidence of a striking defect like phocomelia. Only invincible ignorance would not suspect a toxic reaction in a child born dead because of suffocation from a huge goiter resulting from the mother's ingestion of iodides during pregnancy [13]. But consider for a moment the results obtained in one clinical trial studying patients subjected to operations for cancer. The purpose of the trial was to determine whether an alkylating agent given at the time of surgery might prevent recurrence of cancer. It was found that patients subjected to surgery plus drug were dying three times as often in the immediate postoperative period (first thirty days) as were those patients subjected to surgery alone. *An analysis of the deaths, however, indicated merely an increased incidence of all types of deaths, not a preponderance of any one cause of death.* The same sort of thing has been observed in patients with acute leukemia treated with very high doses of steroid [14]; and an increase in common cardiovascular causes of death has been reported in senile patients treated with estrogen [15]. The situation is reminiscent of the general increase in deaths from many causes that has been seen in some of the analyses of the life history of cigarette smokers [16].

Although experts disagree on the definition of aging, it can be defined as a biological process which causes increased susceptibility to disease. It is known that a large but non-fatal dose of radiation given to young adult mice can cut down life span [17]. Although similar experiments with chemicals in rodents have not been successful in accelerating aging, it seems dangerous to assume that drugs may not cause such effects in man. There is no question, at least, of the relationship between specific disease processes and life span; and for some agents, such as steroids, there is no question of the ability of the drugs to increase the incidence of many "diseases" [18]. In addition, such a situation can give rise to serious recognition problems. It is difficult enough to be sure that a drug like iproniazid caused liver damage when the clinical and laboratory picture mimics en-

demic hepatitis, or that aspirin caused gastrointestinal bleeding when the picture mimics benign peptic ulcer. But reflect on how much more difficult are the enumeration and appreciation of the host of drug-caused ills related to steroids, ranging from diabetes to psychosis, from peptic ulcer to osteoporosis. And if one accepts drugs as the cause of such multiple ills as these, is it not possible to wonder about others? Might the short- or long-term administration of drugs be in some way carcinogenic? (It already has been suggested that they can be diabetogenic [19].) Is the fact that the average pregnant American female has been in the habit of consuming four drugs during pregnancy (excluding nutritional supplements and home remedies) related in any way to the high "normal" incidence of congenital anomalies of all kinds? I know of no significant evidence that such worries are founded on fact, but I also do not know why we should cavalierly rule out such possibilities.

Another large area of difficulty is attributable to the interaction between drugs and certain non-drug factors. There are at least seven classes of compounds known to sensitize the skin of individuals to sunlight [20], but such photo-allergic or photo-toxic rashes follow the taking of drug only if there is exposure of the skin to certain wave lengths. A similar situation is seen in patients who have been on long-term steroid therapy and who are subject to considerable extra risk if exposed to surgery.

A whole raft of other drug reactions might be called "social" interactions. It is well known that mice given amphetamine and other central nervous system stimulants suffer more toxicity from such drugs if they are exposed to other mice than if they are housed individually [21]. There are counterparts of this in man (such as the increased danger of convulsions in the patient who has taken excessive stimulants and is not protected from outside stimuli), but it is obvious that other important kinds of drug-induced disease are related to the presence of one's neighbors. Patients receiving steroids are susceptible to infections of various kinds, including those they acquire from other people in their environment. Patients receiving certain anti-cancer drugs are prey to infections because of the suppression of their white blood cell defenses, and may have to be isolated from other individuals until their marrow can regenerate. Patients receiving antibiotics can have their normal bacterial flora replaced by disease-producing strains acquired from the environment. An especially perverse example of social interaction is caused by resistant strains of bacteria

developing in patients receiving antibiotics. In such cases not only may the person directly involved himself suffer an overwhelming infection from a resistant strain, but he may pass it on to other individuals, in which case a patient may in a sense suffer drug toxicity without ever having received the drug. (There is some resemblance between the latter situation and the infant who suffers a congenital anomaly because his mother took thalidomide or grows up with discolored teeth because she ingested some tetracycline during pregnancy [22].)

In addition to the interactions mentioned, there are the increasingly important interactions *between* drugs. With the flood of therapeutic agents available to the modern physician, patients are being treated more and more with several drugs given simultaneously. Precipitation of digitalis toxicity by washing out potassium from the body by thiazide diuretics or potentiation of all kinds of drugs by monoamine oxidase inhibitors are good examples of this phenomenon. Recently one of these inhibitors, tranylcypromine (Parnate), has been accused not only of potentiating the toxicity of other drugs, but also of producing serious side effects in patients who have been eating cheese [23]. It has been suggested that this is due to the presence in certain kinds of cheeses of amines of biologic import, which in turn act as "drugs" in patients receiving tranylcypromine.

Another source of pharmacologic trouble might be called "breaks in control techniques." In this category I would place technical manufacturing inadequacies of various kinds and laboratory errors, perhaps best exemplified by the danger that a patient on anticoagulants is exposed to because of the inability of a lab to perform proper prothrombin times [24]. Not long ago tetracycline had to have its formulation changed because it became apparent that a reversible type of Fanconi syndrome was produced by the ingestion of outdated antibiotic [25]. Apparently, under certain conditions of humidity and heat, this antibiotic formed toxic degradation products. The substitution of lactose for citric acid in the capsules seemed to be sufficient to remedy the difficulty. Not long ago there appeared a report of a minor epidemic of precocious puberty in youngsters [26] traceable to the adulteration of isoniazid by female sex hormones in an improperly cleaned tablet-making machine. A recent paper pointed out that a toxic halogenated butene is present in minute amounts in the general anesthetic halothane (Fluothane) and that the concentration of this impurity is increased when the anesthetic is used in "copper kettle" vaporizers

[27]. It is not clear that this impurity is indeed the cause of the hepatic necrosis which has been associated with halothane, but it is a possibility. The same can be said of the chloracetanilid impurity present in varying amounts in batches of phenacetin, and which was not formed by the now "obsolete" older chemical process for manufacturing phenacetin. It is provocative to note that reports of phenacetin nephritis in the world literature have appeared subsequent to the change in manufacturing technique —although there are certain facts hard to reconcile with the theory that the contaminant is actually the causal agent of the renal difficulties.

There are certain other "hidden" sources of trouble which plague the physician. One could include here surreptitious self-medication, ranging from hyperthyroidism due to the ingestion of thyroid tablets to puzzling bleeding in patients secretly taking anticoagulants. There is a broad spectrum of danger from such factitious disease, from mild inconvenience to successful self-destruction. There are "medication errors" of various kinds [28], ranging from a pharmacy dispensing the wrong drug to wholesale inability of patients to follow directions about taking medication. Many reports testify that as many as 50 per cent of patients are incapable of following doctors' directions, so that excessive doses of drugs may be occasionally ingested without this fact being readily apparent to the physician. Other potential sources of trouble are antibiotics in milk [29] and color additives in our food or medications (cf., for example, the use of phenolphthalein in chocolate and cake icings and the occasional presence of this agent in chocolate tablet coatings [30]).

Finally, there is the category of indirect pharmacologic harm caused by postponing proper therapy and impairing proper diagnosis. The antibiotic furaltadone (Altafur) is an example of the former. This ineffective antibiotic, when administered to patients with serious staphylococcal infection, harmed the patients perhaps less by its inherent toxicity than by keeping the patients from receiving a truly adequate antibiotic. The same type of consideration applies to obese diabetics who, instead of being tried on weight-reducing diets, are automatically given oral hypoglycemic agents. There is also, however, the question of confusion in diagnostic examinations caused by drugs. Tests of various kinds can be strangely modified by chemicals administered to patients. Examples of this are spurious increases in serum protein-bound iodine or amylase values, false-positive urinary tests of various kinds, megaloblastic marrow changes resembling

Addisonian pernicious anemia caused by barbiturates, and lymphomatous node changes caused by anticonvulsants.

What can we do about these problems? One would hope for more than guilt-laden breast-beating or tortured mutterings of "mea culpa." It should be possible to minimize some of these problems if we approach them rationally. First of all, we need better data on drug toxicity. The recent experiences of the Expert Committee on Enovid set up to advise the Food and Drug Administration indicate how impossible it is to handle toxicity problems sensibly when the basic data are lacking. If one does not really know the incidence of drug-related mortality from thrombo-embolism, and one does not know the incidence of thrombo-embolic disease in a comparable population not taking Enovid, one cannot possibly determine accurately the presence of increased risk, even by applying the most sophisticated statistical techniques. (One wag has suggested that the application of Poisson techniques to fishy data really does not get around the basic trouble.) To handle such problems we must have reliable data.

Furthermore, it is not enough to accumulate reliable toxicity data: they must be publicized. It is an interesting phenomenon that the first report of a new kind of drug toxicity seems to flush out of the bushes a flock of similar reports. This was true of deaths from intravenous injections of mercurial diuretics; it was true of the toxicity I referred to from bunamiodyl; and it was true for aplastic anemia due to chloramphenicol or perchlorate.

We must, too, upgrade toxicologic research, both in quality and in quantity. We must improve our prognostic ability—our ability to predict drug toxicity in going from animals to man—while recognizing that we shall never be able to predict from animal studies every untoward effect in man. In the absence of solid theoretical underpinnings, this approach may have to remain largely empirical, with *post hoc* correlations of reliable animal data and reliable human data. I think that there will be increasing attention paid not only to well-publicized attempts to predict teratogenic effects, but also to the effects of chronic administration of drugs and of interaction of drugs given together.

Toxicology has been a rather dreary field in the past, but it is not inherently so; it can be tremendously exciting. Let me illustrate some of the challenging problems in toxicology. One is amazed from time to time to see a compound which produces remarkably delayed effects. A new poten-

tial anti-cancer agent—a nitroso-urea mustard—can produce extensive toxicity, affecting the marrow, liver, kidneys, pancreas, and lungs, ninety days after therapy is stopped. Aplastic anemia from gold can occur many months after a series of injections. The biliary cirrhosis-like syndrome seen after chlorpromazine can last for many months after cessation of drug. Why these delays? What are the mechanisms involved? In another direction: can one use organ toxicity data for screening anti-cancer drugs? One agent, ortho-p′-DDD, has been used with some success in adrenal carcinoma because it was noted that it seemed to destroy the normal adrenal cortex. It is not impossible that by purposely looking for drugs with selective organ toxicity one may be able to treat cancer of other sites. The already rich harvest in genetic research (the primaquine-sensitive red blood cell defect, the cholinesterase problems mentioned above, etc.) testifies that other rewards await imaginative study of toxicogenetics.

We also need increasing attention to research on improving cause-and-effect relationships in this field. One of the things badly hamstringing the clinician is his limited ability to prove that a given drug is the cause of trouble. This is occasioned not only by delays in onset of toxicity, and failure of toxicity to clear up rapidly when the drug is stopped, but also by the multiplicity of drugs being given and by the ethical considerations involved in later challenging a patient with a drug suspected of having caused trouble. We need more in vitro tests such as those capable of detecting certain kinds of drug-induced thrombocytopenic purpura. And we must pursue such promising leads as the work of Eisen's group in skin testing for penicillin sensitivity with penicilloyl-lysine [31] or Shelley's indirect basophil degranulation test utilizing patient's serum, drug, and rabbit white cells [32].

Most important, however, is the need for increased education of doctors. The physician must have better knowledge about the relative efficacy and toxicity of the compounds available for treating a given condition. Since there are no non-toxic drugs, one is always forced to strike a balance between drug and no drug, or a new drug and older drugs already available. To do this, the doctor must require evidence. It is somewhat depressing to see a compound introduced for prevention of migraine which can give rise to unpleasant and serious side effects without clearcut evidence of how well the drug actually works [33]. It is difficult to see justification for anti-

coagulants of the phenindione series—which have not only the risks attending other anticoagulants, but also certain kinds of hematopoietic, renal, and hepatic toxicity not present with the other drugs. It is confusing to see continued use of such drugs as gold or chloroquin for rheumatoid arthritis when they seem to have little to offer and can occasionally produce irreversible damage.

The physician needs to be increasingly sophisticated about just what the drugs offered him really do. He has to focus on the appropriate goals of therapy. With an agent that has only been shown to lower blood cholesterol, he must think twice before administering it to a patient in the hope that it may also halt progressing coronary artery disease. A drug that lowers blood pressure may or may not prolong life span and decrease mortality from hypertensive vascular disease. A compound that temporarily inhibits the size of a cancerous growth may or may not add comfort and years to the patient's life. The physician must be aware of the temptation to cone down on easily measured parameters which are not necessarily relevant to our ultimate aims. We must not, like the drunk, look for our lost keys under the lamp post simply because the light is better there.

The physician must avoid the temptation to overprescribe. There is a great tendency on the part of patients to expect or demand medication, and there is unfortunately a *furor therapeuticus* in many physicians which demands that every symptom be treated (almost at the spinal reflex level) by administration of a drug. A recent survey of some patients in our hospital receiving methicillin (Staphcillin) showed that during the hospital stay no patient received less than five additional drugs, and one patient received as many as thirty-one. It is difficult to believe that all these drugs were truly indicated. (One suspects rather that some drugs are given to relieve the symptoms caused by others.) During the thalidomide controversy it was depressing to hear physicians admonished not to prescribe any unnecessary drugs for pregnant women. I had always believed that unnecessary drugs should be avoided for *everyone*—I see no reason why those of us who are not pregnant or who are incapable of becoming pregnant should be discriminated against! Drugs should not be given for trivial reasons—not to mention wrong reasons—and ought never be prescribed casually. It is quite obvious that in many cases the less the patient is treated the better off he is. Many trials in the literature show that a placebo-treated group was actually luckier than the group receiving the so-called active

treatment, which often turns out to be therapeutically inert and to produce untoward effects. A recent article on myasthenia gravis reported that patients in crisis from this disease, treated by expert neurologists, showed a much lower mortality when the physicians changed their regimen and gave fewer and less drugs instead of more [34]. Especially, the doctor should not be in a hurry to use the latest drug unless it fulfills some unique niche, since with the passage of time new drugs usually prove less impressively efficacious and more frighteningly toxic.

The physician must be encouraged to develop a high index of suspicion for drug toxicity, particularly about new drugs and multiple drugs given simultaneously. The alert physician, for example, knows that today when a previously well-controlled diabetic is showing deterioration in glucose tolerance, he should automatically ask whether the patient has been receiving thiazide diuretics. Any patient whose disease is not going as well as one would like to see must be scrutinized carefully to make sure that drugs are not the cause of the trouble. (I know several internists who do very well with cases posing problems in diagnosis or therapy by merely stopping all medication; it is amazing, for example, how often fever disappears as a diagnostic problem when all antibiotics are stopped.)

Conclusions

We have in a sense been caught by our own ingenuity. The day is past when we could say, as Oliver Wendell Holmes did, "Throw out opium . . . throw out a few specifics which our art did not discover . . . throw out wine . . . and I firmly believe that if the whole materia medica, as now used, could be sunk to the bottom of the sea it would be all the better for mankind—and all the worse for the fishes." We cannot afford to do without good, new drugs. We can no longer say, as did Hippocrates, ". . . as to diseases make a habit of two things—to help, *or at least to do no harm.*" This injunction is less apt than it was centuries ago, when there were few potent drugs available. Today, when powerful chemicals can cause great good as well as harm, mere avoidance of harm is not enough. Given a choice between no treatment and effective treatment with a risk of toxicity, the modern physician must usually pick the latter. To paraphrase Emerson, it is the fertile soil, not the barren, which breeds fevers, crocodiles, tigers, and scorpions.

We cannot turn back the clock. Yet we need not sink into despondent

paralysis. We must accept the fact that a price has to be paid for therapeutic progress. *Our job is to see to it that the price is not too high because of the use of bad drugs or of good drugs for bad reasons. And it is imperative that we increasingly improve our ability to avoid any dangers that are avoidable.*

If we learn from these difficulties, if we attack our problems intelligently, the result will of necessity be better and more satisfying medical care. Such improvement will not come about automatically, however, but only as the result of our collective and energetic efforts. The situation is in a sense a miniature version of our problems with atomic power. The mind of man has removed the stopper from the medicine jar. The chemical genie, formerly imprisoned within, now stands before us. He is a spirit known to work miracles, but also to wreak havoc—to improve life or destroy it. It is not clear that we are yet sufficiently wise to control the genie adequately. It is quite clear that we can never wish him back into the jar.

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HYPOGLYCEMIC

And still another door, another aisle,
To open and to walk with halting tread
And aching hope: They wait, these fugitive
And helpless, with their hidden, cradled guile,
For us to bring them the unsullied bread
Of our compassion, and the will to live.
Of what avail the magic we instill
Into their streams unless the valid touch
That blesses and the word that penetrates
The darkness of their minds transcend the hill
Of their afflictions and create the crutch
To help them stumble from their bog of hates?
Unless we penetrate that citadel
Of life and sanity—the primal cell?

L. Liberthson