Today's Treatment

Drug-induced diseases

Drug-induced skin diseases

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Drug eruptions are a bit like the Joneses: no one ever quite seems able to keep up with them. The problem is that as soon as the older drugs slip out of use, taking with them their familiar rashes, new fashionable treatments are rushed out of the laboratories. It is often a long time before any one can accept that they also will cause trouble. Practolol was a good example of this: used widely since 1970, it was not until 1974 that its now well-known skin reactions were described.¹

In other ways, however, though drugs may change, the clinical problems remain depressingly the same: a patient develops a rash; he is taking many different tablets; which, if any, of these caused his eruption, and what should be done about it? It is no answer simply to stop all drugs, though the fact that this can often be done casts some doubt on the patient's need for them in the first place. All too often potentially valuable drugs are excluded from further use on totally inadequate grounds. Clearly some guidelines are needed, but no simple set of rules exists that can cover this complex subject. In this short article we can do no more than outline some common-sense steps in the approach to patients with possible drug-induced skin disease. We suggest that the following questions should be asked in every case: (1) Can other skin diseases be excluded? (2) Are the skin changes compatible with a drug cause? (3) Which drug is most likely to be responsible? (4) Are any further tests worth while? and (5) Is any treatment needed? These questions are deceptively simple but the answers are often difficult. Each step will be discussed in turn.

Can other skin diseases be excluded?

Because a patient is taking tablets this does not mean that he cannot suffer from one of the ordinary dermatoses. Scabies, psoriasis, or eczema, which the patient may have had for a long time, may first be noted by a sharp-eyed houseman in the ward, and be thought to be a drug eruption. Perhaps the commonest condition that is mistaken for a drug eruption is asteatotic eczema. This often starts after admission to a ward but is due to fierce washing by the nursing staff rather than to drugs, although diuretics may be a predisposing factor. The highly itchy rash is seen on the already dry skin, usually of the legs, of elderly patients, and can be recognised by its pink linear splits in the stratum corneum.

Occasionally, of course, skin conditions are made worse by drugs given for other diseases. For example, antimalarials (especially chloroquine and mepacrine) and lithium may worsen psoriasis. Acne and dermatitis herpetiformis may flare up after taking cough mixtures containing iodides. Acne can also be induced or made worse by corticosteroids (given after puberty), testosterone, phenobarbitone, phenytoin, and INAH. Oral contraceptives with a high progesterone content are best avoided by women with a tendency to develop acne.

Are the skin changes compatible with a drug cause?

Almost every medical journal contains at least one description of a drug-induced skin disorder, and the thick fall of papers has tended to obscure the outlines of the subject. The same drug may produce completely different eruptions in different patients and quite unrelated drugs may cause similar eruptions. There are, however, several set patterns of reaction that are often drug induced. A thumbnail sketch of some of the commoner ones is given below.

Toxic erythema is the commonest skin reaction to drugs, and the term is used to describe many patterns of erythema. Sometimes the lesions look like measles, or scarlet fever; sometimes an urticarial or erythema-multiforme-like element is prominent; and the lesions may be macular or papular. The lesions are often more pronounced on the trunk than on the extremities. In previously exposed patients the rash may start two to three days after the administration of a drug. If a reaction arises during the first course of treatment the eruption will take longer to develop, often appearing about the ninth day. Fever may accompany the skin reaction. Unfortunately the drug that is responsible cannot usually be identified from the appearance of the rash. Common culprits include antibiotics (especially ampicillin), sulphonamides and related compounds (including thiazide diuretics, frusemide, and sulphonylurea hypoglycaemics), barbiturates, phenylbutazone, and para-aminosalicylic acid.

Erythema multiforme—The target-like lesions appear mainly on the extensor aspect of the limbs. In severe cases bullae may form. Occasionally the mucous membranes are severely affected (the Stevens-Johnson syndrome). Sulphonamides, barbiturates, and phenylbutazone are the commonest offenders.

Erythema nodosum—Sulphonamides and the oral contraceptive pill may produce this well-known reaction pattern.

Allergic vasculitis—In this reaction the inflammatory changes are most severe round blood vessels, especially veins and venules. The clinical changes range from urticaria to necrotic ulcers, and many confusing variants have been described. The sulphonamides, phenylbutazone, indomethacin, and phenytoin, are possible causes.

Purpura—Drugs may produce purpura by causing thrombocytopenia, by damaging the blood vessel, or by affecting

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blood coagulation. The clinical features of drug purpura are seldom distinctive apart from the itchy, brownish, petechial rash on dependent areas that is characteristic of carbromal reactions. Thiazides, sulphonamides, phenylbutazone, sulphonylureas, barbiturates, and quinine are among the drugs reported to cause purpura.

Eczema is a rare result of drug treatment and is characterised by a predominantly epidermal reaction similar to contact dermatitis. It is usually seen when patients, previously sensitised by external exposure, are given the same or a related substance systemically. Penicillin, neomycin, the phenothiazines, and local anaesthetics are common examples.

Exfoliative dermatitis and erythrodermia are descriptive terms used when the entire skin surface is red and scaly. An identical appearance is produced by drugs (phenylbutazone, para-aminosalicylic acid, isoniazid, gold, carbamazepine), severe psoriasis or eczema, or a lymphoma.

Photosensitivity may be defined as an exaggerated response of the skin to ultraviolet light. The rash typically affects the exposed skin of the face, neck, and backs of the hands, and also, in women, the lower legs. Both phototoxic and photoallergic mechanisms may be responsible, but in practice the distinction is often difficult to make. Exacerbations are usually related to spells of good weather, but on occasion the ultraviolet emission from fluorescent lighting may be sufficient. The most common photosensitisers are sulphonamides, sulphonamide-related compounds (thiazide diuretics, frusemide, and sulphonylurea hypoglycaemics), tetracyclines (especially demethylchlortetracycline), phenothiazines, and nalidixic acid.

Drug-related lupus erythematosus may present with a photosensitive rash accompanied by fever, polyarthritides, myalgia, and serositis (pleural and pericardial). The antinuclear factor is invariably present, but antibodies to double-stranded DNA are absent. The illness tends to be less severe than systemic lupus erythematosus and complete recovery often follows withdrawal of the drug, although antinuclear factor may be present for some time. Hydralazine, isoniazid, procainamide, and phenytoin are the commonest causes, but many drugs have been incriminated.

Lichenoid eruptions is a term used to describe eruptions resembling lichen planus. In addition to the flat-topped papules there is often scaling and dermatitic change. The mouth is seldom affected. Chloroquine, mepacrine, gold, arsenic, phenothiazines, and para-aminosalicylic acid are some of the drugs known to cause this reaction.

Fixed eruptions consist of demarcated, round, erythematous plaques that characteristically recur at the same site each time the drug is given. Persistent pigmentation remains after healing. Phenolphthalein, barbiturates, sulphonamides, quinine, and tetracycline may be responsible.

Toxic epidermal necrolysis—In rare cases large sheets of erythema develop and are followed by separation of the epidermis, giving the appearance of scalded skin. Staphylococcal infection (phage type 71) is usually responsible in infants, but in adults the eruption has followed treatment with barbiturates, phenytoin, sulphonamides, phenylbutazone, oxyphenbutazone, and penicillin.

Urticaria—Drugs are rarely the cause of chronic urticaria, but the penicillins and salicylates may be responsible especially in atopic individuals. Aspirin also acts as a non-specific histamine-releasing agent, and patients with urticaria should therefore avoid it. Enough penicillin may be present in dairy products to cause chronic urticaria in penicillin-sensitive patients.

Pruritus—An itchy skin not associated with a rash may be the only evidence of a drug reaction. The contraceptive pill, phenothiazines, and rifampicin may produce this symptom due to biliary stasis. Pruritus may be caused by the overgrowth of candida after systemic antibiotic treatment.

Hair loss is a predictable side effect of drugs such as cytotoxic agents and oral contraceptives. Diffuse hair loss also occurs unpredictably with anticoagulants (heparin, coumarins, and phenindione) and antithyroid drugs (carbimazole and thiouracil).

Pigmentation—Drugs can cause many different types of

pigmentary upset. Perhaps the most common is the development of flat, hyperpigmented areas on the forehead and cheeks (chloasma) caused by oral contraceptives; unfortunately this pigmentation is slow to improve despite stopping the drug. Chlorpromazine and related phenothiazines cause a blue-grey discoloration on light-exposed areas. Heavy metals (silver, gold, bismuth, and arsenic) produce a generalised brown or blue-grey pigmentation. A uniform yellow colour may be the result of mepacrine treatment, while chloroquine produces blue-black patches on the shins, pigmentation of the nails and palate, and depigmentation of the hair.

Which drug is most likely to be responsible?

The patient is still there, liberally dappled with his rash; ordinary dermatoses have been excluded; and the clinical pattern of the rash has been identified as compatible with a drug reaction. Now the problem is to decide which of his many drugs has been responsible for the eruption. Very few drugs are so obliging as to cause an eruption that is absolutely specific; indeed, most drugs can, at one time or another, cause most types of drug rash, though some tend to give rise to particular rashes more often than others.

A knowledge of each drug's track record is all important, and for those without wide personal experience, the best policy is to consult published reports. Bruinsma's *A Guide to Drug Eruptions*² remains a useful dogmatic guide. The known behaviour of individual drugs can best be found in standard text books.^{3 4}

Further help may come from a look at the dates on the prescription sheets. It is quite true that a drug taken for years may suddenly cause a reaction, but this is rather less common than an eruption appearing only a few days after a drug has been started. From this it would seem that the drug most recently introduced into a treatment regimen may be the most likely culprit. But often the records show a bewildering succession of drugs, sometimes in twos or threes, given in brief bursts during a protracted illness. Even a dermatologist cannot always sort out this sort of a mess.

Once the offending drug has been stopped, the eruption will usually start to improve within a few days, though some types, such as lichenoid eruptions, may clear much more slowly. Continued exposure to the substance in an unexpected form (for instance, penicillin in milk) may confuse the issue.

Are any further tests worthwhile?

IN-VIVO TESTS

Readministration—With the possible exception of a fixed eruption, readministration is hazardous. It may produce anaphylactic shock with death in a few minutes. The results can also be misleading as the test dose used should be small and hence may be too small to elicit a reaction. Readministration is probably justified only when no suitable alternative drug exists, and where hyposensitisation might be attempted. One exception is the rash so often seen after ampicillin has been given to patients with glandular fever. Once the mononucleosis has cleared ampicillin can usually be given again with impunity.

Patch tests only detect delayed type hypersensitivity and are therefore of limited use except in contact allergy and perhaps the rare eczematous type of drug eruption. Patch tests may be positive on the plaque of a fixed drug eruption though negative on the rest of the skin.

Prick and scratch tests introduce a small amount of the allergen into the dermis. The preparation of the allergen is of the utmost importance since most drugs act only as allergens after combining with a protein or other macromolecule. In most cases, unfortunately, we do not know how to prepare the complete allergen. Even with penicillin, where a considerable amount is

known about the allergic determinants, a negative reaction to the major haptenic determinant (using penicilloyl-polylysine) does not mean the patient will not react adversely to untested minor determinants when given the drug. These procedures may also produce anaphylaxis and may even induce allergy. The actual injection of small quantities into the dermis is perhaps more reliable than prick or scratch testing but carries a higher risk of anaphylaxis. The reservations expressed above about testing to the correct allergen apply equally to intradermal injections.

IN-VITRO TESTS

In-vitro tests are useful only in drug reactions of allergic origin. It must be emphasised that the detection of drug-specific circulating antibodies proves the occurrence of an immunological response only to that particular drug, and not that the clinical reaction was due to it. Tests for immediate-type drug allergy (anaphylaxis) include detection of reaginic antibodies, measurement of allergen-specific IgE antibodies (RAST), the basophil degranulation test, and the red-cell-linked antigen-antiglobulin reaction (RCLAAR). Type II reactions have been investigated using the direct and indirect antiglobulin tests (Coombs test), inhibition of clot retraction, complement fixation tests, and mixed antiglobulin reactions. Evidence of type III reactions includes measurement of circulating immune complexes (for instance, C1q precipitation) and the demonstration of antigen-antibody-complement complexes in tissues by immunofluorescence. Methods for detecting delayed type hypersensitivity (type IV) are the lymphocyte transformation test and the macrophage migration inhibition test.

The laboratory methods listed above are still largely experimental and do not yield consistent results. In addition they require facilities that are not usually available to the clinician.

Is any treatment needed?

The first approach to treatment of a suspected adverse drug reaction is to withdraw the drug, but several drugs may have to be stopped to ensure that this is done, since it may be impossible to pinpoint the culprit.

Anaphylactic reactions occur so rapidly that the patient presents as an acute medical emergency. Adrenaline is the most effective treatment, and 0.5 ml of 1 in 1000 solution should be injected subcutaneously and repeated if necessary after five

minutes. An antihistamine (such as chlorpheniramine maleate 20 mg) should also be administered parenterally as soon as possible. Corticosteroids are of limited use in the acute phase, but hydrocortisone hemisuccinate, 100-300 mg, given intramuscularly soon after the onset may prove beneficial later.

Most adverse drug reactions, however, are much less dramatic and will subside a few days after the drug is stopped. Only symptomatic treatment is required with topical calamine lotion or crotamiton (Eurax) lotion and a systemic antihistamine—for instance, trimetoprim 10 mg thrice daily. If the reaction is severe a tapering course of oral prednisolone is sometimes given—for example, in the Stevens-Johnson syndrome—but often there is not much objective evidence that this treatment speeds up resolution.

Conclusion

This whole subject is shot through with uncertainties. Even the incidence of drug eruptions seems to be hard to estimate. Most authors reckon that between 1 and 5% of all patients in hospital will develop a drug eruption of one kind or another, and this incidence is inexcusably high.

What can be done about this? Prevention would be better than cure, and the more rigorous screening and purification of drugs before general release might help here. There is, however, still much to be done by the clinician. No one who is asked to see drug eruptions regularly can fail to be depressed by the vast flickering sequence of drugs to which many patients are exposed. Every symptom does not always need drug treatment, and the national drug bills as well as the incidence of drug eruptions could be slashed if all doctors declared war on polypharmacy. Failing this, the laborious and often unsatisfactory clinical detective work must continue, based on probabilities and common sense, and largely unaided by complicated and unreliable laboratory tests.

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A middle-aged woman with diabetes has a whitish pink discoloration of the skin in between her buttocks and around her anus. What might this condition be?

This loss of pigment is probably caused by vitiligo, which has an increased incidence in diabetes. The differential diagnosis is lichen sclerosus et atrophicus, in which the depigmented skin also shows atrophy and in which there may be some follicular plugging near the edge of the affected area. There is some evidence that this condition too is associated with the so-called "autoimmune" disorders. If the diagnosis is in doubt biopsy will provide the answer.

Is measles vaccination likely to result in a diminution of multiple sclerosis?

The cause and cure of multiple sclerosis have still to be found but recent research has opened up many possibilities. Matthews¹ puts forward the hypothesis that in multiple sclerosis there is a genetically induced deficiency in immune mechanisms that permits the persistence in the nervous system of a virus acquired in childhood. In adult life the virus is activated, and this leads to destruction of myelin and to harmful autoimmune reactions to some product or products of myelin breakdown. The measles or possibly herpes simplex viruses are the most likely. The measles virus may lie dormant in the brain for several years before producing subacute sclerosing panencephalitis, but this virus has probably been found on only one occasion.² An increase in measles antibody titres in the blood and

cerebrospinal fluid compared with control values, however, has been an almost consistent finding.³ There have also been reports of increased titres of antibodies to other viruses, in particular herpes simplex. If measles is the main or only virus to which the immune mechanisms are deficient in potential multiple sclerosis patients, vaccination of the entire infant population against measles would theoretically result in a diminution of multiple sclerosis as all children would be prevented from developing measles and thus developing multiple sclerosis. There is also a slight risk that vaccination against measles may result in postvaccinal encephalitis.

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We would remind correspondents who write to our Any Questions? section that this feature is aimed at general readers and is not a service to questioners. Hence we reserve the right to edit queries into questions of general interest, though when appropriate we also send a copy of the original letter to the experts. They prefer not to answer questions on individual case histories without seeing the patient.