DRUG ALLERGY[1]

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Introduction.—The design of this review reflects the continuing change in our approach to drug reactions of allergic etiology. That drugs can induce allergic reactions has been known for years: interest and emphasis have shifted to the conditions which must be met before sensitization occurs. Consequently, this review is divided into (*a*) a tabulation of allergic reactions to drugs which have been published during the period of this review; (*b*) a discussion of some structural characteristics of drugs which sensitize; (*c*) a discussion of the role of the host during various phases of sensitization; and (*d*) a few paragraphs on practical considerations.

The past year has advanced us toward goals which have been apparent for a number of years: to define drug reactions with precision, and to establish the conditions which lead to the formation of antibodies against drugs. Drug allergy requires the presence of antibodies.

Drugs are either complete antigens or antigenic determinants which must combine with a carrier moiety to induce the formation of antibodies. Some, but comparatively few drugs are complete antigens. Many "sensitizing" drugs, on the other hand, produce antigenic determinants during mild or substantial bio-transformation. Numerous metabolic reactions which occur in man—oxidation, reduction and hydrolysis, synthesis and conjugation—have been identified (1, 2). The efficiency of metabolic handling and disposal of drugs is surprising (3), but the rapid development of new compounds leaves some doubt whether microsomal and nonmicrosomal enzymes are always equipped for the orderly processing of synthetic chemicals which evolution might not have foreseen. Some of the conditions which encourage the development of drug allergy have become apparent (4) even though we can foresee that new compounds will result in new and unforeseen reactions. The sequence is comparatively clear: a reactive drug, or the reactive metabolite of a drug, must meet a reactive host.

Allergic reaction to drugs—a survey.—Drug allergy is probably the most serious of "iatrogenic" diseases: reviews which have been published in 1962 illustrate the increasing scope of the problem (5). The Registry on Blood Dyscrasias of the Council on Drugs of the American Medical Association is about to be expanded into a registry of drugs which cause any side-effects whatever their nature (6). The feeling that the matter is urgent and that determined action should be taken to reverse the trend is nearly universal (7).

[1] The survey of the literature pertaining to this review was concluded July 1, 1963.

The number of recorded drug reactions[2] which are—demonstrably or by implication—of allergic origin, has increased so much that analysis in detail becomes uneconomical.[3] Papers describe, by and large, four types of reactions: (*a*) familiar reactions to familiar compounds (Table 1); (*b*) unfamiliar reactions to familiar compounds (Table 2); (*c*) reactions to either type to new compounds or to compounds not previously found to sensitize (Table 3); and (*d*) reactions which have been called allergic by some, toxic by others without sufficient evidence to permit final classification (Table 4).

The term "familiar," applied to drugs, refers to compounds which—like penicillin—are expected to produce untoward effects in a significant number of patients; applied to reactions, the term "familiar" designates the reaction which is typical for a particular drug. In most instances, e.g. in penicillin reactions, familiar reactions will be of the "classical" type of allergy (which has been with us so much longer), i.e., urticaria, rhinitis and bronchial asthma, anaphylactic shock and serum sickness. But this is not uniformly true; leukopenia and agranulocytosis would be "familiar" reactions for aminopyrine and chloramphenicol; thrombocytopenia; the familiar reaction for sedormid or quinidine. "Unfamiliar" reactions are less predictable and, often, more complex; they include purpura, acquired hemolytic anemia, diseases associated with antinuclear antibody and rheumatoid factor, periarteritis nodosa and, conceivably, dermatomyositis. It should be kept in mind, however, that urticaria produced by aminopyrine would also represent an unfamiliar reaction to a familiar drug. The third category deals with drugs of rather recent origin: in some instances, the nature of these reactions is not quite clear. In spite of doubt, we have been liberal in including papers which report reactions to new drugs because they might indicate an unforeseen allergenic potential. Table 4 lists reactions which might be familiar, and even suggestive of allergy, but lack identification of antibody; of these, cholestatic jaundice—induced by phenothiazines or erythromycin lauryl ester sulfate—appears to be the most commonly reported complication.

The tabulation reflects arbitrary decisions in several areas. Penicillin and penicillin derivatives—including the new, semi-synthetic compounds—have been listed in Table 1 in order to keep the references together. Photosensitivity has been classified as an allergic reaction even though its mechanism is still unknown. Symptoms caused by drugs which act as histamine releasers, on the other hand, have not been included since there is good evi-

[2] Individual contributions which are part of anthologies, e.g. in Meyler & Peck's monograph (5), have not been given separate listings in the bibliography of this review.

[3] Our survey of drug reactions has been greatly facilitated by the use of new techniques of medical documentation. We screened more than 600 articles which referred to side effects of drugs: of these, 124 were included in our tabulation (Tables 1 to 4). The experience and assistance of Mr. W. A. Southern, Head, Science Information Services, Abbott Laboratories, have been of great help to us.

TABLE 1

"FAMILIAR" REACTIONS TO "FAMILIAR" DRUGS

ANTIBACTERIALS

Sulfonamides

Sulfachloropyridazine—*b*, *d* (8)
Sulfadimethoxine—*b*, *d* (9, 10)
Sulfadimethyloxazol—*d* (11)
Sulfamethoxazole—*d* (12, 13)

ANTIBIOTICS

Penicillins

Ampicillin—*s* (14, 15, 16)
Benzathine Penicillin G—*a*, *d*, *f*, *k*, *l* (16, 17, 18)
Methicillin—*b*, *d*, *f* (16, 19, 20, 21, 22)
Novobiocin—*b*, *d* (9, 23)
Oxacillin—*b*, *d* (16, 21, 24)
Penicillin—*a*, *d*, *s* (25, 26, 27)
Penicillin G—*a*, *d* (16, 18, 26, 28)
Phenethicillin—*a*, *d* (16)
Potassium Phenoxymethyl Penicillin—*a* (29, 30)
Propicillin—*d* (31)

Tetracyclines

d, *r* (14, 26, 32)

ANTICOAGULANTS

Heparin—*a* (33)

ANTICONVULSANTS

Diphenylhydantoin—*d*, *f* (34)
Ethosuximide—*b*, *d* (35)
Methsuximide—*b*, *d* (35)
Trimethadione—*b* (35)

ANTIHISTAMINES

Chlorpheniramine
Diphenhydramine
Promethazine
Tripellenamine
—*b*, *d*, *k*, *l*, *p*, *r* (36)

ANTI-RHEUMATICS

Oxyphenbutazone—*d* (37)

HORMONES

Insulin—*a*, *d* (38, 39)

LOCAL ANESTHETICS

Procaine—*a*, *d* (40)

SEDATIVES

Carbromal—*c*, *d* (41)

CODE FOR IDENTIFICATION OF TYPES OF REACTIONS PRODUCED BY DRUGS LISTED IN TABLES 1–4

a—Anaphylaxis
b—Blood dyscrasias (affecting WBC, RBC, platelets)
c—"Collagen" diseases (including periarteritis, lupus erythematosus, the nonthrombocytopenic purpuras)
d—Dermatologic (including mucocutaneous lesions, urticaria, angioneurotic edema, exanthema, dermatitis)
f—Fever
h—Cardiovascular symptoms (fibrillation, etc.)
k—Reactions involving kidney
l—Reactions involving liver
n—Neuromuscular symptoms
p—Photosensitivity
r—Respiratory symptoms (including rhinorrhea, bronchial asthma, eosinophilic pneumonitis)
s—Reactions suggesting serum sickness

TABLE 2

"UNFAMILIAR" REACTIONS TO "FAMILIAR" DRUGS

ANALGESICS
- Saligenin—*d* (42)

ANTIARRHYTHMIAS
- Quinidine—*b* (43)
- Procainamide—*c* (44)

ANTIBACTERIALS
- Salicylazosulfapyridine—*b* (45)
- Nitrofurantoin—*a, b, r* (46, 47)

ANTIBIOTICS
- Chloramphenicol—*c, d* (48)
- Streptomycin—*b, d, k* (49)

Penicillins
- Methicillin—*b* (50)
- Penicillin—*a, b, d, l* (51, 52)
- Procaine Penicillin G—*l* (53)

ANTICONVULSANTS
- Diphenylhydantoin—*b, c, d, f* (43, 54)
- Trimethadione—*d* (55)

ANTIMALARIALS
- Chloroquine—*b, d, l* (56)
- Quinine—*b* (43)

ANTIPYRETICS
- Acetophenetidine—*b* (57)

ANTIRHEUMATIC AGENTS
- Gold—*b, d, l* (56)

ANTITHYROID AGENTS
- Carbimazole, Methimazole, Methylthiouracil, Potassium Perchlorate—*b, d* (58)
- Propylthiouracil—*b, d* (58, 59)

ANTITUBERCULOSIS AGENTS
- *Para*-Aminosalicyclic Acid—*d, f, h, r* (60, 61)

DIAGNOSTIC AIDS
- Sodium Diatrizoate—*a, d, n, r* (62)

ESTROGENS
- Estradiol—*d* (63)

MUSCLE RELAXANTS
- Carisoprodol—*d* (64)

TRANQUILIZERS
- Prochlorperazine—*n* (65)

dence that the intolerance to various drugs described in patients with urticaria pigmentosa is due to the direct effect of the chemical on mast cells, not mediated by antigen antibody reaction (132 to 134).

Progress in the investigation of drugs and drug metabolities.—Simple chemical compounds which produce allergic reactions present an attractive experimental tool: for this reason, dermatologists have studied cross-reactivity of sensitizing chemicals for many years. Cross-reactivity proved to be a useful technique (in rabbits) to clarify reactions to antibodies (135).

Experience with simple drugs suggests that minor chemical differences can result in significant differences in metabolic behavior: phenobarbital, for instance, is comparatively innocuous, while deoxyphenobarbital produces frequent and significant side-effects (136).

Occupational exposure presents, as a rule, acceptable correlation between

contact with simple chemicals and subsequent reactions: toluene diisocyanate can produce bronchial asthma (137) in susceptible individuals, but paradichlorobenzene—in the bizarre case of a woman addicted to moth-balls—produced a fixed drug eruption (138). A comprehensive survey of respiratory allergy due to chemical compounds encountered in the rubber, lacquer, shellac, and beauty culture industries implicated ethylenediamine, ammonium thioglycolate, monoethenolamine, and hexamethylenamine as occupational hazards (139).

TABLE 3

REACTIONS TO NEW DRUGS OR TO DRUGS NOT PREVIOUSLY KNOWN TO SENSITIZE

ANABOLIC AGENTS
- Nandrolone—*d* (66)

ANESTHETICS
- Lignocaine—*a* (67)
- Thiopental—*a* (68)

ANTIBACTERIALS
- Amphotericin B—*d*, *k* (69)
- Cephalothin—*d* (70)
- Colimycin—*d* (71)
- Demethylchlortetracycline—*d*, *p* (72, 73)

ANTICHOLINERGICS
- Glycopyrrolate—*d* (74)
- Propyromazine—*d* (75)

ANTICOAGULANTS
- Fibrinolysin—*b*, *d* (76)
- Phenindione—*b*, *d*, *f*, *k*, *l* (77, 78, 79, 80, 81, 82)

ANTICONVULSANTS
- Sulthiame—*n* (83)

ANTIDEPRESSANTS
- Amitriptyline—*d* (84)
- Isocarboxazid—*d*, *n* (107)
- Imipramine—*n* (107)

ANTIHISTAMINES
- Diphenhydramine—*p* (85)

ANTIHYPERGLYCEMIC AGENTS
- Acetohexamide—*d* (86)
- Chlorpropamide—*d*, *l* (87, 88, 89)

ANTIHYPERTENSIVES
- Mebutamate—*d*, *s* (90)
- Methyldopa—*f* (91)

ANTIPARASITIC AGENTS
- Anthiomaline—*d*, *f*, *s* (92)

ANTITHYROID AGENTS
- Potassium Perchlorate—*b* (93)

CHOLINESTERASE INHIBITORS
- Diisopropoxyphosphoryl Fluoride (DPF)—*d* (94)

DIURETICS ANTIHYPERTENSIVES
- Acetazolamide—*b*, *d*, *f*, *n* (95, 96)
- Chlorothiazide—*b*, *d*, *k*, *l* (56, 97)
- Methyclothiazide—*d* (98)
- Polythiazide—*d* (99, 100)

ENZYMES
- Chymotrypsin—*a* (101)
- Varidase—*s* (102)

PLASMA VOLUME EXPANDERS
- Haemacel—*d* (103, 104)

TRANQUILIZERS
- Benzquinamide—*n* (105)
- Chlordiazepoxide—*d*, *n* (106)

VACCINES
- Horse Anti-Human-Cancer Serum—*k*, *s* (108)
- Measles Vaccine—*d*, *f* (109)

TABLE 4

REACTIONS WHICH MAY BE EITHER ALLERGIC OR TOXIC BUT REQUIRE FURTHER CLARIFICATION

ANABOLIC AGENTS
- Norethandrolone—*l* (110, 111)

ANESTHETICS
- Halothane—*l* (112, 113, 114, 115, 116, 117, 118)

ANTIBACTERIALS
- Sulfonamides
  - *l* (119)

ANTIBIOTICS
- Erythromycin Estolate—*f*, *l* (119, 120, 121, 122, 123, 124, 125)
- Ristocetin—*d*, *f*, *k*, *l*, *n* (119)
- Triacetyloeandomycin—*l* (119)
- Tetracyclines
  - Demethylchlortetracycline—*p* (9)

ANTIDEPRESSANTS
- Iproniazid—*l* (111)
- Pheniprazine—*l* (126)

ANTI-DIABETIC
- Chlorpropamide—*l* (111)

CHELATING AGENTS
- Penicillamine—*d*, *n* (127)

TRANQUILIZERS
- Chlorpromazine—*l*, *n* (128, 129, 130)
- Fluphenazine—*d*, *l*, *n* (131)

One would hardly include the past three observations—on chemicals not given for the control of disease—in a survey of drug allergies if it were not for the disturbing facts (*a*) that a significant number of patients had positive skin reactions and, in some instances, circulating antibodies to the unconjugated chemicals; and (*b*) that the chemicals are part of drugs which are in current use. The peculiar state of our chemical environment has made a rigid borderline between drugs and chemicals obsolete.[4] Patients who have become sensitive to simple chemicals as a result of occupational exposure might well react to drugs if the same chemical is part of a drug and freed during metabolic handling. The reverse, of course, is true. If the antigenic determinant of a drug sensitizes a patient, he will react to any nondrug which is metabolized into the same antigenic determinant. It is intriguing to speculate, for instance, about reactions which might be engendered by certified food colors many of which so qualify (140). One is reminded of the demonstration that chlorogenic acid is the chemical which is responsible for

[4] Evidence accumulates that this is an unavoidable conclusion: it seems appropriate, for instance, that this publication, in 1963, devoted considerable space to ME-18, an emulsifier added to margarines which caused, by still unidentified means, skin lesions in many consumers.

the bronchial asthma of workers exposed to the dust from green coffee, chaff and beans (141). While the number of these workers is comparatively small (and roasting inactivates the compound), polyphenolic compounds like chlorogenic acid are common and might be of greater significance than currently suspected.

Penicillin remained the area of major investigation and progress. Studies of sensitization and challenge to the intact molecule were reported both in guinea pigs (142) and man (143). Humoral immune response appears to produce anaphylaxis, urticaria or serum sickness, while cellular immune responses produce morbilliform eruptions or contact dermatitis. The antigenicity of a penicillin-serum protein complex has been confirmed in rabbits (144), but the significance of the various antibodies—particularly of hemagglutinating antibodies—is not quite clear (145).

A study of placental transfer of penicillin antibodies produced some startling results. Maternal and cord-blood sera of 105 mothers and infants were examined for the presence of penicillin antibodies with the bisdiazotized benzidine (BDB) and Ley hemagglutination techniques. It appears that the "BDB antibody"—like the reagin—does not pass the placental barrier, but that the "Ley antibody" is found in 95.1 per cent of the maternal sera and 73.5 per cent of the cord-blood sera of mothers who had received penicillin in the past, but were not clinically penicillin-sensitive. Skin tests were not done (146).

Penicillin reactions have been singled out for extensive study (*a*) because of the widespread use and usefulness of this antibiotic and (*b*) because of some peculiar aspects of penicillin reactions. It is agreed, for instance, that penicillin sensitivity is common, that positive skin reactions to penicillin are rarely obtained, and that—while anaphylactic shock occurs—estimates vary, but are as high as 300 patient deaths per year—a significant number of patients with established penicillin reactions have subsequently, advertently or inadvertently, been given penicillin without ill effects. It appears likely from these observations that penicillin is not an antigen, but produces sensitization by the release of an antigenic determinant. Search for the most likely breakdown-product established clearly that not penicillin, but penicillenic acid—by formation of amide bonds with protein and re-arrangement to penicilloyl—is responsible for penicillin reactions (147 to 152). Penicillenic acid is either a contaminant of penicillin solutions or is formed by metabolic handling. There is a significant increase in positive skin reactions if skin tests are carried out with a synthetic conjugate (penicilloyl-polylysine) rather than with the parent drug (153).

In spite of these advances the riddle of penicillin sensitivity is not yet, or not completely, solved. It is likely that different tests for penicillin sensitivity identify different antibodies. The use of circulating basophils of the rabbit as an indicator system for antigen-antibody reactions of various types, introduced by Shelley, has more recently been applied to penicillin reactions (154, 155). Shelley uses the intact molecule (Penicillin G); the pub-

lished results are encouraging, but the method involves multiple variables. In view of the wide interest which has been aroused by the initial reports, data on large groups of patients with established sensitivities should be available before long.

Since penicillin is on occasion the only effective antibiotic in an otherwise fatal disease, "desensitization" has been tried (156, 157). The first of these two reports describes the serological changes which occurred during treatment. A patient with subacute bacterial endocarditis and positive skin reactions to diluted penicillin G (100 units/ml), was given rapidly increasing doses of penicillin G—beginning with 100 units after prophylactic injection of epinephrine HCl and diphenhydramine. This was followed by 1000, 10,000, 100,000, and 1,000,000 units at intervals of thirty minutes, and by a regimen of 1,000,000 units of procaine penicillin every six hours for six weeks without ill effects. Skin tests became negative, skin sensitizing antibody was never found in the patient's serum, but the hemagglutination titer rose, temporarily, during her hospitalization. While most patients with anaphylactic reactions have demonstrable reagin titers, there is no apparent correlation between hemagglutinating antibodies and reagins. In other words, there is no simple yardstick for the use of desensitization, which is a calculated risk and not recommended as a standard procedure.

The role of the host in the development of drug reactions.—A correlation of exposure to penicillin and subsequent sensitization indicates that only a fraction of exposed patients (and almost no children) develop sensitivities. Since degradation of penicillin to penicillenic acid occurs easily, it is fair to assume that the "permissiveness" of the host is essential for development and course of drug reactions.

In the preceding section, it was suggested (*a*) that most drugs are not complete antigens or "natural haptens"; (*b*) that biotransformation of drugs creates antigenic determinants; and (*c*) that the formation of an antigenic metabolite-protein conjugate is likely to stimulate the formation of antibodies, but is not necessarily followed by symptoms in specific tissues, or by symptoms at all.

It has been shown that absorption and metabolic handling varies not only from host to host, but also in the same host at different times. Genetic make-up; developmental factors—as the absence of glucuronyl transferase which causes chloramphenicol toxicity in "biochemically immature" animals and man; diet, e.g. vitamin A and biotin deficiency (158, 159); and the simultaneous administration of drugs which act on related enzyme systems might accelerate or retard metabolic rate or metabolic pathway (160).

Once the antigenic determinant has formed, it must combine with the protein moiety of the eventual antigen. It has been said that the higher incidence of reaction to drugs which are given during infection—as compared with drugs which are given prophylactically—might be due to an increase in possible binding sites during tissue injury.

Once the antigenic conjugate has formed, the response of the host is not uniform. Some of the factors which influence sensitization, for instance age, have been under close scrutiny for some time. The possible importance of diet has been rediscovered. Studies on a small number of volunteers on low protein diets indicate that not only the quantity, but the quality of dietary protein influences antibody response to typhoid O and H antigens and tetanus toxin (161). There is no reason why this should not be equally true for antigenic material in general.

The extent of genetic control is uncertain. It is frequently said that the incidence of penicillin reactions is higher in atopic than in non-atopic individuals (162), but the evidence is not convincing. Burnet's recent essay on auto-immune disease (163) deals at length with host factors, e.g. with the possible role of disturbed cellular homeostasis as a prerequisite for the development of reactions. Interestingly enough, Burnet does not list any drugs as possible antigenic determinants. Actually, we are impressed by recent work which implies that we might have underestimated the role of genetics. Highly inbred strain 2 guinea pigs form antibodies to certain determinant groups of insulin which are "non-antigenic" for strain 13 guinea pigs (164).

Practical considerations.—Drug allergy represents a specific, indirect and circuitous form of drug reaction which is clearly distinguished from toxic reactions which are caused by a direct effect of a chemical on the tissues of the host. Toxic reactions are frequently (but not always) caused by the intact drug; in fact, toxicity might well be part of the basic pharmacological design. Allergy is never intentional; and while, as we have said before, intact drugs might, on occasion, induce allergic reactions, it is our intention in this review to underscore the growing awareness of the role of metabolites in the development of sensitization.

It is not always predictable whether biotransformation of drugs will produce toxic metabolites or antigenic determinants. The basic sequence is the same whether the end-effect is toxic or allegic. In principle, it should be simple to differentiate between toxic and allergic reactions; in practice, toxic and allergic reactions might be so similar that proper classification is difficult if not impossible. Photosensitivity is a typical example. Some authors talk about "photo-toxic," some about "photo-allergic" reactions. It is possible, of course, that drugs produce more than one type of reactions (165), but the interpretation of hepatic injury which follows the administration of phenothiazines, is still uncertain (166). It might be helpful to design more stringent criteria. The renal changes produced by phenacetin, for instance, must be toxic (167); while side reactions of antibiotics, e.g. griseofulvin (168, 169) or furaltadone (170) including nausea, fever, "tightness of chest," and "drug rash" are often so vague and transitory that they cannot be properly evaluated and catalogued. Even so, it is imperative that they be recorded as precisely as possible, since it might take years to identify the entire range of reactions which might be attributed to a drug. The tetracyclines are a clas-

sical example of this lag (171, 172). Unfortunately, the host contributes to the confusion. A tabulation of multiple side-effects of fourteen groups of drugs, gathered from sixty-seven publications, demonstrates that somatic changes as varied as leukopenia, photosensivitity, pruritus, skin rashes and even impairment of liver function might follow administration of placebos (173), a rather frightening outcome.

If metabolites rather than drugs per se induce antibody formation, the question of normal and abnormal biotransformation of new drugs requires careful attention. During preparation of this review, we have asked a number of pharmaceutical companies for information about enzymatic breakdown and excreted metabolites of a random selection of widely prescribed drugs. The tabulated returns provide much food for thought. Several antibiotics are excreted without demonstrable change (Table 5). This is surprising

TABLE 5

DRUGS REPORTED TO BE EXCRETED WITHOUT CHANGE

ANTIBIOTICS	OTHERS
Chloramphenicol	Acetazolamide
Erythromycin stearate	Cyclamate
Tetracycline	Chlorothiazide
Chlortetracycline	
Oxytetracycline	
Demethylchlortetracycline	
Novobiocin	
Triacetyloleandomycin	

in view of the fact that some of these antibiotics cause sensitization and toxic reactions. The number of drugs for which metabolic data are not available (or, while suspected, have not been demonstrated in experimental studies) is large (Table 6), but the increasing number of drugs with established enzyme requirements and identified metabolites is encouraging (Table 7).[5]

Conclusions and predictions.—By and large, the analysis of drug allergies which we have reported makes it clear that drugs which sensitize must have an "antigenic potential," but that the predominant variable is not the drug, but the host. The host, however, is elusive. Drug reactions might be predictable, if we had assays for the enzyme state of patients at the time at which drugs are administered. There is little hope that such assays will become prac-

[5] The tabulation represents a mere skeleton based on the comprehensive information which has been made available to us. Unfortunately, individual credits would exceed the limits of this review. We wish to acknowledge the interest and generous cooperation of the medical departments of pharmaceutical manufacturers who are identified by the generic names of the drugs which are listed in Tables 5, 6 and 7.

TABLE 6

DRUGS FOR WHICH ADEQUATE METABOLIC DATA ARE NOT AVAILABLE

ANALGESICS AND NARCOTICS
- Phenazocine

ANTIBIOTICS
- Griseofulvin

ANTICOAGULANTS
- Bishydroxycoumarin
- Anisindione

ANTIDIABETICS
- Tolbutamide

ANTIHISTAMINES
- Dimenhydrinate
- Diphenylpyraline
- Chlorpheniramine
- Phenindamine
- Methapyrilene
- Pyrrobutamine
- Pyrilamine
- Diphenhydramine

AUTONOMIC DRUGS
- Methantheline
- Isopropamide
- Pyridostigmine
- Methscopolamine
- Cyclopentamine
- Hydroxyamphetamine
- Benzphetamine
- Methoxyphenamine
- Tridihexethyl Chloride
- Phenmetrazine

COUGH DEPRESSANTS
- Carbetapentane

DIAGNOSTIC AIDS
- Ipodate

DIURETICS-ANTIHYPERTENSIVES
- Bendroflumethiazide
- Trichlormethiazide

PSYCHOPHARMACOLOGICAL AGENTS
(hypnotics-sedatives-tranquilizers)
- Acetophenazine
- Trifluoperazine
- Thiopropazate
- Pipamazine
- Prochlorperazine
- Trimeprazine
- Perphenazine
- Phenaglycodol
- Tranylcypromine
- Methyprylon
- Nialamide
- Hydroxyzine
- Chlorprothixene
- Trimethobenzamide
- Ethchlorvynol

tical within the near future. Moreover, studies of drugs prior to release are usually carried out on normal animals and normal volunteers, but the patient who takes a drug is not necessarily normal. We do not know what illness does to "normal" metabolic pathways. With this consideration in mind, we are inclined to believe, for instance, that the statement that several antibiotics are excreted without change should be viewed with caution.

The strengthened control of new drugs by the Food and Drug Administration has increased the number of tests which establish acute and subacute toxicity, but the published rules do not make any attempt to judge the antigenic potential of new chemicals. It is likely that allergic reactions to drugs will continue to increase and will make re-orientation of our screening

TABLE 7

DRUGS FOR WHICH SOME OR MOST METABOLITES AND ENZYMATIC PATHWAYS HAVE BEEN IDENTIFIED

ANALGESICS	COUGH DEPRESSANTS
Dextro-propoxyphene*	Levo-propoxyphene*
ANTI-ARRHYTHMIA AGENTS	DIURETICS-ANTIHYPERTENSIVES
Procainamide	Hydralazine†
ANTIBACTERIALS	PSYCHOPHARMACOLOGICAL AGENTS
Sulfisoxazole	(hypnotics-sedatives-tranquilizers)
Sulfadimethoxine	Promazine
ANTIBIOTICS	Thioridazine
Erythromycin Estolate	Thiethylperazine
ANTICONVULSANTS	Fluphenazine
Trimethadione	Trifluprομazine
Methyl-phenyl-ethyl hydantoin	Chlorpromazine
Diphenylhydantoin	Glutethimide
ANTIHISTAMINES	Pentobarbital
Tripellenamine	Mephenoxalone*
ANTITHYROID AGENTS	Chloral hydrate
Propylthiouracil	Chlordiazepoxide
AUTONOMIC DRUGS	Hydroxydione
Methamphetamine	Amitryptyline
Methysergide (maleate)	Meprobamate
	Mebutamate
	Carisprodol
	OTHERS
	Aspartate

*= Dog.
†= Pigeon liver.

procedures mandatory. Some of these procedures do not require experimentation, once the obligatory make-up of an antigenic determinant has been established. Since acetyl salicylic acid, for instance, does not fulfill the basic requirements for antigenic determinants, aspirin intolerance is probably not of allergic origin. Yet, the limitations of this approach are obvious. In theory it should have been predictable that thalidomide—derived from a "natural" amino acid, glutamic acid or glutamine—might not be metabolized like glutethimide or barbiturates since it carries an acylated amino group instead of two hydrocarbon residues in the alpha position of the ring system. Glutethimides and barbiturates, however, are inactivated by oxidation, i.e. by introduction of a hydroxyl group, or by the formation of carbonyl or carboxyl groups in the hydrocarbon moeity, while thalidomide is hydrolysed

into glutamic acid derivatives which are "unnatural" and might, conceivably, act as antimetabolites (174).

It is psychologically difficult, of course, on the one hand to maintain a high level of suspicion and on the other hand to continue synthesis and, especially, clinical trial of new drugs; but this is exactly what must be accomplished. It was brought home to us, recently, how much more sophisticated we have become. In an extraordinary study of the natural history of auto-immune diseases, Holmes & Burnet demonstrated that the NZB/B1 strain of mice develops serological and pathological evidence of "spontaneous" sensitization: positive Coombs test, hemolytic anemia, and glomerulonephritis (175). During a seminar in which these findings and their implications were discussed, the question was raised whether we were justified in disregarding a sentence which is part of "Materials and Methods" and sounds innocent enough: "the diet of the breeding stock is supplemented with Barastoc chicken mix and dried skim milk powder." The composition of the supplements is not known to us. Would it be permissible, someone said, to speculate that this particular strain of mice might be genetically unable to handle some of these foods, or, perhaps, some additives which they might contain, and might respond with the unexpected formation of an antigenic determinant? It seems to us that this is precisely the issue which we must face before we can curb the increase in allergic reactions to drugs. One reads so often lately that such reactions are part of the price which we must pay for living longer and at reduced risk. It might be well to remember (*a*) that such statements offer little consolation to the patient as a person who happens to suffer from drug-induced disease, but (*b*) that for the community at large, in spite of everything, the price is low.

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