DRUG-INDUCED IMMUNOLOGICAL EFFECTS ON THE LIVER

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Untoward immunological effects induced by drugs can be of two kinds: drug allergy, and tissue damage secondary to an allergic reaction. Our prime concern here will be to discuss effects on the liver resulting from drug allergy since reports on indirect damage are relatively uncommon.

CLASSIFICATION OF UNWANTED EFFECTS OF DRUGS

It is important to distinguish drug allergies from other unwanted effects of drugs. Probably the most satisfactory classification of all unwanted effects is that suggested at a Symposium on Sensitivity Reactions to Drugs, held in Liège in 1958 (Rosenheim and Moulton, 1958) (table I).

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<thead>
<tr>
<th>Table I. Unwanted effects of drugs.</th>
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<tbody>
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<td>a. Absolute.</td>
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<td>b. Relative.</td>
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<td>2. Intolerance.</td>
</tr>
<tr>
<td>3. Side effects.</td>
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<td>a. Specific.</td>
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<tr>
<td>b. Non-specific</td>
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<td>4. Secondary effects.</td>
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<tr>
<td>5. Idiosyncrasy.</td>
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We are concerned here only with the last group which the Symposium defined as "those reactions to drugs in which clinical symptoms are conditioned by previous exposure to and sensitization to the drug. They are mediated by an antigen-antibody reaction". This definition, although adequate at the time of its formulation, requires some modification in the light of newer knowledge, in particular extension of the definition "mediated by antigen-antibody reaction" to include the phenomenon of cellular allergy. A classification of allergic reactions was proposed by Gell and Coombs (1968).

CLASSIFICATION OF ALLERGIC REACTIONS

Type I. Anaphylactic, reagin-dependent.

Free antigen reacts with tissue cells which have been passively sensitized by antibody produced elsewhere.

Type II. Cytotoxic.

Antibody reacts with (a) cell surface or (b) with antigen or hapten which has attached to cell surface. Complement is usually necessary for cell destruction.

Type III. Damage by toxic complexes.

Antigen and antibody react in the region of antigen excess to form complexes which are toxic to cells or if deposited in blood vessel walls or basement membranes cause local inflammation.

Type IV. Delayed, tuberculin type, cell-mediated.

Initiated by specifically modified mononuclear cells reacting with allergen or antigen deposited at a local site.

It will be seen that three of these classes involve the participation of antibody, whilst the fourth (cellular or delayed allergy) involves specifically modified mononuclear cells.

It is rarely possible to classify an untoward reaction unequivocally as a drug allergy, the available evidence being largely incomplete and circumstantial, but there are certain criteria which may be applied (Davies 1972).

(1) The drug, or some metabolic product must form covalent bonds with protein.
(2) The drug or a chemically closely related substance must have been given before.
(3) The allergy is long lasting (i.e., months to years rather than days to weeks).
(4) The symptoms are those of accepted allergies.
(5) A skin test or some affirmative in vitro test is positive.

DIAGNOSIS

These difficulties in terminology are associated with problems in diagnosis. Three groups of reactions may lead to a diagnosis of drug-allergy.

(a) Reactions where the diagnosis of allergy is beyond reasonable doubt. In such cases there is definite evidence relating the reaction to the drug; symptoms appear only in relation to drug administration; the drug is a known sensitizer; antibodies are demonstrable by in vitro tests or passive transfer; the symptoms are typically allergic.

(b) Border-line cases. In such cases one or more pieces of essential evidence may be missing.

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Usually there is an inability to demonstrate the presence of antibodies. Skin tests used for this purpose are notoriously unreliable and suitable antigens may not be available. The drug may be a new one whose sensitizing potential is unknown.

(c) Toxic reactions. Confusion of thought can be the only reason for attributing these to allergy. Unfortunately, such confusion exists.

TYPES OF ALLERGIC REACTIONS TO DRUGS

Lowell (1955) has classified sensitivity reactions to drugs.

A. Allergic.
   (1) Rash, usually maculopapular, but variable.
   (2) Urticaria and angioneurotic oedema.
   (3) Serum disease syndrome.
   (4) Acute allergic shock or acute anaphylaxis.
   (5) Eosinophilia.
   (6) Exfoliative dermatitis.
   (7) Asthma.

B. Probably allergic.
   (1) Fever alone.
   (2) Purpura (often not thrombocytopenic).
   (3) Henoch-Schönlein purpura.
   (4) Agranulocytosis.
   (5) Necrotizing anginitis.
   (6) Migratory pulmonary infiltrations with eosinophilia.

C. Possibly allergic.
   (1) Leukopenia.
   (2) Anaemia.
   (3) Nephritis or nephrosis.
   (4) Aplastic anaemia.
   (5) Acute haemolytic anaemia.
   (6) Hepatitis.
   (7) Peripheral neuritis.

Undoubtedly, many objections could be raised to this scheme, especially with the apportionment of syndromes between groups B and C, and in time it is likely that some reactions will be changed from one group to another. But a perusal of the literature leads to the conclusion that few new types of reaction will appear, and few will be eliminated. It is noteworthy that Lowell (1955) placed hepatitis in the "possibly allergic" group.

The lists of drugs which have been implicated as causative agents of allergic liver damage are very long indeed (Paronetto and Popper, 1969; Tomasi, 1965) and here we will consider four examples only.

(1) Penicillin.

Penicillin allergy must be the most fully documented of all drug allergies and, possibly because of the large amount of work carried out, it most clearly satisfies the criteria we have outlined above. The hapten is not benzyl penicillin, but the degradation products, penicillic and penicilloic acids, the antigen being penicilloyl-protein formed by a co-valent linkage through the ε-amino groups of lysine residues in protein. The allergy may belong to any of the four types of Gell and Coombs (1968). Type I reactions may be manifest as urticaria, rhinitis or oedema, Type II as haemolytic anaemia, Type III as serum sickness due to the formation of complexes between circulating antibody and excess antigen, and Type IV as contact sensitivity.

A number of confirmatory in vitro tests have been used in the diagnosis of penicillin allergy including haemagglutination (Levine, Fellner and Levytška, 1966; Levine et al., 1966) basophil degranulation (Perelmutter and Khera, 1970), lymphocyte transformation (Voss, Redmond and Levine, 1966; Halpern, Ky and Amache, 1967) and a variety of skin tests (Redmond and Levine, 1967).

In spite of an extraordinarily wide range of allergic symptoms exhibited by individuals sensitive to penicillin, only one case of liver involvement has been noted and this diagnosis was based on the following symptoms which coincided with re-administration of the drug: oedema of the face, fever, general malaise, shock, eosinophilia, jaundice and hepatomegaly and swollen lymph glands (Meyler, 1966). It seems at least worthy of consideration that in this case some, if not all, of these symptoms may have had causes other than penicillin allergy, since no other confirmatory evidence for allergy was presented.

(2) Para-aminosalicylic acid (P.A.S.).

Liver damage has been reported following a few weeks' treatment with PAS and 25 per cent of the patients exhibiting an allergic reaction to PAS were found to have jaundice due to hepatocellular damage (Meyler, 1966).

Simpson and Walker (1960), in their review of 229 cases of allergy to PAS (the diagnosis not always being supported by challenge), found fever in 224 patients, skin rashes in 167, hepatomegaly in 61, jaundice in 53, and lymphadenopathy in 51. Arthralgia and eosinophilia have also been described (Smith and Springett, 1966; Bower, 1964).

Evidence of allergy more convincing than the
clinical symptoms presented above is the rapid recurrence of symptoms when a small dose is given after a recovery period (Simpson and Walker, 1960). There are also reports of a positive response to challenge and to patch testing (Simpson and Walker, 1960; Lichtenstein and Cannemeyer, 1953). Meyler (1966) quotes a report of 10 patients in whom shock was caused by the intravenous administration of PAS and 4 of the patients had antibodies to PAS. In rare cases haemolytic anaemia appears during PAS therapy and this has been shown to have an immunological basis (MacGibbon et al., 1960; van Loghem, 1960). This serological evidence and a report of a positive response in the lymphocyte transformation test (Sarkany, 1967) provide possibly the strongest evidence that the liver manifestations caused by PAS may well have an allergic basis. It is worth pointing out, however, and the relevance will appear when we come to discuss halothane, that liver involvement is only one of very many allergic manifestations seen with PAS.

**Chlorpromazine.**

Clinical evidence frequently leads to the assumption of an allergic pathogenesis of the jaundice accompanying treatment with chlorpromazine (Whitfield, 1955; Werther and Korelitz, 1957), but this is not the only interpretation of the findings. The evidence that chlorpromazine jaundice is an allergic phenomenon is countered by equally convincing data that it is not. In support of the allergic hypothesis are the findings that jaundice occurs only in 1–5 per cent of patients and appears 2–4 weeks after the beginning of treatment (Meyler and Herxheimer, 1968): jaundice is of the cholestatic type and may be accompanied by fever, rashes, eosinophilia and mild hepatomegaly (Bacon, 1964; Gutman, 1957). Readministration of small doses causes hepatic dysfunction in 70 per cent of those previously exhibiting jaundice (Hollister, 1957). However, jaundice may disappear during continued therapy—and it has not always reappeared on readministration of the drug (Hollister, 1957; Schneider, Daughtery and DeVore, 1958). Jaundice has been reported following a single dose of chlorpromazine (Sussman and Sumner, 1955; Waldman and Fishman, 1957) and this, coupled with an estimate of histological and functional liver abnormalities in as many as 50 per cent of patients given the drug, suggests that drug allergy is not the sole or even the main cause of jaundice (Zimmerman, 1968).

Work in vitro has shown no characteristic immunological abnormalities detectable by electrophoretic or immunofluorescent techniques (Bolton, 1967) in patients suffering from prolonged chlorpromazine jaundice. There is no lymphocyte transformation in the presence of the drug (Sarkany, 1967) but antimitochondrial antibodies have been detected in 4 out of 7 patients with chlorpromazine jaundice (Rodriguez et al., 1969). It is known that chlorpromazine can produce mitochondrial damage by combination with these organelles, and the antibodies to mitochondria may be considered to result from this damage (Teller, Deuber and Kopac, 1967).

Some cases of agranulocytosis appear to have an immunological basis but more usually no antibody is detectable (Pisciotta et al., 1958). Pisciotta (1965) explains the agranulocytosis as being due to an effect of the drug on the bone marrow of individuals which may be particularly sensitive due to an enzyme deficiency. It seems possible that chlorpromazine-induced jaundice is an idiosyncratic rather than a hypersensitive reaction.

**Halothane.**

The incidence of postoperative changes has increased considerably over the last two decades, regardless of the anaesthetic agent used. Since halothane is now used in over 70 per cent of all anaesthetic procedures, it is not surprising that attempts have been made to link halothane with liver damage. It is not our purpose to offer evidence for or against this association but to discuss the proposition that the damage represents an allergic reaction to halothane.

Postoperative fever, blood eosinophilia, jaundice and histological evidence of liver damage have been ascribed to an allergic reaction (Paronetto and Popper, 1969), but many of the findings concerning the jaundice associated with halothane are inconsistent with the allergic hypothesis.

These inconsistencies include the following: neither the drug nor any of its known metabolites are chemically reactive; hepatotoxicity may follow the first anaesthesia; and the sensitivity may last for only a short time (cf., the criteria listed above). Two other aspects must be dealt with in a little more detail. First the absence of the more common manifestations of allergy. We know of no allergy to exogenous allergen where the liver is the only organ exhibiting allergic manifestation.

The in vitro evidence for halothane hypersensitivity is very weak. Paronetto and Popper (1970)
claim successful transformation of lymphocytes in 10 out of 15 patients suffering from hepatitis attributed to halothane. This claim is open to question on a number of counts. The value accepted as evidence of stimulation was surprisingly close to the control value in a number of cases. The incubation medium was varied to give a maximal stimulation in the test group (those showing jaundice) but not in the controls (healthy patients or those with other liver damage). One patient who did not show lymphocyte stimulation on incubation with autologous serum did so if foetal calf serum was substituted; however, the controls, which showed no stimulation, were incubated only with autologous serum. Only two negative control patients, i.e. those who did not develop jaundice after halothane administration were included. The authors did not consider the possibility that the apparent increase in lymphocyte transformation was an over-compensation for a previous depressant effect of anaesthesia on the transformation of lymphocytes by non-specific stimuli (Park and Brady, 1971). There was also some evidence of cross reaction with methoxyflurane. It is interesting to note that in contrast to true allergic reactions which can be elicited for periods up to several years, the in vitro sensitivity to halothane was shown to persist only for a few weeks. Other workers have been unable to show lymphocyte transformation in cases of halothane hepatitis (Sarkany, 1972; Dumonde, 1972).

Of the many cases of hepatitis attributed to halothane only 2 patients, both anaesthetists, had a controlled readministration of the drug. (Klatskin and Kimberg, 1969; Belfrage, Ahlgren, and Axelsson 1966). Both individuals developed malaise and liver dysfunction while at work, with recovery while absent from work. The symptoms recurred on readministration of a test dose of halothane. In the case described by Klatskin and Kimberg (1969) in which the patient was observed for some time after the diagnosis of halothane hepatitis, the symptoms did not always recur on recommencing work where exposure to halothane was inevitable. Other cases of hepatitis associated with occupational exposure to halothane, one of a factory worker involved in the production of halothane and one of an anaesthetist, have been reported but no details were presented (Klon, Schaffner and Popper, 1969).

It seems possible that every drug, past, present and future, has been or will be reported to cause an allergic reaction in at least one individual. Publications themselves give very little indication of the relative sensitizing capacities of various drugs. Undoubtedly the majority of reactions never appear in the literature; many cases may not even have been recognized as such; a multiplicity of drugs may have been used, rendering it difficult to identify the allergen. Again, publication of a reaction (ascribed to allergy) to a given drug is often followed by a shower of similar reports (frequently as "letters to the Editor"), yet the drug may be an uncommon sensitizer. The incidence of sensitivity bears a direct relationship to the popularity of the drug: statistics on incidence will therefore vary from time to time.

The present review of the literature leads inescapably to the conclusions that liver damage is one of the rarer forms of drug allergy: in contrast, the tendency to ascribe such damage to allergy is common. It is exceedingly difficult to disprove conclusions reached on a basis of circumstantial evidence which is frequently no more than a statement that the drug in question was used.

We deplore these often facile assumptions (based simply on lack of evidence to the contrary) that a given reaction is due to drug allergy. Allergy is a precisely definable phenomenon and we have given criteria which may assist in the diagnosis.

At the same time it would be foolish to deny that liver damage can never result from drug allergy and we also appreciate the difficulties inherent in providing definite evidence (lack of suitable antigen, dangers inherent in challenge and so on) but we would ask for more consideration to be given not only to the nature of allergy but also to the other possible causes of adverse reactions.

REFERENCES
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