RECENT LABORATORY STUDIES AND CLINICAL OBSERVATIONS ON HYPERSENSITIVITY TO DRUGS AND USE OF DRUGS IN ALLERGY

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The classification of reactions to drugs as allergic or clearly nonallergic (the latter consisting of hyperreactions and meta-reactions) has been previously reviewed (17) with reference to the definition of allergy itself. In the previous review it was suggested that the term hypersensitivity be used for reactions that could not yet be clearly classified as either allergic or nonallergic in nature. The present review is concerned chiefly with clinical observations and laboratory studies published during the period June, 1959 to May, 1960 and will be restricted to examples of drug allergy and drug hypersensitivity, as defined above. Clear-cut hyperreactions and poisoning by gross overdosage will be omitted. The authors must point out that their terminology has no particular intrinsic merit over that used by other writers. If the reader wishes further details of the terms briefly described above, he can, by referring to the published definition of the terms (17), learn what types of reactions are and are not likely to be considered in this review. The basis for deciding that a given reaction probably has no allergic basis has been previously discussed (16, 17, 18), but decisions will continue to be difficult. Many of the hypersensitivities considered in this review may eventually prove not to depend on the presence of antibodies, but this fact does not make them any less interesting or important.

The recent development of techniques permitting the demonstration of circulating antibody in the serum of certain patients allergic to penicillin suggests that one may some day hope to demonstrate antibodies in many other reactions that are already, on clinical grounds, considered to be allergic in nature. If this should come about, we may then be justified in concluding that failure to demonstrate antibody in other, more dubious situations strongly suggests that no antibody exists. At present such a conclusion would be rash, and even in the future one would wish to search for antibodies not only in the serum but elsewhere. The work of Ley *et al.* (71) with "penicillinized" erythrocytes has been followed by a recent interesting study in which Epp (31) demonstrated circulating antibody against penicillin in nine of 20 persons stated to be allergic to penicillin. Epp used bis-diazotized benzidine to couple penicillin with erythrocytes and detected the

presence of antibody by hemagglutination. Furthermore, specific inhibition by the antigen was demonstrated. Cross-reactions between different penicillins suggested that the penicillin molecule per se not the side chain, was the antigen. Unfortunately, the report does not indicate whether only those patients with reactions such as anaphylaxis or urticaria had demonstrable antibody in their serum or whether patients with, for example, dermatitis had such antibody also. By the Prausnitz-Kustner technique antibodies were demonstrated in two of seven post-mortem sera of patients who had died of penicillin anaphylaxis (80).

Before hyperreactions and intoxications from overdosage are dismissed, it would perhaps be useful to describe a few instances reported during the period covered by this review in order that the reader may decide for himself whether he considers the classification and restrictions valid. Evidence of extrapyramidal disturbances produced by prochlorperazine (Compazine) in eight patients (104) probably indicates hyperreaction even though one of the eight had a past history of allergy to a sulfonamide, one patient was known to be allergic to peanuts, and not all the patients had received large doses. The known effects of phenothiazines on the central nervous system are such that the changes observed in these patients probably represent merely an exaggeration of a fundamental pharmacological effect of the drug. The reported patients were presumably individuals who would be among the most responsive if a dose-response curve for this particular effect were carried out in a large population. As another example, the series of 16 patients who received large doses of ristocetin (the definition of a large dose in this series being more than 50 mg./kg. per day or the use of a solution of more than one mg./ml. in concentration) probably did not all have allergic reactions to the drug (42). Among the 16 patients, 11 had hematologic complications; decrease in platelets, leucocytes, and erythrocytes were all observed. However, the author of the above report found in rabbit experiments and *in vitro* studies that direct destruction of platelets could occur when high concentrations of the drug were used. The reaction was reversed in man and animals when the dosage was reduced, but skin rash and fever were also reported in several patients. Therefore, even though the concentration of ristocetin achieved in the patients was apparently sufficient to cause a direct effect on platelets, it would still be unwise to say that allergic reactions to this drug do not occur (see also the discussion of phenacetin, furaltadone, etc., below). The leukopenia, anemia, and gastrointestinal reaction produced by desacetyl methyl colchicine (27) were also most probably a result of overdosage in the instance reported, although the occurrence of a maculopapular rash in the patient should be noted.

Anaphylaxis

Acute, severe systemic reactions may be produced by a variety of drugs, including chemotherapeutic agents, horomones, local anesthetics, x-ray con-

trast media, sclerosing agents, and, occasionally, other injected, ingested, or inhaled drugs. Antigenic substances deliberately used in skin testing or hyposensitization are also obviously potentially dangerous (119). However, it appears likely that sclerosing agents, when inadvertently released in appreciable amounts into the general circulation, may cause direct intoxication needing no antibody for its mediation. The frequency with which reactions to x-ray contrast media occur immediately after the initial injection of the agent has been noted by several observers. Although most types of reaction usually reported to occur after a clearly recognizable period of sensitization may occasionally occur on first administration to a person with no known previous exposure [as in 27 of 216 cases of reactions to penicillin (73)], the reactions that occur during intravenous urography and other procedures using intravenous injections of similar compounds have usually been reported after initial exposure. A recent review (50) records 31 deaths in more than three million urograms.

Apropos of the occurrence of clearly allergic reactions after first known exposure to a drug, one often speculates that a previous, unknown exposure sensitized the patient. This speculation is consistent with Ljaljevic's (73) finding that penicillin, the commonest drug allergen in his series, was also the commonest cause of allergic reactions occurring promptly after first known exposure, for one would logically expect this widely used and frequently antigenic drug to be a common source of unknown or forgotten sensitizing exposure. Penicillin in foods may play a role here (see below) but forgotten exposure from previous medical treatment seems highly possible.

Local anesthetics are known to produce clearly allergic reactions, e.g., contact dermatitis, and allergic reactions may account for some of the deaths following use of local anesthetics. For example, a patient who developed respiratory distress and died 20 minutes after taking a throat lozenge containing benzocaine and tyrothricin was shown at autopsy to have edema of the larynx (54). Although tyrothricin cannot be exculpated with absolute certainty, the known propensity of local anesthetics to cause allergic reactions makes the benzocaine a much more likely offender. However, the known effects of local anesthetics on the central nervous system and on the myocardium make convulsions or sudden severe hypotension, respectively, likely whenever a large "bolus" of injected local anesthetic accidentally reaches the brain or myocardium. Therefore, many of the severe and even fatal reactions that occur after topical use of local anesthetics, as in dentistry, may well be related to vagaries of absorption rather than to allergy (2). Incidentally, the decision that some new local anesthetic is to be labeled by fiat and decree "not a 'caine' drug" will probably not confer any magical lack of toxicity on the drug.

It is not surprising to find that various proteins injected for therapeutic purposes may induce severe systemic reactions; gamma globulin (5), chymotrypsin (72), and other preparations of blood proteins (10) have

caused severe reactions. These reactions should not necessarily be expected always to follow the pattern of classic anaphylaxis, since direct effects from certain proteins, particularly enzymes, might also be expected. However, in a patient who developed hypotension, angioedema, and fever after intravenous injection of human fibrinolysin, immunologic studies suggested the presence of antibodies against fibrinolysin and against streptokinase activator (10).

Recent reports of severe systemic reactions from drugs include an instance of facial edema, urticaria, and shock after intravenous administration of succinyl choline, with recurrence of the skin reaction on readministration (66) and an instance of dyspnea, chest pain, urticaria, and angioedema occurring 10 minutes after the first intravenous injection of vancomycin to a patient with a previous history of allergy to sulfonamides (100). The latter patient is stated to have subsequently developed an allergic reaction to novobiocin. Although anaphylaxis to penicillin is well known, a recent report of electrocardiographic changes observed during such a reaction (7) is of interest. Auricular fibrillation, conduction defects, and evidence of myocardial injury were noted. The author of the report suggests that the heart itself may actually participate in the anaphylactic reaction. However, the possibility of cardiac changes secondary to other effects of anaphylaxis, such as anoxia, is difficult to rule out.

The data reviewed by Seevers (106) suggest an incidence of one to 10 deaths from anaphylaxis per 10 million injections of penicillin. It has been estimated that about 10 per cent of the cases of penicillin-induced anaphylaxis result in death (25).

Serum Sickness Syndrome

Neuritis has previously been reported to be an occasional accompaniment of the serum sickness syndrome. Farme (35) has reported pachymeningitis as an apparent sequel developing slowly after a serum sickness reaction probably due to penicillin. The patient recovered after craniotomy and cortico-steroid therapy.

Angioedema and Urticaria

Angioedema and urticaria have been described as part of the systemic reaction in certain instances already noted in the section on anaphylaxis (10, 54, 66, 100). Death from angioedema of the larnyx following administration of sulfobromophthalein has been reported (111). A report of angioedema of the gastric mucosa, mimicking carcinoma, is of interest (11). In addition, erythromycin (93) and griseofulvin (46) have been presumptive causes of urticaria in recent reports; the reaction to the latter drug also included angioedema. Urticaria was again reported as the commonest form of reaction to penicillin (73).

Dermatitis

Epstein & Kligman (33) showed that contact dermatitis requires the participation of intact vessels and depends upon the passage of cells rather than fluid from the lumen of the vessels into the extravascular space.

Exfoliative dermatitis has in the past been known to be associated with simultaneous damage in internal organs, e.g., the liver. In the past year reports of exfoliative dermatitis occurring after administration of penicillin (116) and phenindione (14) have noted the occurrence of simultaneous renal damage. The patient with renal insufficiency after penicillin had improvement in renal function after administration of penicillinase. The patient reacting to phenindione had jaundice as well as the presence of protein, casts, and white and red blood cells in the urine. Although the hematuria following administration of phenindione may have simply been attributable to the anticoagulant effect of the drug, the other urinary findings suggest more extensive renal injury.

A report of contact dermatitis in a woman who had been working with a new phenothiazine derivative (47) serves to remind us of two points previously established in drug allergy. First, the onset of contact dermatitis in workers exposed to new drugs in the course of their development may be an omen of subsequent sensitizing capacity of the drug in the clinic. This has previously been noted with drugs such as penicillin. Second, patch tests in the above patient showed cross-reactions with those phenothiazines which, like the compound that originally sensitized her, contained a chlorine in the 2 position on the phenothiazine ring. Although the results suggested that the nature of other substituents on the phenothiazine ring was less significant, the compound 2-chlorophenothiazine was too insoluble to allow satisfactory testing in this study, and the role of other substituents, in addition to chlorine, could not be entirely dismissed. Phenothiazine compounds without a chlorine atom in this position did not cause cross-reactions. The correlation of sensitization with the structure of one portion of a molecule has previously been noted with other drugs, e.g., local anesthetics.

Twenty-eight cases of contact dermatitis caused by neomycin were reported (95). Cross-reactions between neomycin and streptomycin may occur (41). Exfoliative dermatitis (77) and erythema multiforme with the Stevens-Johnson syndrome (43) were reported after administration of sulfamethoxypyridazine (Kynex). The role of this sulfonamide in causing the exfoliative dermatitis was confirmed by the fact that a challenging readministration of the drug subsequently caused a recurrence of the reaction in a lesser form. Although this is of considerable scientific interest, one wonders whether the challenge is wise in a patient who has undergone such a severe reaction. A fatal septicemia has been recorded (102) as the final complication of a severe skin reaction to this drug. Among the more recently introduced drugs that can apparently produce skin and mucosal reac-

tions is chlorpropamide (59, 101, 112). However, the incidence of sensitization to this drug is difficult to determine, because the patients who are taking it are almost invariably diabetic and the development of itching and skin eruptions in diabetic patients may be due to other causes. In a report of several instances of contact dermatitis (sometimes with subsequent persistent changes in pigmentation) caused by local application of strong concentrations of mono-benzylether of hydroquinone, Dorsey (28) has estimated the incidence of contact dermatitis from this ointment as 13 per cent.

Photosensitivity after administration of a drug is a problem that is presumably separate from the one under consideration in this review. Therefore, photosensitivity will be mentioned here only to record that the list of drugs capable of provoking photosensitivity has been expanded by the inclusion of some recently developed drugs, including chlorothiazide and hydrochlorothiazide (52, 53, 88) and demethylchlortetracycline (Declomycin) (34, 83). Promethazine (Phenergan) has continued to cause dermatitis; a report (32) of dermatitis appearing at the site of local application after exposure to light (photocontact dermatitis) demonstrated this phenothiazine to be the offender. Biopsy showed vesicles and eosinophilia. A useful discussion of dermatologic reactions to drugs is found in Fromer's (41) review.

Depression of the Blood and Blood-Forming Organs

Reviewing records of 66 patients who died from agranulocytosis in Denmark during the period 1951 to 1957, Mosbech & Riis (84) found 25 cases attributable to drugs. The physician who once sees a patient with one or several of the lines of formed elements of the blood wiped out by a drug reaction is not likely to forget the experience, particularly if he sees a patient die from this complication and finds, on reviewing the history, that the patient had received the drug for a relatively minor indication. A previous brief review (18) noted the evidence that certain instances of depression of white blood cells or platelets are very probably mediated by antibodies, whereas certain drug-induced anemias have been clearly shown to be associated with an enzymatic defect. In the aforementioned review it was pointed out that laboratory and clinical studies had made possible a prediction that certain drug-induced hemolytic anemias would be found to be nonallergic in nature, a fact subsequently demonstrated. However, it is obvious that drugs capable of causing a reaction such as hemolytic anemia through a nonallergic mechanism may still cause other disturbances that probably depend upon the presence of antibody. This situation has, in fact, been reported. Thus, furaltadone has been reported (21) to cause a maculopapular and urticarial skin eruption. Thrombocytopenia and leukopenia have also occurred in patients receiving furaltadone (21). Even more striking is the report that phenacetin and *p*-aminosalicylic acid may cause hemolytic anemia in some patients by a mechanism requiring the presence of

antibodies (74). Thus, the drugs apparently cause the same reaction by different mechanisms in different patients.

Circulating substances causing agglutination or lysis of platelets have been found in many instances of drug-induced thrombocytopenia. Bishop, Spencer & Bethell (9) have pointed out that search for antibodies *in vitro* now has clinical value as a preliminary test and sometimes obviates the need to consider the riskier *in vivo* challenge. Circulating leuko-agglutinins have occasionally been demonstrated in leukopenia. Circulating antibodies against certain other diseased tissues, e.g., heart, are currently thought not to be causally related to the disease of the antigenic organ (19, 85). Nevertheless, the antibodies against formed elements of the blood directly destructive of the blood cells in certain instances, and the presence of antibodies against white cells or platelets is consistent with certain other facts pointing to the allergic nature of such drug reactions. These considerations have been previously reviewed (17, 18).

The demonstration that certain instances of leukopenia or thrombocytopenia are apparently mediated by antibodies is still a far cry from implicating antibodies in all such depressions. Several possible objections must be considered. First, in many instances of leukopenia or thrombocytopenia a search for antibodies has failed to reveal any. For example, in a recent report (20) of thrombocytopenia caused by diethylstilbestrol and confirmed by repeated recurrences on readministration, no antibodies were found. In this instance there was also a moderate leukopenia of 2000 to 5000. The authors point out that estrogens have previously been reported to cause marrow aplasia with hypoplastic anemia and thrombocytopenia. We have the impression that antibodies have been demonstrated most often in instances of "pure" thrombocytopenia, rather than thrombocytopenia associated with depression of other formed elements of the blood. The estrogen-induced thrombocytopenia reported above did have one manifestation vaguely suggesting that an antibody may have existed in the skin, for the patient developed pruritus. There was no purpura.

Second, the frequency with which drugs containing the amino-benzene nucleus, or a closely related structure, cause depression of the formed elements of the blood leads one, rightly or wrongly, to recall the "bad reputation" of compounds related to para-aminophenol and phenylhydroxylamine with regard to effects upon the bone marrow. One may reasonably wonder whether the individual who suffers depression of the formed elements of the blood after receiving such drugs may not differ from the majority of individuals in that the unlucky individual metabolizes the drug in a different way rather than develops antibodies against it.

Third, the duration of "sensitization" should be noted. For example, administration of the phenothiazine drugs has been followed by agranulocytosis in numerous instances. Korst (69) reviewed 58 cases of agranulocytosis in patients who had received chlorpromazine and 11 cases in patients

who had received promazine. Pisciotta (91) reviewed 18 instances of agranulocytosis after administration of chlorpromazine. Whereas many allergic reactions to drugs occur most frequently during the second week of drug administration, agranulocytosis in patients receiving phenothiazines seems to occur most often during the fourth to sixth weeks (91) and sometimes even later, though usually within the first 15 weeks (69) after administration of the drug has begun. Agranulocytosis in patients receiving phenindione occurs most frequently after the third week but before the end of the third month (8, 108, 113). Furthermore, in a recent report of thrombocytopenia due to hydrochlorothiazide (45), not only was the initial reaction slow to appear after administration of the drug had commenced, but the recurrence that followed reinitiation of hydrochlorothiazide therapy apparently did not take place until the second course of administration had been carried out for more than two weeks. When thiouracil was widely used in the treatment of thyrotoxicosis, the onset of agranulocytosis was noted most commonly between the fourth and eighth weeks.

Obviously, compounds that tend to provoke agranulocytosis or thrombocytopenia only after a period of several weeks' administration will not attract attention as frequent causes of these reactions unless they are drugs likely to be administered for long periods of time. Tranquilizers, anticoagulants, diuretics, and antithyroid drugs, among others, meet this requirement. The treatment of tuberculosis offers another occasion to administer drugs for long periods. Thrombocytopenia caused by sodium para-aminosalicylate was first noted in one patient (49) after he had been receiving the drug for three years; readministration of the drug after recovery from thrombocytopenia led to a recurrence of the reaction in an hour. The report that 81 of 91 patients who suffered nonhematologic allergic reactions to various drugs during the initial course of systemic administration of the drug did so within the first 14 days (73) may, to some degree, simply reflect the fact that many of the drugs were not given in a prolonged course. [Thus, comparing a drug not likely to be given in a long course with one that is likely to be so given, only three of 55 penicillin reactions occurred after 14 days in patients receiving their first course of therapy, as contrasted to seven of 27 streptomycin reactions; the difference is significant ($P < 0.05$).] But the evidence still generally suggests that depression of the formed elements of the blood usually develops after a period of time that seems to be considerably longer than the sensitization period in the usual allergies. In the case of erythrocytes, one might consider the prolonged survival of circulating erythrocytes as a factor, but this explanation does not account for the prolonged "sensitization" before depression of platelets or leukocytes occurs. Furthermore, once the depression of platelets or leukocytes has started, it develops very rapidly in many instances.

One would like to reduce all depression of formed elements of the blood to one common effect of the offending drugs, but at present the only com-

mon effect that we can see even dimly is the possibility that both direct intoxication of the formed elements of the blood and depression mediated by antibodies depend, in the last analysis, upon the ability of certain compounds to react in some particular way with proteins of the formed elements. There seems little reason to doubt that depression of the formed elements, regardless of its cause, may involve both destruction of circulating elements and destruction of their precursors in the marrow or lymph nodes. It has previously been noted (18) that even when mediation by antibodies is assumed, one has no basis for knowing the exact pattern of the reaction until he can learn more about the exact location of antigen and antibody.

Hydrochlorothiazide (see above) was also implicated as a cause of several instances of thrombocytopenia in another report (87), and circulating factors causing platelet agglutination and lysis were shown in some cases in this report. Not all purpura attributable to drugs of the chlorothiazide group has been found to be thrombocytopenic. Like other drugs, chlorothiazide may precipitate purpura of the Henoch-Schonlein type (38). A patient who developed a leukopenia of 1300 (98 per cent lymphocytes) while receiving salicylazosulfapyridine (Azulfidine) had developed a skin rash on the fourth day after the beginning of drug therapy; the drug had, therefore, been discontinued for three days. Four days after the reinitiation of drug treatment the white blood count was 4350. The patient continued to take the drug for 23 days and at the end of this time was admitted to the hospital because of exhaustion. At this time the white blood count was found to be 1300. Twelve days after the administration of the drug had again been stopped the patient's serum contained a factor reacting with leukocytes in the presence of the offending drug (96). These cases are further indications of the fact that other, presumably allergic, reactions such as skin eruption may accompany drug-induced depression of the formed elements of the blood.

Regardless of the fact that a "sensitization" period of several weeks often elapses before development of drug-induced blood reactions in some patients, the occurrence of leukopenia (white blood count of 3500) in a patient who had been receiving tolbutamide for eight months (13) would still raise a considerable question about the causal role of the drug in such an instance, rare examples to the contrary notwithstanding. In fact, this patient was later shown to have acute leukemia. Leukemoid reactions may occur during the course of recovery from drug-induced leukopenia and have, of course, a more benign prognosis. A leukemoid reaction was reported during recovery from one of the aforementioned instances of phenindione-induced leukopenia (113).

Because patients with leukopenia are particularly susceptible to infection and because infection may also lead to depression of the bone marrow on occasion, one should not be surprised to find a history of exposure to chemotherapeutic agents in a certain number of patients who have leuko-

penia with or without depression of other formed elements of the blood. However, a history of exposure of chloramphenicol is found in a suspiciously high proportion of cases of aplastic anemia. In a recent study (105) of aplastic anemia, a modified tabulation of 607 cases of aplastic anemia originally reviewed by Welch, Lewis & Kerlan (122) showed that 26 had received only chloramphenicol, 66 had received chloramphenicol plus other drugs, and 32 had received sulfonamides. Chlortetracycline, oxytetracycline, barbiturates, anticonvulsants, and antihistaminic drugs had been given to 12, 11, 25, 17, and 8 patients respectively. Thirty-seven patients in this series had a history of exposure to antipyretics or related compounds. Aplastic anemia has followed chloramphenicol administration to patients suffering from mild infections not likely, per se, to cause depression of the bone marrow (22). The presence of the nitro- and amino-benzene group in the chloramphenicol and sulfonamide molecules, respectively, may, as previously noted, be a significant factor in their toxicity. When one considers the degree of increased risk of aplastic anemia resulting from chloramphenicol administration, he must in fairness admit that the increase in risk, though definite, seems slight. But physicians would be well advised to remember also that the increased risk, thought slight, seems definite. Although it would be difficult to deny the role of secondary infection in increasing the illness of patients with drug-induced agranulocytosis, the onset of the reaction itself seems to be accompanied by prompt systemic symptoms in many individuals, symptoms that are probably not entirely due to subsequent infection but are more probably associated with the drug reaction itself. Headache, fever, and general malaise were noted in some of the reports of phenindione-induced agranulocytosis mentioned above, and early systemic symptoms have been described in many previous reports of drug-induced agranulocytosis.

Other drugs implicated in recently reported instances of agranulocytosis are amodiaquine (67), chlorpropamide (112), and thenalidine (Sandostene) (1, 89). Sulfamethoxypyridazine has been implicated as a cause of thrombocytopenia (60), and, indeed, the latter drug has in other respects continued to carry on the bad name of the sulfonamide family in causing serious drug reactions. The over-all incidence of reactions to sulfamethoxypyridazine has been estimated (60) as about 6 per cent, this incidence being considerably less than that of reactions to sulfathiazole, slightly less than that of reactions to sulfadiazine, and somewhat more than that of reactions to sulfisoxazole (Gantrisin). The ability of certain sulfonamides to inhibit carbonic anhydrase was an important factor in the development of the diuretic drug, acetazoleamide. In acetazoleamide the substitution of a heterocyclic ring for the benzene ring of the sulfonamides has apparently not relieved this drug of the familial tendency to cause hematologic reactions. Fatal agranulocytosis from acetazoleamide was recorded in a report (57) in which instances of aplastic anemia and thrombocytopenia ascribed to

acetoazoleamide were also reviewed. Chloramphenicol and ristocetin have been mentioned above as causes of depression of formed elements of the blood; however, they are not the only antibiotics so implicated. In reviewing reactions to antibiotics, Seevers (106) noted that novobiocin and fumagillin have produced leukopenia in some patients.

The earlier hope that corticosteroids would decrease the mortality in patients with drug-induced agranulocytosis has, for the most part, met with disappointment. Since corticosteroid treatment of patients with normal numbers of leukocytes may increase the risk of infection, which may then sometimes secondarily depress the bone marrow, agranulocytosis may at times itself be an indirect complication of corticosteroid therapy. Such instances do not appear to be common, as compared with other complications of corticosteroid therapy. A possible example of this sequence of events is found in the case reported by Rosketh (97), though even here the history of previous irradiation of the patient makes interpretation difficult. Corticosteroids may well aid in the treatment of drug-induced thrombocytopenia. In the latter instance platelet transfusions can also be considered, but Bishop (9) has found these to have limited value in drug-induced thrombocytopenia.

In a particularly discouraging case of agranulocytosis following use of chlorpropamide (65), the white blood count, which was 2050 (6 per cent neutrophils) on the patient's admission, rose to 6000 (75 per cent neutrophils) after 10 days in which treatment consisted of corticosteroids, chemotherapy, and omission of the offending drug. Yet the marrow showed little evidence of recovery and cessation of corticosteroid therapy after four weeks was soon followed by death, the peripheral white blood count and neutrophil percentage having again fallen to low levels.

Hepatic Reactions

It now seems very likely that drugs may damage the liver by several distinct mechanisms. Although clinicians, pharmacologists, and pathologists have probably suspected this for a long time, at least two advances in important detail have been made relatively recently. First, the mechanism of "direct toxicity" of carbon tetrachloride has been studied (15) with results that bring us quite far from the attitude that was, in effect, our previous explanation of this toxicity, namely. "Of course it damages the liver—it's poison!" Second, the instances in which hypersensitivity appears to play a role in hepatic damage from drugs have also been separated into at least two categories, obstruction and hepatocellular damage, a dichotomy already well known in other types of liver disease. The drug-induced obstruction is, however, intrahepatic. Intrahepatic obstruction from drugs such as chlorpromazine is sometimes, but not always, reproduced by readministration of small doses of the drug to a patient who has recovered from a previous reaction, and, in certain instances, hepatic reaction to the drug

coincides with other, more obvious manifestations of drug allergy. Other phenothiazine drugs, e.g., prochlorperazine (Compazine) (109), have been implicated in reactions of this type, and several authors have pointed out that drugs unrelated to the phenothiazines can also produce this type of obstructive jaundice. The onset of jaundice due to chlorpromazine has usually occurred after the patient has been receiving the drug for one to five weeks. But the onset of intrahepatic obstructive jaundice has been reported in one patient seven days after cessation of a 109-day course of norethandrolone (Nilevar) (107). The presumption that norethandrolone was indeed the offending drug is probably valid, for norethandrolone has also been implicated as a cause of intrahepatic obstruction in several other reports. Reichel *et al.* (94) have reviewed the evidence for and against allergy as the mechanism of drug-induced intrahepatic obstruction. In reviewing the evidence, including the facts that the primary site of damage seems to be the bile canaliculi (see below) and many individuals who do not suffer jaundice develop minor aberrations of hepatic function tests while receiving chlorpromazine, we are inclined to wonder if drugs such as chlorpromazine may damage the lining of the bile channels to a minor degree in many patients and then actually sensitize the damaged area in only a few. The analogy with contact dermatitis due to drugs that are themselves primary irritants of the skin comes to mind. However, such a concept of "contact cholangitis" is highly speculative at present and ignores the many profound differences between the skin and the biliary passages.

The amine oxidase inhibitor, iproniazid, has been shown occasionally to cause a form of hepatic inflammation associated with more widespread cellular injury and necrosis. A review of 22 patients with the latter reaction (36) showed that the daily dose of iproniazid was 25 to 200 mg., the duration of treatment before the development of jaundice was two to 12 weeks, the total dose of drug given was 0.65 to 9.45 gm., and seven deaths occurred. It may be significant that three patients developed jaundice only during a second course of therapy and that the duration of the second course of therapy was only four to 14 days before jaundice appeared. Another review (99) of 90 patients with jaundice after iproniazid administration showed that the drug had been taken for a period ranging from four days to about six months before onset of the jaundice; 20 of the patients died. The hepato-cellular necrosis with inflammatory reaction caused by drugs such as iproniazid and β-phenylisopropylhydrazine (Catron) (6) is considerably more dangerous than the reaction of intrahepatic obstruction caused by drugs such as chlorpromazine. Popper & Shaffner (92) have reviewed various aspects of the classes of hepatic injury from drugs, especially the pathology of such reactions. They postulated that intrahepatic obstruction from drugs such as chlorpromazine begins with alteration in the membranes of the liver cells forming the bile canaliculi. Popper & Shaff-

ner gave useful lists of drugs implicated as causes of each class of reaction. To this list of drugs causing obstruction one may now add 4.4′ diamidino-diphenylamine hydrochloride (M & B 938) (26). Although the hepatic reaction to metahexamide was left in the unclassified group by Popper & Shaffner, this drug has been reported as a cause of hepato-cellular damage (75), and, in this instance, readministration of the drug after recovery led to accelerated reappearance of abnormal liver function tests. Although the results of such readministration are of considerable interest, one must carefully weigh the potential danger of readministration. The authors of the latter report suggest that the aminophenyl group may be important in the ability of hypolyglycemic agents, such as metahexamide and carbutamide, to cause jaundice. However, jaundice has also been reported after administration of chlorpropamide (92, 101) which does not contain the aminophenyl group; in the latter instance hepatic biopsy and laboratory tests suggested obstructive jaundice, and there were associated skin and mucosal lesions. Morgenstern (82) noted elevation of the serum glutamic-pyruvic transaminase in one of 12 patients receiving chlorpropamide. The patient also developed a papular skin eruption.

Although several phenothiazines have, as noted above, been implicated as causes of jaundice, Hollister, Caffey & Klett (58) found no cases of jaundice in 500 schizophrenic patients given phenothiazine drugs, nor in 99 given phenobarbital over a 12-week period. Five phenothiazines were used; only 100 of the patients received chlorpromazine, however. Among the 599, eosinophilia, abnormal findings in tests of hepatic function, and apparently allergic dermatitis occurred in 98, 96, and 21, respectively. The incidence of these abnormalities was not significantly higher in patients receiving phenothiazines than in patients receiving phenobarbital. The "phenobarbital control" makes this a particularly useful study.

The jaundice observed in some patients receiving novobiocin poses a special problem. It has been suspected that a yellow degradation product of the drug, rather than serious injury to the liver, is responsible for the jaundice. A recent report (23) suggests interference with the conjugation of bilirubin in the liver. This explanation was invoked to explain the genuine increase in serum bilirubin giving the indirect VandenBerg reaction, whereas other tests suggested mild disturbance of hepatocellular function.

Miscellaneous Studies and Reports

In his review of 216 patients with "drug allergy," Ljaljevic (73) included a few instances of headache, vomiting, and diarrhea. The relation of phenindione to steatorrhea has been noted in one report (63). As primary reactions, the relation of headache and most gastrointestinal reactions to drug allergy is not clear, although headache and acute gastrointestinal symptoms are not surprising concomitants of fever or severe systemic reactions, respectively. Gastric angioedema has been noted above. Ljaljevic recorded

35 instances of joint manifestations; these probably should be considered part of the serum sickness syndrome. The predominance of penicillin as a cause of the latter (31 of the 35 cases) agrees with the experience of others. Topical exposure (ointments, inhalations, etc.) was blamed in 23 of Ljaljevic's 120 patients with reactions to penicillin. The undesirability of topical use of penicillin has been stressed by many but deserves incidental mention again here. Ljaljevic stated that contact sensitization to penicillin took a relatively long time to develop in patients exposed by working with the drug, as compared to those sensitized by other methods. Andersen (3), surveying 6832 patients given penicillin, reported the over-all incidence of reactions as only 1.3 per cent. Analysis of Andersen's data suggests a significantly ($P < 0.05$) greater incidence of reactions in patients receiving benzathine penicillin (six reactions in 159 patients) than in the combined group of those receiving procaine or crystalline penicillin (73 reactions in 5050 patients). Andersen stated that an allergic background could be demonstrated in 67 per cent of the 74 patients who developed delayed reactions. The view that patients with a history of other allergies are especially prone to develop drug allergy has been accepted by many but has not always been supported by the evidence (78). Some of the disagreement may stem from the difficulty in assessing "allergic background."

The likelihood of significant exposure to penicillin in patients receiving injections from syringes containing penicillin residuals or eating various foods has continued to receive attention (86). Welch (121) points out that antibiotics are used in the preservation of poultry and fish, and in crop sprays. Penicillin was found to be present in detectable concentrations in 3.7 per cent of 1170 milk samples (61). The concentrations ranged from 0.006 to 1.22 units per ml. Tetracyclines were found in 2 per cent of the samples tested, and one sample contained bacitracin. The possibility that such sources may cause unnoticed sensitizing exposure or provoke reactions in occasional exquisitely sensitive individuals is difficult to dismiss, especially in the case of penicillin. Whereas a very rare individual may be highly sensitive to tetracyclines, the latter are not common causes of drug allergy and those who are allergic to tetracyclines are not necessarily highly sensitive to them (25).

The various eye lesions caused by antimalarials (55, 56, 67), though of considerable interest, do not appear to fall within the scope of this paper. The report of pancreatitis from chlorothiazide (62) and the appearance of abnormal findings in the chest at x-ray examination of patients receiving diphenylhydantoin (81) are certainly interesting but difficult to evaluate at present. A possible relation to collagen disease comes to mind, but the reports cited give little support to this possibility.

Treatment of Allergic Reactions

Consideration of reactions in which drugs are, themselves, the allergens must on occasion blend with consideration of the use of drugs in the treat-

ment of allergic reactions in general. Pharmacotherapy is often useful in the treatment of reactions caused by drugs, and the drugs used in the treatment of various allergic disorders may themselves sensitize the patient. Nevertheless, these two considerations are obviously not the same. The final section of this review is in effect, therefore, a separate, brief discussion of recent developments in the use of drugs in treatment of allergy.

Until recently the liberation of histamine following the reaction between antigen and antibody was considered the one reasonably well-established basis for many allergic reactions. There now exists experimental evidence suggesting that several substances are liberated during allergic reactions. Among the latter substances are serotonin (76, 118), bradykinin (70), slow-reacting substance (12), and acetylcholine (44, 114, 117). For example, it has been shown that serotonin, slow-reacting substance, and histamine are liberated from the bronchial musculature of asthmatic patients when tissue specimens obtained at operation are placed in contact with the specific antigen (103). In another experiment Tiffeneau (114) found that asthmatic patients were significantly more reactive to aerosols of histamine and acetylcholine than normal individuals. MacHaffie *et al.* (76) found serum serotonin levels much higher in allergic individuals than in normals. Vaccarezza & Peltz (117) reported that plasma cholinesterase activity was higher in allergic individuals than in normals and that the elevation of cholinesterase seemed to be proportional to the severity of the patients' symptoms. The significance of this finding is difficult to assess.

Nevertheless, the exact role played by each of these liberated substances in different allergic manifestations and the relative importance of each substance is still unknown. This may well be the fundamental reason for the relatively few real advances in the treatment of allergy that have occurred recently.

If one accepts the fact that the aforementioned substances probably do play an important role, however, one can establish an outline of possible as well as actual approaches to therapy from the pharmacological point of view. Specific desensitization, elimination of the allergen, suppression of the antigen-antibody reaction, prevention of liberation of histamine and other important intermediates, block of receptors for these intermediates, antagonism of the effects of the reaction between intermediates and their receptors, and miscellaneous methods of suppressing the "general reactivity" of the patient may all be considered.

Before considering these approaches in more detail, we must point out that many studies of the treatment of allergy suffer from lack of precision in the criteria for cure or improvement and also suffer from lack of controls. The former defect is admittedly difficult to overcome completely, but more attention to correcting the latter would, with proper experimental design, lessen the bad effect of the former. (In defense of allergists we must add the truism that studies in other fields of therapy often suffer from the same defects.) It is obviously unjustified to criticize all studies equally

and indiscriminately, and, therefore, as space does not permit detailed individual consideration of each study reported here, it is hoped that the reader whose interest is attracted by any given report mentioned below will turn to the original paper and evaluate the results after considering these highly important details of experimental design.

Specific desensitization has been useful in many allergies. Barré (4) claimed that injection of a combination of histamine and serum globulin caused improvement in many asthmatic patients and postulated that an immunity to histamine was produced. This concept, though interesting, is difficult to assess. In allergy to drugs, attempts to desensitize the patient against the offending drug have occasionally been useful but, in general, the uncertainty of good results, the possibility of dangerous reactions, and the preferability of prevention by avoiding exposure to the offending drug all combine to make specific desensitization a method that is at present seldom useful in drug allergy.

An interesting example of destruction of the allergen is the use of penicillinase. Spectacular improvement following the use of penicillinase has been reported at times (64, 116). It has been reported that patients who do not respond to the first or second dose of penicillinase will probably not respond to subsequent doses. The antigenic nature of penicillinase (120) and the difficulty in judging its effectiveness from uncontrolled studies have limited its use.

Drugs blocking the liberation of histamine and other intermediates have not achieved an established place in clinical practice at present, but experimental work in laboratory animals has been carried out in this area (70).

Blocking of receptors by antihistaminic drugs is well known, but, as Dr. Lloyd Beck has pointed out in discussions with the authors, presently available compounds leave much to be desired as regards specificity and effectiveness in blocking response to large doses of histamine. Among recent clinical reports is that of Hansel (51) who treated 225 patients suffering from chronic allergic coryza with a new preparation combining three antihistaminics with different durations of action (doxylamine, pheniramine, and pyrilamine). The duration of effect of one tablet was stated to be about 12 hours. He reported excellent results in 80 per cent of the patients. Flothow *et al.* (39) reported excellent results in the treatment of various respiratory allergies with a combination of ephedrine and the antihistaminic drug, phenyltoloxamine.

Kimura, Young & Richards (68) described a new piperazine derivative, homochlorcyclizine, with the following properties: antiserotonin activity *in vitro* and *in vivo,* antihistaminic, anticholinergic, and anti-slow-reacting substance activities, and ability experimentally to protect animals against active and passive anaphylaxis. Fisherman *et al.* (37) tried this compound in 442 patients with various allergies and reported favorable results, especially in asthma, urticaria, and rhinitis. In theory this compound should

be highly useful in the treatment of allergy, but further clinical proof is, of course, needed.

It has been claimed that gamma globulin binds histamine (4). Gamma globulin may be beneficial in patients with certain allergic reactions; Crepea & Friedlander (24) reported improvement in 50 per cent of 84 children treated with three injections of gamma globulin over two weeks. The mechanism of improvement after gamma globulin in Crepea's series could, of course, be attributable to factors not at all related to histamine binding.

Antagonism of the effects of the reaction between mediator and receptor is the principal method of therapy available to us at present, using such drugs as epinephrine, aminophylline, etc. Recent advances in this area have not been striking.

Among miscellaneous measures lessening the reactivity of the allergic patient, the use of corticosteroids and ACTH has certainly been an important advance. The more recent attempts to develop corticosteroids with a more favorable ratio of therapeutic effectiveness to toxicity have not been very successful (29, 40, 90) except for decrease in toxicity associated with mineralocorticoid effect. Prolonged use of any currently available corticosteroid in asthma and other chronic allergies has serious disadvantages (110). Therefore, one must carefully consider the indications and justification for use of corticosteroids in allergic reactions, a subject discussed in detail by Rose *et al.* (98) in an interesting paper. Where superficial skin allergies make topical therapy feasible, systemic effects of corticosteroids may be avoided (79). The ineffectiveness of corticosteroids in the immediate treatment of anaphylaxis should be noted (25) since the use of these agents in such treatment is often reported.

As psychic factors are considered by many to be important in allergy, it is not surprising that tranquilizing drugs have been used in the treatment of allergy in many recent studies (30, 48, 115). In view of the seriousness of such conditions as asthma, the frequent failure of other modes of treatment, the known ability of tranquilizers to affect certain functions of the nervous system, and the real possibility that psychic factors may at least exacerbate allergic conditions make it unjustifiable to dismiss such work in a cavalier fashion. Moreover, the effects of many tranquilizers on the autonomic nervous system may confer on these drugs a further usefulness here that is unrelated to psychic effects. But even though one must sincerely wish success to any attempt to improve the treatment of severe allergies, one may wonder whether the defects noted in some of the previous work in allergy—lack of precise criteria and lack of controls—are likely to be any less prominent as psychiatrically oriented studies become more frequent.

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