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THE INTERNIST AND ALLERGIC DRUG REACTIONS

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Undesirable effects of drugs seem to be increasing. More attention is being paid to them both by the lay public and by medical men not least as a result of some widely publicized incidents in recent years (e.g. the thalidomide tragedy). Two main factors are responsible for the rising incidence:

1. The ever greater multiplicity of medicines. It is estimated that up to the present some 350.000 substances (13) have been used as drugs. Today about 1.000 of these are still with us. Undesirable effects may be induced by the majority of these 1.000 substances; at least 500 of them may be sensitizing.
2. Nowadays practically everybody comes into contact with various drugs, and medicine consumption is going up at an accelerating rate. Moreover, we are exposed to drugs in all sorts of circumstances where we least expect them. Here it will suffice to mention such things as the use of vitamins, hormones, cosmetics, preservatives, bactericides, various chemical additives, sera and vaccines, antibiotics added to milk and milk products, stimulants in Coca-Cola, tonic water, insecticides, etc. In such circumstances cross-sensitization is an important factor both between different drugs, and between drugs and chemicals which, though not drugs themselves, are related to drugs chemically and immunologically.

In medical practice it may be extremely difficult to establish whether drugs may be associated with manifestations of disease. In the following I shall seek to elucidate the significance of allergic drug reactions in internal medicine. A classification of the side-effects of drugs is presented in Table 1 (after Rosenheim).

TABLE 1
Undesirable Effects of Drugs.

1. Overdosage owing to excessive intake, accumulation, defective metabolism or delayed excretion.
2. Intolerance, increased individual susceptibility.
3. Side-effects, e.g. sedative action of antihistaminics.
4. Secondary effects, e.g. moniliasis after antibiotics, osteoporosis after cortisone.
5. Teratogenic effects, e.g. after thalidomide.
6. Idiosyncrasy due to congenital enzymatic defects, e.g. in some negroes in whom primaquine induces haemolysis owing to deficiency of glucose-6-phosphate dehydrogenase.
7. Allergic or hypersensitivity reactions mediated by an antigen-antibody reaction in patients sensitized by previous exposure to the substance.

Since a variety of allergic manifestations may be induced by practically any drug, a long list of manifestations would result if the manifestations produced by a particular drug were specified for every drug. Such lists may be found in various handbooks and at first sight may give the reader the impression that all drugs may induce practically any manifestation (2, 7, 16, 21). Such is not the case however. Here it should be noted, however, that too many physicians tell patients who complain of drug reactions that "It's probably allergic". The practice of always blaming allergy is a nuisance. An allergic drug reaction should be taken very seriously, for not seldom the patient will have to continue living with his allergy. And potentially fatal conditions may be induced if, by mistake, negligence or intention, the patient is given a small dose of the drug he is allergic to. Hence it is essential to make as correct a diagnosis as possible.

Table 2 (after *Gronemeyer*, 13) specifies those drugs against which allergies commonly occur.

TABLE 2
Common Allergy-Inducing Drugs.

1. Apronal (sedormid)	11. Phenolphthalein
2. Arsenicals	12. Phenothiazine
3. Barbiturates	13. Pollen extracts
4. Gold	14. Pyrazolone compounds
5. Hydantoin	15. Quinine and quinidine
6. Iodides	16. Salicylates
7. Mercurials	17. Sera and vaccines
8. Local anaesthetics	18. Streptomycin
9. Organ extracts (ACTH, insulin)	19. Sulpha drugs
10. Penicillin	20. Thiouracil

These and the other drugs produce a series of manifestations from various organs. Such manifestations are listed in Table 3.

TABLE 3
Organs Involved in Various Allergic Manifestations to Drugs.

<i>Organs</i>	<i>Manifestations</i>
C. N. S.	"Drug fever", psychoneuroses, psychoses.
Haemopoietic organs	Leukopenia, agranulocytosis, aplastic anaemia, thrombocytopenia.
Liver	Hepatitis (mild to severe parenchymal damage).
Kidneys	Proteinuria, tubular blockage, nephritis, lower nephron nephrosis.
Respiratory organs	Laryngeal oedema, asthma, Loeffler's syndrome.
Digestive tract	Diarrhoea, gastritis, enterocolitis.
Mucous membranes	Stomatitis, gingivitis, conjunctivitis, rhinitis, vaginitis.
Vascular system	Vascular spasm, periarteritis nodosa, thrombophlebitis, nodular vasculitis, serum sickness.
Joints	Arthritis, lupus erythematosus disseminatus.
Skin	Urticaria, Quincke's oedema, dermatitis, erythema, purpura, etc.
General	Allergic shock.

The question now arises, how can these manifestations be related to antigen-antibody reactions? As some of the problems

involved are extremely obscure I shall confine myself to a brief discussion on some of the best known explanations of allergic drug reactions.

1. It is well established that many drugs give rise to the production of antibodies which agglutinate, precipitate or brake down erythrocytes, leukocytes, lymphocytes and/or platelets. This action is exerted on the circulating blood corpuscles as well as in the bone marrow. Accordingly the manifestations from haemopoietic organs specified in Table 3 can readily be explained.

2. Antigen-antibody reactions are accompanied by disintegration of mast cells, releasing histamine and other substances. It is known that histamine gives rise to pruritus, swelling and erythema in the skin, urticaria, vasodilatation with hypotension, increased vascular permeability, headache, dyspnoea with asthma, enhanced bronchial secretion, increased production of gastric alimentary secretions and enhanced peristalsis. A high proportion of the specified manifestations can be explained in the light of one or more of these mechanisms.

3. Animal experiments have disclosed that allergic tissue reactions can be induced by means of an antigen-antibody reaction (4, 5, 12, 18). The following allergic tissue reactions are some of the more important ones. Capillary dilatation with increased permeability and exudation. When the capillary injury is severe it may give rise to petechial or purpura-like haemorrhages. The glomerular capillary may be damaged. The local capillary injury is accompanied by exudation of inflammatory cells, predominantly mononuclear forms, but also polynuclear elements among which eosinophils may be present. In more chronic conditions, the mononuclear phagocytes are transformed into epithelioid cells and giant cells so that the reaction becomes of tuberculoid type. Concomitantly these is often collagen degeneration and necrotizing vasculitis. A picture resembling periarteritis nodosa may also arise. Inflammatory lesions can be demonstrated in the lungs, in addition one sees neuritis, enlargement of the lymph nodes, diffuse interstitial nephritis with exudation of allergic type, etc.

Accordingly:

a. Most of the specified manifestations from various organ systems can be explained, and also

b. the manifestations produced form a distinctive pattern in which the part played by an antigen-antibody reaction can be detected, even though the underlying causes of the tissue reaction are not understood in all details.

Let us now turn to more practical problems. Suppose we have a patient who possibly has drug allergy. How can the condition be diagnosed? The first thing to keep in mind is that the patient's history is the most important clue and often the only one. Hence a detailed history of the patient's disease is essential and particular attention should be paid to:

- (I) previous exposure to the drug or to immunologically related substances,
- (II) a latent period during which antibodies could have been formed,
- (III) whether the observed manifestations can be attributed to an antigen-antibody reactions and agree with our knowledge of allergic reactions to a particular drug.
- (IV) the occurrence of other allergies.

Let us now consider tests for a more definite confirmation of a suspected drug allergy. Such tests tend to be distrusted, but it is none the less important to make them because from time to time they do yield an unequivocal result. Furthermore, recent advances in immunology may in due course render some new methods capable of improving the diagnostic accuracy. The most common methods are listed in Tables 4 and 5.

As a general statement about tests *in vivo* it may be said that they are suitable for screening, that their results not seldom may be negative even in clear cases of allergy, that some of them are not without danger, and that they therefore should not be regarded as especially good methods for either demonstrating or eliminating the presence of drug allergies. If skin reactions are present, an epicutaneous test should be con-

sidered. If mucous membrane reactions occur, the conjunctival test could be tried. In the absence of manifestations from skin or mucous membranes, these *in vivo* tests are rather unhelpful.

TABLE 4
Tests in Vivo for Suspected Drug Allergies.

- a. The conjunctival test. Suitable as an initial test. The drug should be instilled as a solution sufficiently dilute to ensure that the eye is not harmed.
- b. The epicutaneous test. Also suitable as an initial test. The technique varies, sometimes the drug is applied directly, sometimes diluted with water, physiological saline, or a suitable solvent (2, 3, 24).
- c. The intracutaneous test. Should always be preceded by an epicutaneous test. Here, too, the drug must be diluted.
- d. The Prausnitz-Küstner reaction, direct or reversed. This reaction must be used with due regard to the risk of infectious substances being transferred to or from the control subject (14).
- e. The provocation test. Tests of this type must be applied with great care and are directly contraindicated for drugs capable of harming the bone marrow, e.g. butazolidin (16). Such tests have been described which employ either the leukocyte index or the platelet index (23).

TABLE 5
Tests in Vitro for Suspected Drug Allergies.

- a. The agglutination reaction. Various procedures are employed: on erythrocytes either directly or after tannin treatment; on leukocytes or platelets, or on acrylic particles of varying diameter (usually 2-4 μ) (1, 6, 22).
- b. The lysin reaction. Analysis for the presence of lysins against different kinds of blood corpuscles. Lysins seldom occur isolated and are often simultaneously agglutinins (25).
- c. Precipitation reactions. Most conveniently carried out with the aid of Ouchterlony's gel diffusion procedure (15, 17).
- d. Determination of complement of antiglobulin consumption (20).
- e. Inhibition of clot retraction (11).
- f. Plasma clearing and nephelometry. Two procedures whose value remains in dispute (10).
- g. Determination of tissue-bound antibodies by Coon's procedure. This is an extremely complicated test which, in essence, is an advanced development of the precipitation reaction (8, 9).

As a general comment on the *in vitro* tests for suspected drug allergies the following may be said. Often they are rather complicated, many requiring immunological training and access to specialized laboratory equipment. In certain cases these tests should certainly furnish convincing proof of drug allergy. The techniques are in need of development, however, and more experience of them is called for. But in my opinion this should prove a fertile field for research, not least because these procedures without exception are entirely harmless to the patient.

To illustrate the above I have examined case notes for 378 patients admitted in on Allergy ward as well as for all our out-patients treated during 1959 and 1960. One hundred of the hospitalized patients complained of drug allergy, but 48 could be eliminated. Among the out-patients 37 had manifest drug allergy. Thus altogether 89 cases with 102 drug allergies were analysed. These are compiled in Table 6.

TABLE 6

Drug	Male	Female	Total	No. with other allergies	
				Previously	Currently
Iodides	16	14	30	4	25
Penicillin	10	10	20	3	8
Salicylates	8	10	18	4	12
ACTH	6	4	10	—	10
Sulpha	6	4	10	3	4
PAS	2	2	4	1	—
Quinin-quinidine	2	1	3	1	—
Meprobamate ...	2	—	2	—	1
Barbiturates	1	1	2	1	1
Bromides	1	—	1	1	—
Liver extracts ...	—	1	1	—	—
Bultzolidin	1	—	1	1	—
Total	55	47	102	19	61

Table 6 suggests that the predominant causes of drug allergy nowadays are: Iodides, penicillin and salicylates. More-

over, it appears that patients with drug allergy often have or have had other kinds of allergy. No sex difference is apparent.

SUMMARY

1. Drug allergies are becoming an increasingly serious problem.
2. The diagnosis of drug allergy is difficult but most important.
3. The causes of manifestations of drug allergy are discussed.
4. *In vivo* and *in vitro* tests for drug allergy are considered.
5. A representative series from a Swedish allergy department is presented.

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