DRUG-INDUCED DISEASES[1]

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Current concern over the untoward effects of drugs used in therapy (40 new diseases or syndromes from drugs (56, 107)) has evoked large and small commentaries (115), analyses (39), symposia (124), panel discussions, and compilations of raw indictments with a variety of designations (98) for undesirable results of the use of drugs: *Adverse Effects of Drugs* (55, 113), *Hazards of New Drugs* (103), *Side Effects of Drugs* (98, 99), *Diseases of Medical Progress* (107), *Drug-Induced Diseases* (100), etc. While all deal with data which have much in common, implicit in the differences in titles are classifiable differences in the nature of drug reactions.

These differences, however, are not yet clearly established. Although he is responsible for two editions of a book on the *Side Effects of Drugs* (98, 99) and has edited one on *Drug-Induced Diseases* (100), Meyler does not indicate or even seem to sense any difference between them; yet, side effects has special meaning which seems to have gotten lost in the Babel. Although this is not the view of the Adverse Reaction Committee of the American Medical Association, adverse effects of drugs have been described by a member of the Food and Drug Administration (127) as having no connection with adversity or drug hazard. *Diseases of Medical Progress* (107) is an encyclopedic accumulation (based on a stupendous bibliography) of reports on unusual events of varying degrees of seriousness, recorded with little regard to the nature, mechanism, circumstance, duration, evidence,or ultimate course but with concern for its temporal connection with the use of drugs. Which among the following is side effect, adverse effect, idiosyncrasy, allergenic reaction, intolerance, toxic effect, disease of medical progress, or drug-induced disease: acute barbiturate poisoning with respiratory depression and death, addiction after meprobamate, glaucoma after atropine, systemic lupus erythematosus after hydralazine, agranulocytosis after aminopyrine, hemolysis after pamaquin, methemoglobinemia after acetanilid, scotoma after chloroquin, hemochromatosis after iron, peripheral neuritis after thalidomide, phocomelia after thalidomide, hepatitis after iproniazid; hepatomegaly, pancreatitis, osteoporosis, peptic ulcer after cortisone, myopathy after colchicine, baldness after triparanol (MER/29), impotence after MER/29, cataracts after MER/29, virilism after androgens, thyroid dysfunction after cobalt, nephrosis after trimethadione, discoloration of teeth after tetracycline, parkinsonism after chlorpromazine, deafness after dihydrostreptomycin, vestibular disturbance after kanamycin.

Sir George Pickering (116) pointed out that the uncritical use of terms not only tends to make them meaningless but, what is worse, it also makes scientific communication difficult and imprecise. "If we are to advance knowledge and not destroy it . . . we must set our faces against loose or obscure or

[1] The survey of literature pertaining to this review was concluded in July, 1964.

unnecessary jargon. We must pay attention to the meaning of the words we use." For the purpose of this review, it is well, therefore, to establish a definition of "drug-induced disease" which distinguishes its borders from those of other untoward effects of drugs. Although they are to be found elsewhere, it will be helpful in this endeavor to bring together definitions of toxic effect, adverse effect, side effect, drug idiosyncrasy, intolerance, and drug allergy.

"Adverse effect" has broad and far reaching implications in that, as well as toxic effects as defined below, it also includes non-pharmacologic consequences of drug use: e.g., the population explosion in India resulting from effective antimicrobial therapy and the geriatric problem which we now have as a result of advances in drug therapy.

It is significant that there are classifications of drug reactions which do not include toxic effects (115, 124). I believe that the term has special value when used in a broad and relatively nonspecific way. In any event, because it is so commonly used, toxic effects cannot be completely ignored.

The "toxic effects" of a drug are the consequences of its pharmacologic actions, by whatever mechanism and for whatever reason, occurring promptly or after a latent period, directly or indirectly, as a result of one or more effects on tissue or functional activity by the drug or its metabolic derivatives. A toxic effect is a pharmacologic effect which has become undesirable and is a threat to normal physiologic function, if not a threat to life. Usually by being excessive, toxic effects may be attributed to the pharmacologic effects of a drug which also provide its therapeutic usefulness. Or, they may be associated with other facets of the pharmacologic properties of the drug. And, of course, toxic effects result from drugs which have no therapeutic value—industrial chemicals, chemicals which are used only for destructive purposes, and agents which are not intended for man or animal and affect them only by accident.

The "allergic drug reaction" is an immunologic reaction to drugs which can only develop in subjects in whom the specific antibody is already present, usually as the result of previous exposure to the drug. The basic pharmacologic effect, in the allergic reaction, is the formation of antigen from drug. Theoretically, therefore, an allergic drug reaction cannot occur the first time a subject receives a drug, whereas the toxic reaction can. The allergic reaction is also distinguished by the facts that the same group of allergic phenomena, i.e., asthma, urticaria, angio-edema, anaphylactic shock, dermatitis, certain blood dyscrasias, and collagen disturbances, are produced by drugs with widely disparate pharmacologic actions, and that their pharmacologic actions bear no relationship to the allergic reactions.

A "side effect" is a pharmacologic effect other than the one sought for in the particular use of the drug (102, 104). Thus, a side effect need not be adverse, non-therapeutic, or even unpleasant, or it may be a fatal effect. While a side effect is usually undesirable, it is inaccurate to make it appear to be a less formidable event than other adverse drug reactions. Often a pharmacologic action leads to a side effect in one context and a therapeutic effect in another. Depression of atrioventricular conduction is a side effect of digitalis

when used in the treatment of congestive failure in a case with a normal sinus rhythm but it is a therapeutic effect in a case of atrial fibrillation because, in the latter, depression of conduction is one of the pharmacologic actions leading to its therapeutic effect. In both cases, however, depression of atrioventricular conduction which induces complete atrioventricular dissociation is a toxic effect. Glaucoma caused by atropine is, however, both side effect and toxic effect. Hypoglycemia is the side effect of the sulfonamides which led to the oral hypoglycemic agents. Alkalosis due to carbonic anhydrase inhibition is a side effect of sulfonamides which led to a series of oral diuretics and a therapy of glaucoma. The term side effect is so often badly used and abused that it rarely conveys meaningful information and it could, therefore, be abandoned with benefit.

"Drug idiosyncrasy" has been defined by Rosenheim (124) as uncharacteristic pharmacologic reactions in particular patients: e.g., excitement after barbiturate. "Drug intolerance" (124) is characterized by the production of typical pharmacologic effects by unusually small doses of drug. It is distinguished from the allergic reaction to drugs, which often also occurs after very small doses, which is a specific antigen-antibody reaction. While properly the same as drug allergy, "hypersensitivity" is avoided in this review because it is often also used to imply drug intolerance or idiosyncrasy and, therefore, may lead to confusion.

"Drug-induced disease" implies a response to drug in which a disease results from its use; it does not imply any kind of pharmacologic effect. It is proposed to designate as drug-induced diseases only those consequences of the use of drugs which are characterized by functional disturbances which persist after the offending drug has been withdrawn and has been grossly eliminated. The disturbance may be entirely functional or it may be secondary to permanent or slowly reversible tissue changes. Intensity and seriousness are not relevant, for they do not determine in any case whether a disease-state exists. Whether drug-induced or not, irreversible organic change without functional impairment is not a disease. By these criteria, moniliasis after tetracycline, peptic ulcer after cortisone, persistent urticaria after penicillin, persistent parkinsonism after chlorpromazine, irreversible systemic lupus erythematosus after hydralazine, aplastic anemia after sulfadiazine, agranulocytosis after chlorpromazine, hepatitis after iproniazid, and glaucoma after atropine, are all drug-induced diseases; whereas, death due to overdosage with barbiturates or digitalis, baldness after MER/29, or loss of a toe due to ergotamine are not drug-induced diseases.

The persistence of the functional disturbance necessary to designate a drug effect as a drug-induced disease calls for a judgment, but this also applies to the decision of whether functional disturbances, not related to drugs, constitute diseases. Among selections made on such an arbitrary basis, there will inevitably be some marginal decisions. Some otherwise important drug reactions will be omitted from this review, but the impropriety of calling them diseases will have been the basis of their omission.

A feature of the definition is that, rather than by chemical, organ sys-

tem, or therapeutic category, it favors classification along lines relating to the functional basis of the drug-induced disease; it must fail to the extent that the functional bases of some drug-induced diseases are not established. It may be presumed, however, that, with understanding, all drug-induced diseases can be classified approximately as follows: (*a*) disturbances in defense mechanisms; (*b*) disturbances of function due to cell injury; (*c*) deficiency or imbalance of essential materials; (*d*) genetic and developmental disturbances; (*e*) chemical carcinogenesis; and (*f*) disturbances in microbial ecology.

By common definition, all chemicals become drugs when they produce effects in man or animal. However, because current interest in the problem arises from concern over new therapeutic agents, this review will be limited to effects of drugs when used in the therapy or prevention of disease in man. A large number of functional disturbances, and by the definition given, drug-induced diseases, which are known will, therefore, be omitted: e.g., diseases due to industrial poisoning, pesticides, environmental poisoning of many sorts, and deliberate and accidental gross overdosage with drugs. Some instances however, may be used to demonstrate the potential of special categories of chemicals for inducing disease. This review cannot be exhaustive; in general, it will mention outstanding examples. Because of the difficulty in developing substantial proof of such effects in man, the best examples of drug-induced diseases are not always new ones; old ones will, therefore, be used in some cases. Many reports in the current clinical literature implicating new drugs in one way or another as the cause of disease will not be considered here because they do not provide sufficient data and require further investigation.

Disturbances In Defense Mechanisms

It could be argued that all disease, drug-induced and otherwise, is due to insufficiently effective defense mechanisms. However, when a drug induces a specific and definable defect in the body's defense mechanisms, which under other circumstances would have operated in its interests and with the aid of which a disease would not have developed, the disease which develops may be considered to be caused by a drug-induced defect in defense mechanisms. Disturbances in defense mechanisms may be divided into several functional categories so far as drug-induced diseases are concerned: (*a*) depression of resistance to infection; (*b*) induction of drug allergy; (*c*) induction of tolerance, dependence, and addiction; and (*d*) disturbances of inflammatory and reparative processes.

Depression of resistance to infection.—There is a substantial literature, and it is now common knowledge, that a fairly generalized depression of resistance to infection is induced by the corticosteroids. No other group of drugs has this property in so highly developed a form. Fatal moniliasis, otherwise very rare, has been reported in aplastic anemia treated with antibiotics and steroids (10, 145). It has been well demonstrated that tuberculosis, asymptomatic pneumonia, and other infectious diseases may also develop during steroid therapy (131).

In bone marrow depression caused by antineoplastic agents, there is also severe depression of resistance to infection. In this situation, unusual systemic fungal infections have been reported (95, 131).

Allergic disease.—Immunologic disturbances are disturbances of defense mechanisms. This applies to the development of allergy to drugs as well as to foreign protein. While some drugs and drug groups are more allergenic than others, there is yet no rule for predicting relative allergenicity and any drug may, on occasion, induce the allergic state. Although there are a few drugs which are antigens, this appears to be the exception; most drugs are not complete antigens. The mechanism of the development of drug allergy according to the hapten concept has been described by Carr (23, 24) and others (27, 129) as the combination of drug or drug metabolite (35, 69) with circulating protein to form antigen with the subsequent formation of antibody. In such cases, it is the hapten, not the protein moeity, which accounts for the specificity of the allergic reaction; the protein is, of course, a homologous protein. The pharmacologic effect, in this case, is the formation of the antigen; the hapten-protein combination represents the drug-receptor result of the pharmacologic action. When the drug is subsequently used, antibody reacts to induce the allergic reaction which is an immunologic response.

The hapten may be a drug metabolite and not the original drug itself (35, 69). In the case of penicillin allergy, the evidence is strong that the hapten is the metabolic derivative, penicillenic acid (133). Because of this, penicillin allergy usually applies to all forms of penicillin regardless of the substituents or addition groups which account for difference in absorption, destruction in the gastrointestinal tract, rate of elimination, and even antimicrobial activity.

Allergic reactions to drugs include the standard allergic manifestations: anaphylactic shock, rhinitis, asthma, angioedema, fever, serum-sickness-like reactions, urticaria, other forms of dermatitis, photosensitivity, vascular disturbances and some rarer forms of allergic reaction, some collagen disturbances, certain types of blood dyscrasia, and possibly hepatitis. Certain allergic manifestations characteristically develop after particular drugs, but no rule holds and, of course, there is no way of predicting the allergic manifestations of new drugs. Tables from the review by Samter & Berryman (129) illustrate the characteristic reactions of certain drugs, as well as the wide variety of drugs known to induce allergic reactions. At present, penicillin in all its forms is the most serious offender.

In the case of drug allergy, the presence of specific antibody is a functionally abnormal state which continues long after the use of the drug has been discontinued; for as long as the antibody is present, the administration of the drug may cause serious or fatal reaction. These constitute diseases no less than the allergic states characterized by episodic reactions such as hay fever or asthma attributable to foreign protein. The state of drug allergy may, therefore, be considered to be a drug-induced disease.

There is no question concerning most instances of anaphylaxis, rhinitis, asthma, angio-edema, urticaria, photosensitivity, and many dermatologic

manifestations which are well-recognized allergic reactions, but, in some of the more unusual drug reactions such as hepatitis, blood dyscrasias, and collagen diseases, circulating antibody has not been demonstrated and in these, it is still an unsettled question whether some instances belong to the drug allergy group and whether some instances represent other forms of adverse reaction. The distinction is far from academic; it relates to the measures which must be taken to determine such a potential in new drugs as well as how to treat the reactions after they occur.

It seems more probable than otherwise that cases of drug-induced hepatitis do not, or only very rarely, belong in the allergic group (117), although some investigators hold that many, if not all, cases of cholestatic jaundice are probably allergic. Hepatitis caused by drugs is discussed elsewhere in this review.

The evidence for blood dyscrasias as allergic drug manifestations is mixed, and varies largely with the specific dyscrasia and sometimes with the circumstance. The basic defects may differ with each type of drug; drug-induced blood dyscrasias should not, therefore, be lumped together in discussions of adverse reactions, as they are in Tables I, II, and III. Since they are so frequently assumed to belong to the group of allergic reactions, this may be an appropriate place to segregate them. Regardless of evidence for the occasional allergic basis for aplastic anemia and agranulocytosis (106) (which is not substantial), a direct toxic effect on bone marrow remains the probability for many drugs [such as chloramphenicol and more recently, for one of the semisynthetic penicillins, methicillin (Staphcillin) (26, 47, 58, 76, 77, 89, 112, 146)]. To some extent, current confusion may be related to the misuse of the term hypersensitivity which suggests intolerance but means allergy.

In thrombopenic purpura with anemia, evidence suggests allergy as the most likely basis for drug reaction even in cases in which the mode of previous exposure is obscure (43, 46). Many drugs fall into this category. An allergic reaction to a combination of para-amino-salicylate and antibacterial agents, resembling mononucleosis and characterized by lymphadenopathy, lymphocytosis, rash, and splenomegaly has been reported (30). Megaloblastic anemia has been reported after many anticonvulsant drugs; it may well be due to drug-induced folic acid deficiency (25, 112).

Kellermeyer (83) and Discombe (37) suggest that in some instances (nitrofurans, some sulfonamides, acetophenetidin, menadione) hemolytic drug reactions may be attributable to drug allergy, although, as recounted below, a great many hemolytic reactions arise from glucose-6-phosphate dehydrogenase deficiency of the red cell.

Collagen disease.—Periarteritis nodosa and systemic lupus erythematosus have been established as consequences of drug use. Periarteritis has been noted after a large number of drugs and is said to be the late consequence of the typical allergic effect on endothelial cells. Lupus erythematosus is usually described as an entirely reversible hydralazine (Apresoline) reaction. However, cases of persistent systemic lupus, due to hydralazine as well as to other

TABLE I[a]

DRUGS OR CHEMICALS SHOWN BY DIRECT OR CIRCUMSTANTIAL EVIDENCE TO BE ASSOCIATED WITH BLOOD DYSCRASIAS

Acetanilid[b]	Pamaquin[b]
Acetazolamide	Phenindione
Acetophenetidin[b]	Phenylbutazone
Allylisopropylacetylurea	Phenylhydrazine[b]
Aminopyrine	Primaquine[b]
Aminosalicylic Acid[b]	Primidone
Arsphenamine	Probenecid[b]
Benzene	Promazine
γ Benzene Hexachloride	Sulfamethoxypyridazine[b]
Carbutamide	Pyrimethamine
Chloramphenicol	Quinacrine
Chlordane	Quinidine
Chlorothiazide	Quinine
Chlorpromazine	Ristocetin
Chlorpropamide	Stibophen
Colchicine	Streptomycin
Diphenylhydantoin	Sulfacetamide[b]
Dipyrone	Sulfadiazine
Gold Salts	Sulfanilamide[b]
Imipramine	Sulfisoxazole[b]
Lead	Sulfoxone[b]
Mepazine	Thiazolsulfone[b]
Meprobamate	Thiobarbital
Methimazole	Thiouracils
Methylphenylethylhydantoin	Tolbutamide
Naphthalene[b]	Trimethadione
Nitrofurantoin[b]	Trinitrotoluene

[a] From Erselev & Wintrobe (48).

[b] These drugs have been associated with the induction of hemolytic anemia, principally in patients with glucose-6-phosphate dehydrogenase-deficient cells.

TABLE II[a]

DRUGS COMMONLY ASSOCIATED WITH DEVELOPMENT OF LEUKOPENIA

Phenothiazines	Methimazole
Tetracyclines+Penicillin	Thiouracils
Sulfonamides	Insecticides (Chlordane, Lindane, DDT)
Pyrazolons	Barbiturates
Chloramphenicol	Acetylsalicylic Acid (Aspirin)
Hydantoins	

[a] From Erselev & Wintrobe (48).

TABLE III[a]

DRUGS COMMONLY ASSOCIATED WITH DEVELOPMENT OF PANCYTOPENIA

Chloramphenicol	Insecticides (Chlordane, Lindane, DDT)
Tetracyclines+Penicillin	Pyrazolon Derivatives
Sulfonamides	Barbiturates
Phenothiazines	Acetylsalicylic Acid (Aspirin)
Hydantoins	

[a] From Erselev & Wintrobe (48).

TABLE IV[a]

DRUGS COMMONLY ASSOCIATED WITH DEVELOPMENT OF THROMBOCYTOPENIA

Sulfonamides	Pyrazolon Derivatives
Quinidine	Insecticides (Chlordane, Lindane, DDT)
Tetracyclines+Penicillin	Thiouracils
Chloramphenicol	Barbiturates
Phenothiazines	Acetylsalicylic Acid (Aspirin)

[a] From Erselev & Wintrobe (48).

drugs, have now been described. The allergic basis is not definitely established in either the reversible or the nonreversible cases of lupus, although many are inclined to think of it as an allergic drug reaction (11, 73, 140, 141).

Vascular and capillary changes have been described after many drugs. Since these capillary responses often resemble those seen in common allergic reactions such as urticaria and angio-edema, they may be allergic reactions.

Myocarditis, distinctly different from the myocarditis of diphtheria, but resembling the myocarditis of serum sickness, has been reported after sulfonamides, neoarsphenamine, and other sensitizing drugs. So, too, some cases of peripheral neuritis, associated with perineural edema and capillary changes may have an allergic basis (122).

Drug allergy is an important drug reaction, not only because of its frequency and the seriousness of some manifestations, but also because its implications are so broad. Because, as already stated, metabolic intermediates, which are the same for large groups of drugs, may be the haptens implicated in the development of antigen and antibody and because there may also be crossover, the potential scope of drug-induced allergy extends greatly, often making it unpredictable, especially when the metabolic pathways of drug degradation are not known. It also emphasizes the important possibility of drug sensitization by the small amounts of chemicals, not used as drugs but present in insecticides, pesticides, weed killers, antibiotics, antiseptics, solubizers, etc., which may be found in milk, meat, fowl, other food, cosmetics, drugs, vaccines, and even in paints in our environment (17, 31, 33, 90, 120, 125, 136, 149, 150, 153).

Addiction and Tolerance.—Addiction and tolerance are related processes. Since tolerance is a drug-induced defense mechanism, i.e., one which reduces vulnerability to the drug, it, as well as addiction which is one of the direct and immediate concomitants of tolerance to some drugs, belongs to the category of drug-induced disease caused by a disturbance of defense mechanisms. Since withdrawal reaction is a functional disturbance which persists after a drug is with withdrawn and is one of the causes of continued addiction, drug dependence is a drug-induced disease. The importance of addiction currently extends beyond ancient narcotics to modern tranquilizers: e.g., meprobamate (Miltown, Equanil), glutethimide (Doriden), ethinamate (Valmid), ethchlorvynol (Placidyl), methyprylon (Nodular), and chlordiazepoxide (Librium). The same danger applies also to sedatives and barbiturates, and may well include pep pills [amphetamines, phenmetrazine (Preludin)] and perhaps all drugs which affect mood, although the very widely used phenothiazine tranquilizers have not yet been implicated (49).

There are varieties of drug withdrawal reactions after drugs other than the typical morphine withdrawal syndrome, e.g., convulsions after barbiturates and some of the tranquilizers and the adrenal insufficiency symptom and symptom rebound after corticosteroid withdrawal, which may be considered drug-induced diseases. Steroid effects such as myopathy, periarteritis, pancreatitis, polyneuropathy, also involving cell damage, may, since they tend to develop during interruption of therapy or as distinct withdrawal reactions, belong to the general category of disturbances of defense mechanisms (140, 141).

Tolerance has another serious implication. Should tolerance, in the case of a pathogen, develop to a much-needed drug, as it does to streptomycin during the course of treatment of tuberculosis, the disease reappears in a new state—a treatment-resistant state. This is an example of drug-induced disease of drug-tolerance—the treatment-resistant disease (79, 109).

Disturbances in inflammative and reparative processes.—This is a category of drug-induced disease which was recognized only after the advent of cortisone and the train of congeners which followed it which depress mesenchymal inflammatory responses and reparative processes much more intensively than the previously-available, modest anti-inflammative agents like aspirin.

While peptic ulcer, after the steroids, has been said to be related to increased gastric acidity and digestive enzyme content, such a rise cannot be always demonstrated after their use. Regardless of the effects which cortisone congeners may have on gastric acidity, it is fair to assume that just as these drugs retard wound healing by their specific anti-inflammative action, so they may depress the normal rate of replacement of normally desquamated epithelium of the intestine and, thereby, facilitate bleeding and the development of ulcers. A similar process, rather than the commonly accepted one of local irritant action,may also apply to aspirin and other minor anti-inflammative agents, such as butazolidin,which are also associated with intestinal bleeding and peptic ulcer and it may, therefore, be anticipated in the case of new anti-inflammative drugs (6, 9, 139, 143).

Disturbances in Function Attributable to Cell Injury

Drugs may induce irreversible cell or even organ damage which causes no persistent functional difficulty, e.g., baldness after triparanol (MER/29) (87) or loss of a toe after ergotamine. Such changes can no more be considered diseases than baldness occurring naturally or loss of a toe through trauma. On the other hand, slowly reversible cell injury in the liver, kidney, or nervous system may result in long-lasting functional disturbance as substantial as those caused by pathogenic processes commonly associated with infectious or degenerative disease.

Liver damage by drugs is well recognized. Popper (117) and others (119, 130, 135) describe several types of drug effects on the liver. The first is a direct hepatocellular effect without inflammation, after carbon tetrachloride, phosphorus, and chloroform. Halothane (Fluothane) has also been implicated, but current expert opinion and retrospective studies do not appear to support the indictment (137). Today, this type of liver damage occurs infrequently, perhaps because drugs may be relatively successfully screened for it in animal experiments.

The second type of liver injury arises from a cholestatic effect which has been reported after a large number of drugs: e.g., tetracyclines, phenothiazines, methyltestosterone, norethisterone, norethandrolone (Nilevar), sulfadiazine, thiouracil, arsphenamine, chlorpropamide (Diabinese), para-aminosalicylic acid, carbarsone, many of the antineoplastic drugs, and others (41, 44, 74). The mechanism of the stasis is not understood. Although considered by some to be an allergic reaction, and may be so in some instances, this is not an accepted view. Cell injury, which is sometimes irreversible despite discontinuation of the drug, may result from the stasis. The mortality rate is low, but occasionally the reaction is fatal.

The third type of liver injury is direct hepatocellular damage with inflammatory reaction which has been reported after iproniazid (Marsilid) and other monamine oxidase inhibitors such as phenelzine (Nardil), nialamide (Niamid), and isocarboxazide (Marplan) as well as after cinchophen, zoxazolamine (Flexin), para-aminosalicylate, mercaptopurine, sulfamethoxypyridazine (Kynex). phenindione (Danilone, Hedulin), pyrazinoid acid amide (Pyrazinamide), and methexamide (130, 135). The pathologic picture is similar to that of viral hepatitis. The possibility of activation of an already present virus by drug in these cases. resulting in actual viral hepatitis, has been suggested. This concept, however, has not been substantiated by identification of the virus (117). Occasionally, the liver damage becomes extensive, and the disease is fatal.

Fatty changes in the liver after tetracyclines which do not fit into the categories listed above have been reported (41).

Nephrosis after primadone (Mysoline), quinine (86), neomycin (45), colistin (Coly-Mycin)(152), versenates (121), probenecid (Benemid) (51), tolbutamide (Orinase), trimethadione (Tridione) (71), paramethadione (Paradione) (154), phensuccimide (Milontin) and other anti-convulsants (101), chlorothiazide (Diuril), (1) mercurial diuretics (19, 54), and a number

of other drugs has been established (60). In many instances, the renal changes are irreversible to that extent there is the drug-induced disease, nephrosis.

In the last few years, a substantial literature has accumulated regarding the possibility of renal disease with tubular, glomerular, and renal papillary damage from analgesic combinations, but with special reference to phenacetin, since this was the only drug present in all the mixtures. Renal disease complicated by infection developed in a number of patients who took huge doses (of the order of 5 to 7 gm per day) for many years. The syndrome has not been noted after smaller doses or short periods of ingestion. It has been suggested without evidence that a metabolite of phenacetin or an impurity was involved (28, 72, 91, 132).

Since the implication of phenacetin in this condition, many analgesic mixtures on the market have dropped phenacetin and have substituted NAPA (n-acetyl para-aminophenol). Since NAPA is probably the metabolite of phenacetin responsible for its analgesic effect, it seems unlikely that the substitution will make any pharmacologic difference in this analgesic combination. Experiments on rats indicate similar adverse potential in NAPA and phenacetin (3).

Myopathy with chronic weakness has been reported after colchicine (84) and steroids (20). In the latter it is suggested that the danger is greatest with the fluorinated steroids. Permanent pathologic changes in striated muscle is the basis of the chronic weakness. In some cases, there is slow recovery of muscle strength, although anatomic changes may persist. The suggestion that creatine synthesis is inhibited is not proven.

Neuropathy is not a rare drug complication (154); it is a well-recognized effect of isoniazid and has also been reported after steroid therapy (81). Demyelination of the spinal cord by tri-*o*-cresyl phosphate has been shown in the rat to arise from a neurotoxic metabolite (50, 61). The neuropathy of thalidomide has been largely forgotten, although it was this effect which led Dr. Frances Kelsey to keep the drug off the American drug market. Polyneuropathy has also been reported after endrin and other insecticides (80) and after excessive use of insulin (108). As already noted, the polyneuropathy after steroids may be a withdrawal effect (81).

Deafness has been attributed to drugs. Irreversible deafness with a variable latent period was not rare when dihydrostreptomycin (134) was commonly used in tuberculosis. It occurs less frequently now. Vestibular disturbances after streptomycin, usually reversible or incompletely reversible but clinically dealt with by adaptation, was a common occurrence when that drug was more frequently used than now. Both deafness and vestibular damage have been reported after kanamycin (154).

Retinopathy has been described after many drugs, but chloroquin has been most frequently implicated (4). In the case of chloroquin, although corneal lesions also develop, they disappear, whereas the retinal damage does not. Central scotoma due to macular deterioration results in permanent blindness (118, 138). Glaucoma has been reported not only after atropine but also after other anticholinergic drugs, and it appears to be a hazard even after

some of the antidepressant drugs with anticholinergic actions such as imipramine (Tofranil) and amitriptyline (Elavil). Irreversible cataracts have been reported after triparanol (MER/29) and other drugs (87).

Organic changes in the intestinal tract have long been known to be a consequence of irritant or corrosive agents such as mercuric chloride. Attracting most attention at present, is the ulcerogenic potential of two groups of drugs: common minor non-narcotic analgesics, such as aspirin and the corticosteroids. Various reasons have been given: hyperacidity and increased digestive enzyme production after corticosteroids (which has also been denied), and local irritation by aspirin. I hold the view, already stated, that ulcer and intestinal bleeding may well be attributable to depression of rate of reparative replacement of normally desquamated intestinal epithelium; hence, these diseases arise from depression of reparative processes.

Acute pancreatitis is an intestinal complication of steroid therapy requiring elucidation which has also been thought to be a withdrawal reaction (110).

A large variety of blood dyscrasias, developing after the use of drugs, may well result from bone marrow depression in general or some specific element of it. Dyscrasias which seem to be unequivocally allergic are discussed in an earlier section. There are many chemicals like benzene and aniline and most of the cytotoxic anticarcinogenic agents, which regularly and dependably depress bone marrow, the degree being related to dosage. Wintrobe and others feel that the chloramphenicol effect on bone marrow is a pharmacologic action of this kind, following a typical dosage response curve, and, that where serious effects develop from small doses, it represents not drug allergy but drug intolerance (48). The same may be true of these dyscrasias after other drugs. Thus, pancytopenia and most instances of agranulocytosis are most likely pharmacologic effects in intolerant individuals and are not instances of drug allergy.

Amyloidosis has been described in patients with Hodgkin's disease who receive cytotoxic drugs. In mice previously treated with sodium caseinate, nitrogen mustard has accelerated the development of amyloidosis (22, 144).

Deficiency or Imbalance of Essential Materials

Destruction or exhaustion by drugs of enzymes, hormones, electrolytes, and other essential materials may cause disease.

Depletion of catecholamine stores by reserpine has led to a syndrome of weakness, diarrhea, drowsiness, as well as unusual hypotensive reactions during the use of general anesthetics. This condition may last for two weeks or longer after the drug has been withdrawn.

With modern drugs, serious and prolonged effects attributable to enzyme destruction are conceivable. Many of the insecticides and pesticides which may contaminate our food or environment are capable of such effects. DFP (di-isopropyl fluorophosphate) has produced permanent motor disturbances by esterase destruction in cats (105); a similar effect in man by drugs is, therefore, a possible complication of modern pharmacotherapy.

Some deficiencies may be genetic but are uncovered through the use of drugs. Hemolytic reaction to drugs is, in some cases, a true idiosyncrasy, as in pamaquin hemolysis in negroes with an inborn red cell deficiency (12, 37, 78, 142, 151). In such a case, renal damage could be a secondary development of the hemolysis. In kernicterus in the newborn, enzyme deficiency has also been shown to be the fundamental defect (14, 40). While there are authentic cases of hemolytic anemia due to glucose-6-phosphate dehydrogenase deficiency in the red blood cell, there are also other types of hemolytic drug reactions caused by many other drugs: e.g., nitrofurans, some sulfonamides, acetophenetidin, and menadione, in which an allergic basis is a strong possibility (83). A genetic deficiency has been postulated which accounts for thyroid disease in some infants receiving cobalt (147). Drugs such as the sulfonamides may, through antibacterial action, induce folic acid deficiency which may result in disturbances in blood formation. Chalmers reports cases of megaloblastic anemia after anticonvulsant drugs in which he postulates, with some evidence, such a deficiency (25).

Serious and long-persistent depression of the clotting mechanism is a pharmacologic effect of the anticoagulant drugs; these drugs are a frequent cause of hemorrhagic disease.

Extrapyramidal reactions have become a common drug reaction since the widespread use of tranquilizers. As many as 39 percent of nearly 4000 cases receiving chlorpromazine or congeners on long-term therapy developed such an effect, evidenced by typical parkinsonism, dyskinesia, or akathisia (5). In most cases, the condition is completely reversible when the drug is stopped, but in rare instances it is permanent. It has been said, without proof, that it is due to interference "with the catecholamine-serotonin system" (96). There is also the possibility of cellular damage in the nervous system, but this too has not been established.

Disturbances in electrolyte balance are common after the free use of electrolyte solutions before and after surgery, as a result of the widespread and long-continued use of modern diuretics, and because of the still common regular use of alkali in gastrointestinal disturbances. Acute but readily reversible disturbances are, by all odds, the more common, but persistent irreversible disturbances have also been seen. Renal damage due to alkalosis and hypokalemia have been reported (72).

Genetic and Developmental Disturbances

Although it has long been recognized that cortisone congeners are teratogenic, only since the publicity regarding thalidomide has considerable attention been focused on this category of drug-induced disease. A large number of drugs have been shown to be teratogenic under a variety of experimental conditions in a variety of animals: e.g., thalidomide, antimetabolites, alkylating agents, steroids and other hormones, hypoglycemic agents, hypocholesteremic agents, as well as a large number of chemicals not used in medicine. In addition, there are reports of teratogenic effects in animals from unusually large doses of chlorpromazine (Thorazine) and congeners,

glutethimide (Doriden), alkaloids, salicylates, phenylbutazone (Butazolidin), sulfadiazine, sulfamerazine, some antibiotics, various antihistamines, ergotoxin, caffeine. Current statements regarding teratogenicity of drugs tend to be descriptive of local actions with respect to the state of fetal development rather than to implicate some dynamic physiologic system (21).

Because of considerable species difference and importance of dosage, laboratory findings, although positive, must be critically evaluated before they can be said to apply to man. The fact is that although fetal deformity attributable to drugs is not rare in the experimental animal, it is rare in man. Complicating the matter of examining drugs for potential teratogenicity are the matters of the development of drug tolerance and accelerated elimination through accelerated metabolism. If a drug is given regularly too long before the critical period for teratogenic effect, it is possible that tolerance will develop or metabolism will be markedly accelerated and that the test will fail to exert the drug's full teratogenetic potential. In addition, observations in man fail to take into account fetal resorptions that may result from drug use.

Cyclophosphamide (Cytoxan), an alkylating agent, if used in the treatment of Hodgkin's disease during the first trimester of pregnancy, is suspected of causing congenital anomalies (64). Since they are mutagenic, it is possible that many antineoplastic agents are teratogenic in man as well as animals, but, because of the condition of the patient and the usually short but fatal duration of the illnesses in which they are used, this is an unlikely drug effect in man.

The use of oral progestins and methyltestosterone by the pregnant mother has a virilizing effect on the fetus which is persistent after birth (65, 70). Other hormones have caused developmental imbalance which has not led to monsters but to structural disproportion (42). Observations of deposition of tetracyclines in bones suggest the possibility of developmental effects due to that group of drugs. The reader is referred to reviews on teratogenic effects of drugs by Cahen (21), Gerarde (59), and Mellin (97).

Chemical Carcinogenesis

Many chemicals have been shown to induce carcinoma in the animal, and there is a substantial industrial experience with chemical carcinogenesis in man. Frankly carcinogenic materials, such as the alkylating agents and other antineoplastic drugs, are commonly used in therapy, and there are some, such as the estrogenic hormones and iron dextran, which induce experimental carcinoma in animals but have not been demonstrated to do so in man, while only colloidal thorium dioxide (Thorotrast) is cited as the proven instance of a commercially marketed drug which has caused carcinoma in man after being used in an acceptable way (29, 154). The lack of evidence in man, however, does not rule out the possibility that the danger is greater than it seems.

There may be considerable species difference in carcinogenic effects of drugs which tends to invalidate animal screening procedures. This explana-

tion appears to hold in the case of estrogenic hormone which causes carcinoma in the rat but despite wide use for about 30 years has not been demonstrated to be carcinogenic in man. Species differences also seems to apply to iron dextran (Imferon). The mechanism of the chemical-induced hepatoma in the rat, which has been known since 1932, does not seem to apply in man. It is known that griseofulvin (Fulvicin, Grifulvin) by intramuscular injections causes carcinoma in the rat (123). Griseofulvin is widely used in man, but carcinoma has not been attributed to its therapeutic use. It is presumed, by some, that oral use and slow absorption account for the lack of carcinogenicity in the clinical experience in man. However, this explanation is inadequate since griseofulvin is well enough absorbed in man to be present in the skin and is also used for extended periods. It is possible that carcinogenic effects have not been observed in man after the use of antineoplastic agents because of the terminal or near terminal state of the patients in which they are used, and it is also possible that drugs which are carcinogenic in man are not carcinogenic in the experimental animals used in screening (2, 7, 15, 18, 29, 38).

The experience in industry that chemicals and drugs can cause carcinoma in man is a substantial one: e.g., arsenic, beryllium, naphthylamine, benzidine, coal tar, and others. Bladder carcinoma is an especially well-recognized industrial hazard. There are also known chemical carcinogens in our environment and there are the data that tobacco smoking may be carcinogenic. These make it clear that the possibility of chemical carcinogenesis in man is a real and present danger (75, 154).

It was hoped that chemically induced experimental carcinoma might provide understanding of the basic mechanisms involved. An impressively long list of chemicals with carcinogenic properties in the laboratory animal has been studied (13, 16, 36, 67, 68, 82, 92, 93, 123, 126). But the studies have not led to understanding of chemical carcinogenesis or provided useful clues for the screening of drugs. Findings in animals are, at best, only suggestive. If nothing else, however, they point to the possibility of carcinogenesis through the use of drugs, especially since there are chemicals which induce experimental carcinoma in animals after a single dose. Thus, the chronic use of drugs is not a limiting factor in this hazard (94, 114).

There are some suggestive findings that there is a danger of carcinogenesis from some drugs now in use (drugs which depress bone marrow, and isoniazid) even though the association has not been clearly demonstrated. Experiments in mice and rats indicate that before the development of leukemia from benzol there is a leukopenic stage. On the basis of this observation, it is suggested that patients who recover from bone marrow depression from drugs be carefully watched for the development of leukemia. The need for such a precaution is supported by the clinical association of pyrazolon derivatives with both leukemia and leukopenia. Cellular changes after isoniazid, as used in the treatment of tuberculosis, and, especially the increasing incidence of carcinoma in healed tuberculosis scars and cavities, suggest the possibility of a connection between the therapy of tuberculosis and the increase in pulmonary malignancy (75)

There is also the possibility that in some cases, as in experimental carcinoma after urethan and croton oil, cocarcinogens are involved, i.e., two or more drugs operate in such a way as to induce carcinoma, whereas neither alone in any dose has the effect (128). While cocarcinogens may constitute a real danger in man, this has not been demonstrated. Of course, their identification as factors in malignancy in man would be exceedingly difficult. In experimental carcinogenesis, many agents have been shown to be procarcinogens rather than proximate carcinogens and require metabolic alteration to induce their effect. In the case of man, no such distinction has been possible even though it may also apply to him.

Complicating the picture of establishing the liability of drug carcinogenesis in man are the facts that species differences are great; that for most agents which are carcinogenic in the laboratory, repeated long-term exposure is needed; that no form of immediate cellular reaction to them has been demonstrated; that necessary dosage and time of exposure do not follow any rule; that there is no proven mechanism of chemical carcinogenesis; and that there is the possibility that unidentified metabolites, rather than the agent itself, may be proximate carcinogen or cocarcinogen. The almost unlimited ingestion by man of food colors and other food additives, and exposure to environmental contaminants which if not carcinogens may possibly be cocarcinogens greatly broadens the possibilities of drug carcinogenesis (34, 85, 148). All make the problem of drug screening for carcinogenic potential in man an exceedingly difficult one.

Disturbances in Microbial Ecology

The contribution of the normal resident flora of the skin and intestine to health has been appreciated for some time. Disease due to disturbances in microbial balance has long been suspected and the suspicion misused at the turn of the century in widespread therapy of "intestinal auto-intoxication" with bacillus acidophilus. During the first 40 years of this century, difficulties due to disturbances in microbial balance never resulted from the use of anti-infective drugs simply because there were no drugs which could safely and effectively alter microbial life in man. But such ecologic disturbances have become the hallmark of the antibiotic era. The tetracyclines are said to be the most important offenders in this regard. It needs, therefore, only to be mentioned that, as a result of the use of antibiotics, superinfections with monilia and staphylococci, the latter causing serious and even fatal enterocolitis, are commonplace despite knowledge of the cause (32, 52, 53, 57, 63, 66). Urologic infections by Gram-negative organisms, pseudomonas, and proteus, once uncommon, and which are relatively resistant to antibiotics, are on the increase as the result of the effect of antibiotics on formerly common invaders of the urinary tract. Skin superinfections resulting from disturbed skin ecology tend to be generally ignored in most tracts on antibiotics (88).

The change in character of staphylococcus infection from a penicillin-sensitive form (25 percent resistant to a now extremely resistant form 75 percent resistant) is an outstanding development of penicillin therapy. Here,

either through mutation or breeding out, staphylococci tend to elaborate penicillinase and to destroy penicillin, whereas, originally, they did not have this ability and were dramatically vulnerable to ordinary penicillin. Antibiotic consumption, in general, and the development of antibiotic resistance by microorganisms have been shown to be positively correlated (8, 62, 111).

For all practical purposes, therefore, infection by the penicillin-resistant staphylococcus and all other antibiotic resistant infections which are on the increase are drug-induced diseases. These special forms of infections, i.e., those which are in excess of the number usually present before the antibiotic era, are with us as a consequence of the widespread use of penicillin and other potent antibiotics, hence drug-induced diseases.

It is well to note, however, that drugs in general and potent antimicrobial agents in particular, now also form an important element of our environment and that they cannot be withdrawn without creating at least as great a disturbance in our ecologic stability as that which resulted from their introduction (103).

LITERATURE CITED

1. Abry, J., and Cavusoglu, M., N. Y. *State J. Med.*, **60**, 1638–40 (1960)
2. Andrews, W. C., *Obstet. Gynecol. Survey*, **16**, 747–67 (1961)
3. Angervall, L., Lehmann, L., and Lincoln, K., *Acta Path. Microbiol. Scand.*, **54**, 283–86 (1962)
4. Arden, G. B., Friedman, A., and Kolb, H., *Lancet*, **1**, 1164–65 (1962)
5. Ayd, F. J., Jr., *J. Am. Med. Assoc.*, **175**, 1054–60 (1961)
6. Baragar, F. D., and Duthie, J. J. R., *Brit. Med. J.*, **1**, 1106–08 (1960)
7. Barnes, J. M., and Schoental, R., *Brit. Med. Bull.*, **14** (2), 165–67 (1958)
8. Bauer, A. W., Perry, D. M., and Kirby, W. M. M., *J. Am. Med. Assoc.*, **173**, 475–80 (1960)
9. Beck, I. T., Fletcher, H. W., McKenna, R. D., and Griff, H., *Gastroenterology*, **38**, 740–49 (1960)
10. Bendel, W. L., Jr. and Race, G. J., *Arch. Internal Med.*, **108**, 916–24 (1961)
11. Benton, J. W., Tynes, B., Register, H. B., Alford, C., and Holley, H. L., *J. Am. Med. Assoc.* **180**, 115–18 (1962)
12. Beutler, E., in *The Metabolic Bases of Inherited Disease*, Chap. 32, 1031–67, (Stanbury, J., Wyngaarden, J. B., and Fredrickson, D. S., Eds., McGraw, New York, 1960)
13. Block, M., *Clin. Pharmacol. Therap.*, **1**, 748–57 (1960)
14. Boggs, T. A., Chown, B., Day, R. A., Diamond, L. K., Sturgeon, P., and Zuelzer, W. W., *Blood*, **14**, 591–601 (1959)
15. Bonser, G. M., Clayson, D. B., and Jull, J. W., *Brit. Med. Bull.*, **14**(2), 146–52 (1958)
16. Boyland, E., *Brit. Med. Bull.*, **20** (2), 121–26 (1964)
17. Brodie, B. B., *Pharmacologist* **6**(1), 12–26 (1964)
18. Brookes, P., and Lawley, P. D., *Brit. Med. Bull.*, **20**(2), 91–95 (1964)
19. Burston, J., Darmady, E. M., and Stranck, F., *Brit. Med. J.*, **1**, 1277–79 (1958)
20. Byers, R. R., Bergman, A. B., and Joseph, M. C., *Pediatrics*, **29**, 26–36 (1962)
21. Cahen, R. L., *Clin. Pharmacol. Therap.*, **5**, 480–514 (1964)
22. Cardell, B. S., *Brit. Med. J.*, **1**, 1145–48 (1961)
23. Carr, E. A., Jr., *Pharmacol. Rev.*, **6**, 365–424 (1954)
24. Carr, E. A., Jr., and Aste, G. A., in *Ann. Rev. Pharmacol.*, **1**, 105–24 (1961)
25. Chalmers, J. N. M., in *Sensitivity Reactions to Drugs*, 17–27 (Presented at Council Intern. Organ. Med. Sci. Symp., 1957, Thomas, Springfield, Ill., 1958)
26. Chalmers, T. M., *Brit. Med. J.*, **1**, 747 (1964)
27. Chase. M. W., in *Sensitivity Reactions to Drugs*, 125–34 (Presented at Council Intern. Organ. Med. Sci. Symp., 1957, Thomas, Springfield, Ill., 1958)
28. Clausen, E., *Acta Med. Scand.*, **172**, 419–26 (1962)
29. Clayson, D. B., *Chemical Carcinogenesis* (Little, Brown, Boston, 1962)

30. Cohen, A. A., and Lawrence, S. H., *Ann. Internal Med.*, **46**, 893–906 (1957)
31. Conney, A. H., and Burns, J. J., in *Advan. Pharmacol.*, **1**, 31–58, (Garattini, S., and Shore, P. A., Eds., Academic, New York, 1962)
32. Cook, J., Elliott, C., Elliot-Smith, A., Frisby, B. R., and Gardner, A. M. N., *Brit. Med. J.*, **1**, 542–47 (1957)
33. Council on Drugs, *J. Am. Med. Assoc.*, **171**, 49–51 (1959)
34. Daniel, J. W., *Toxicol. Appl. Pharmacol.*, **4**, 572–94 (1962)
35. Davies, G. E., in *Sensitivity Reactions to Drugs*, 149–72 (Presented at Council Intern. Organ. Med. Sci. Symp., 1957, Thomas, Springfield, Ill., 1958)
36. Dickens, F., *Brit. Med. Bull.*, **20**, (2) 96–101 (1964)
37. Discombe, G., in *Sensitivity Reactions to Drugs*, 6–16 (Presented at Council Intern. Organ. Med. Sci. Symp. 1957, Thomas, Springfield, Ill., 1958)
38. Dockerty, M. B., Smith, R. A., and Symmonds, R. E., *Proc. Staff Meetings Mayo Clinic*, **34**, 321–28 (1959)
39. Done, A. K., in *Drugs of Choice 1964–1965*, 815–36, (C. V. Mosby, St. Louis, Mo., 1964)
40. Done, A. K., *Clin. Pharmacol. Therap.* **5**, 432–79 (1964)
41. Dowling, H. F., and Lepper, M. H., *J. Am. Med. Assoc.*, **188**, 307–09 (1964)
42. Editorial, *J. Am. Med. Assoc.*, **255**, 623–24 (1956)
43. Editorial, *Brit. Med. J.*, **1**, 1395 (1964)
44. Einhorn, M., and Davidsohn, I., *J. Am. Med. Assoc.*, **188**, 802–6 (1964)
45. Einspruch, B. C., and Gonzalez, V. V., *J. Am. Med. Assoc.*, **173**, 809–11 (1960)
46. Engelfriet, C. P., and Van Loghem, J. J., in *Drug-Induced Diseases*, 51–64, (Presented at Boerhaave Courses Post-graduate Med. Educ. Symp., The Netherlands, Meyler, L., and Peck, H. M., Eds., Thomas, Springfield, Ill., 1962)
47. Erslev, A. J., *J. Am. Med. Assoc.*, **188**, 531–32 (1964)
48. Erslev, A. J., and Wintrobe, M. M., *J. Am. Med. Assoc.*, **181**, 114–19 (1962)
49. Essig, C. F., *Clin. Pharmacol. Therap.*, **5**, 334–43 (1964)
50. Fassett, D. W., in *Ann. Rev. Pharmacol.* **3**, 267–92 (1963)
51. Ferris, T. F., Morgan, W. S., and Levitin, H., *New England J. Med.*, **265**, 381–83 (1961)
52. Finland, M., and Weinstein, L., *New England J. Med.*, **248**, 220–26 (1953)
53. Florey, M. E. *The Clinical Application of Antibiotics*, **4** (Oxford Univ. Press, London, 1960)
54. Freeman, R. B., Maher, J. F., Schreiner, G. E., and Mostofi, F. K., *Ann. Internal. Med.*, **57**, 34–43 (1962)
55. Friend, D. G., *Clin. Pharmacol. Therap.*, **5**, 257–62 (1964)
56. Friend, D. G., and Hoskins, R. G., Med. Clin. North Am. **44**(5), 1381–92 (1960)
57. Garrod, L. P., in *Sensitivity Reactions to Drugs*, 109–17 (Presented at Council Intern. Organ. Med. Sci. Symp., 1957, Thomas, Springfield, Ill., 1958)
58. Garrod, L. P., in *Sensitivity Reactions to Drugs*. 92–100, (Presented at Council Intern. Organ. Med. Sci. Symp., 1957, Thomas, Springfield, Ill., 1958)
59. Gerarde, H. W., in *Ann. Rev. Pharmacol.*, **4**, 223–46 (1964)
60. Glushien, A. S., and Fisher, E. R., *J. Am. Med. Assoc.*, **160**, 204–6 (1956)
61. Godfrey, C. M., *Can. Med. Assoc. J.*, **85**, 689–91 (1961)
62. Goodier, T. E. W., and Parry, W. R., *Lancet*, **1**, 356–57 (1959)
63. Goslings, W. R. O., in *Drug-Induced Diseases*, 181–88, (Presented at Boerhaave Courses Post-graduate Med. Educ. Symp., The Netherlands, Meyler, L., and Peck, H. M., Eds., Thomas, Springfield, Ill., 1962)
64. Greenberg, L. H., and Tanaka, K. R., *J. Am. Med. Assoc.*, **188**, 423–26 (1964)
65. Grunback, M. M., Ducharme, J. R., and Moloshok, R. E., *J. Clin. Endocrinol.*, **19**, 1369–80 (1959)
66. Guthe, T., Idsoe, O., and Willcox, R. R., *Bull. World Health Organ.*, **19**, 427–501 (1958)
67. Haddow, A. *Brit. Med. Bull.*, **14** (2), 79–92 (1958)
68. Haddow, A., *Brit. Med., Bull.*, **20** (2), 87–90 (1964)
69. Halpern, B. N., in *Sensitivity Reactions to Drugs*, 135–48 (Presented at Council Intern. Organ. Med. Sci. Symp., 1957, Thomas, Springfield, Ill., 1958)
70. Hayles, A. B., and Nolan, R. B., *Proc. Staff Meetings, Mayo Clinic*, **32**, 41–44 (1957)
71. Heymann, W., Hackel, D. B., Hunter,

J. L. P., *Pediatrics*, **25**, 112–18 (1960)

72. Hollander, W., Jr., in *Diseases of the Kidney*, Chap. 21, 675–711 (Strauss, M. B., and Welt, L. G., Eds, Little, Brown, Boston, 1963)
73. Holley, H. L., *Ann. Internal Med.*, **55**, 1036–39 (1961)
74. Hollister, L. E., *Clin. Pharmacol. Therap.*, **5**, 322–33 (1964)
75. Hueper, W. C., *Clin. Pharmacol. Therap.*, **3**, 776–813 (1962)
76. Huguley, C. M., Jr., in *Disease-A-Month* (Yearbook Med. Publ. Inc. Chicago, Oct., 1963)
77. Huguley, C. M., *J. Am. Med. Assoc.*, **188**, 817–18 (1964)
78. Jandl, J. H., *Ann. Internal Med.*, **58**, 702–9 (1963)
79. Jawetz, E., *Brit. Med. J.*, **2**, 951–55 (1963)
80. Jenkins, R. B., and Toole, J. F., *Arch. Internal Med.*, 113, 691–95 (1964)
81. Johnson, R. L., Smyth, C. J., Holt, G. W., Lubchenco, A., and Valentine, E., *Arthritis Rheumat.*, **2**, 224–49 (1959)
82. Karnofsky, D. A., and Clarkson, B. D., in *Ann. Rev. Pharmacol.* **3**, 357–428 (1963)
83. Kellermeyer, R. W., Tarlov, A. R., Brewer, G. J., Carson, P. E., and Alving, A. S., *J. Am. Med. Assoc.*, **180**, 388–94 (1962)
84. Kontos, H., *New England J. Med.*, **266**, 38–39 (1962)
85. Kraybill, H. F., *Clin. Pharmacol. Therap.*, **4**, 73–87 (1963)
86. Lang, P. A., and Jones, C. C., *J. Am. Med. Assoc.*, **188**, 464–66 (1964)
87. Laughlin, R. C., *J. Am. Med. Assoc.*, **181**, 339–40 (1962)
88. Lever, W. F., *Histopathology of the Skin*, 3rd ed. (Lippincott, Philadelphia, 1961)
89. Levitt, B. H., Gottlieb, A. J., Rosenberg, I. R., and Klein, J. J., *Clin. Pharmacol. Therap.*, **5**, 301–6 (1964)
90. Lipman, W. H., *GP*, **15**, 94–98 (1957)
91. Lorenzen, I., in *Drug-Induced Diseases*, 175–79 (Presented at Boerhaave Courses Post-graduate Med. Educ. Symp., The Netherlands, Meyler, L., and Peck, H. M., Eds., Thomas, Springfield, Ill., 1962)
92. Lundin, P. M., *Brit. J. Cancer*, **15**, 838–47 (1961)
93. Magee, P. N., and Schoental, R., *Brit. Med. Bull.*, 20 (2), 102–6 (1964)
94. Mantel, N., *Clin. Pharmacol. Therap.*, **4**, 104–9 (1963)
95. McCabe, W. R., and Jackson, G. G., *Arch. Internal Med.*, **110**, 856–64 (1962)
96. McGeer, P. L., Boulding, J. E., Gibson, W. C., and Foulkes, R. D., *J. Am. Med. Assoc.*, **177**, 665–70 (1961)
97. Mellin, G., and Katzenstein, M., *New England J. Med.*, **267**, 1184–93 (1962)
98. Meyler, L., Ed., *Side Effects of Drugs*, 3rd ed. (Excerpta Medica Foundation, The Hague, 1960)
99. Meyler, L., Ed., *Side Effects of Drugs*, 4th ed. (Excerpta Med. Found., The Hague, 1963)
100. Meyler, L., and Peck, H. M., Eds., *Drug-Induced Diseases*, (Presented at Boerhaave Courses Post-graduate Med. Educ. Symp., The Netherlands, Thomas, Springfield, Ill., 1962)
101. Millichap, J. G., and Kirman, B. H., *Lancet*, 1, 1074–75 (1953)
102. Modell, W., *J. Am. Med. Assoc.*, **176**, 945–46 (1961)
103. Modell, W., *Science*, **139**, 1180–85 (1963)
104. Modell, W., *Clin. Pharmacol. Therap.*, **5**, 265–72 (1964)
105. Modell, W., Krop, S., Hitchcock, P., and Riker, W. K., Jr., *J. Pharm. Exptl. Therap.*, **87**, 400–13 (1946)
106. Moeschlin, S., in *Sensitivity Reactions to Drugs*, 77–91, (Presented at Council Intern. Organ. Med. Sci. Symp., 1957, Thomas, Springfield, Ill., 1958)
107. Moser, R. H., Ed., *Diseases of Medical Progress*, 2nd ed. (Thomas, Springfield, Ill., 1964)
108. Mulder, D., Bastron, J., and Lambert, E., *Neurology*, **6**, 627–35 (1956)
109. Munch-Peterson, E., and Boundy, C., *Bull. World Health Organ.*, **26**, 241–52 (1962)
110. Nelp, W. B., *Arch. Internal Med.*, **108**, 702–10 (1961)
111. Newman, C. R., *Ann. Internal Med.*, **45**, 409–44 (1956)
112. Nieweg, H. O., in *Drug-Induced Diseases*, 77–90, (Presented at Boerhaave Courses Post-graduate Med. Educ. Symp., The Netherlands. Meyler, L., and Peck, H. M., Eds., Thomas, Springfield, Ill., 1962)
113. Norman, P. S., and Cluff, L. E., in *Drugs of Choice 1964–1965*, Chap. 3, 50–65, (Mosby, St. Louis, 1964)
114. Orr, J. W., *Brit. Med. Bull.*, **14** (2), 99–101 (1958)
115. Peck, S. M., *J. Mount Sinai Hosp.*, N. Y., **30** (1), 1–14 (1963)

116. Pickering, G., *Lancet*, **2**, 115–19 (1961)
117. Popper, H., and Schaffner, F., *Ann. Internal Med.*, **51**, 1230–52 (1959)
118. Reed, H., and Campbell, A. A., *Can. Med. Assoc. J.*, **86**, 176–78 (1962)
119. Rees, K. R. *Ciba Found. Symp. Enzymes and Drug Action, 1962*
120. Remmer, H., *Ciba Found. Symp. Enzymes and Drug Action, 1962*
121. Reuber, M. D., and Bradley, J. E., *J. Am. Med. Assoc.*, **174**, 263–69 (1960)
122. Rich, A. R., in *Sensitivity Reactions to Drugs*, 196–208, (Presented at Council Intern. Organ. Med. Sci. Symp., 1957, Thomas, Springfield, Ill., 1958)
123. Roe, F. J. C., and Lancaster, M. C., *Brit. Med. Bull.*, **20** (2), 127–33 (1964)
124. Rosenheim, M. L., in *Sensitivity Reactions to Drugs*, 1–5, (Presented at Council Intern. Organ. Med. Sci. Symp., Rosenheim, M. L., and Moulton, R., Eds., Thomas, Springfield, Ill., 1958)
125. Rosenthal, A., *J. Am. Med. Assoc.*, **167**, 1118–21 (1958)
126. Roush, G. Jr., and Kehoe, R. A., in *Ann. Rev. Pharmacol.* **4**, 247–64 (1964)
127. Saiger, G. L., *The Food and Drug Administration Information Center on Adverse Reactions and Hazards*, (Presented at Drug Information Services Conference, American Society of Hospital Pharmacists, Lexington, Ky., 24 Feb. 1964)
128. Salaman, M. H., and Roe, F. J. C., *Brit. Med. Bull.* **20** (2), 139–44 (1964)
129. Samter, M. and Berryman, G. H., in *Ann. Rev. Pharmacol.* **4**, 265–80 (1964)
130. Schaffner, F., *J. Am. Med. Assoc.*, **174**, 1690–95 (1960)
131. Schimmel, E. M., *Ann. Internal Med.*, **60**, 100–10 (1964)
132. Schreiner, G. E., *Ann. Internal Med.*, **57**, 1047–52 (1962)
133. Schwartz, R. H., and Vaughan, J. H., *J. Am. Med. Assoc.*, **186**, 1151–57 (1963)
134. Shambaugh, G. E., Jr., Derlacki, E. L., Harrison, W. N., Hous, H., Hous, W., Hildyard, V., Schuknecht, H., and Shea, J. J., *J. Am. Med. Assoc.*, **170**, 1657–60 (1959)
135. Sherlock, S. in *Drug-Induced Diseases*, 157–74 (Presented at Boerhaave Courses Post-graduate Med. Educ. Symp., The Netherlands, Meyer, L., and Peck, H. M., Eds. Thomas, Springfield, Ill., 1962)
136. Siegel, B. B., *Bull. World Health Organ.*, **21**, 703–13 (1959)
137. Slater, E. M., Gibson, J. M., Dykes, M. H. M., and Walzer, S. G., *New Eng. J. Med.*, **270**, 983–87 (1964)
138. Smith, J. L., *Arch. Ophthalmol.*, **68**, 186–90 (1962)
139. Stubbé, L. Th. F. L., in *Drug-Induced Diseases*, 145–55 (Presented at Boerhaave Courses Post-graduate Med. Educ. Symp., The Netherlands, Meyer, L., and Peck, H. M., Eds., Thomas, Springfield, Ill., 1962)
140. Symmers, W. St. C., in *Sensitivity Reactions to Drugs*. 209–22, (Presented at Council Intern. Organ. Med. Sci. Symp., 1957, Thomas, Springfield, Ill., 1958)
141. Symmers, W. St. C., in *Drug-Induced Diseases*, 123–36 (Presented at Boerhaave Courses Post-graduate Med. Educ. Symp., The Netherlands, Thomas, Springfield, Ill., 1962)
142. Tarlov, A. R., Brewer, G. J., Carson, P., and Alving, A. S., *Arch. Internal Med.*, **109**, 209–34 (1962)
143. Tegner, W. *Brit. Med. J.*, **1**, 1587–88 (1962)
144. Teilum, G., *J. Lab. Clin. Med.*, **43**, 367–74 (1954)
145. Torack, R. M., *Am. J. Med.*, **22**, 872–82 (1957)
146. Turner, N. A., *Med. J. Australia*, **1** (10), 361–62 (1964)
147. Washburn, T. C., and Kaplan, E., *Clin. Pediat.*, **3**, 89–92 (1964)
148. Weisburger, J. H., and Weisburger, E. K., *Clin. Pharmacol. Therap.*, **4**, 110–29 (1963)
149. Welch, H., *J. Am. Med. Assoc.*, **170**, 2093–96 (1959)
150. Welch, H., Lewis, C. N., Weinstein, H. I., and Boeckman, B. B., *Antibiot. Med.*, **4**, 800–13 (1957)
151. Williams, R. T., *Ciba Found. Symp. Enzymes and Drug Action, Introduction to Section 5, 1962*
152. Wolinsky, E., and Hines, J. *New England J. Med.*, **266**, 759–62 (1962)
153. Zapp, J. A., Jr., and Clayton, J. W., Jr., in *Ann. Rev. Pharmacol.* **3**, 343–56 (1963)
154. Zbinden, G. in *Advan. Pharmacol.* **2**, 1–112 (Garattini, S., and Shore, P. A., Eds., Academic Press, New York, 1963)

CONTENTS