Drugs and the skin

The clinical aspects of drugs and disease of the skin

I. B. SNEDDON

From the Department of Dermatology, University of Sheffield

It is a truism that almost any drug can produce any sort of reaction, and in the diagnosis of all types of skin eruption drug reactions either allergic or otherwise must be considered. As has been repeatedly emphasized drug eruptions have now replaced syphilis as the great mimic. The clinical aspect of drug reactions is such a vast topic that I wish to narrow it down to those reactions which simulate disorders which can be produced by naturally occurring disease. Unfortunately as yet there is no satisfactory bedside investigation which is of real value to the clinician in the confirmation of the diagnosis of a drug reaction. Ethical objections very reasonably prevent one using the patient as an experimental model to confirm the diagnosis and much of the evidence has to be circumstantial.

It has, however, been shown by statistical study that the more drugs one gives a patient the more probable it is that drug reactions occur; the magic number appears to be three (Hurwitz, 1969). If over three drugs are given the incidence of reaction rises very remarkably. In the elderly, particularly those with renal failure, drug reactions are more frequent and in many cases there is a dosage effect; the higher the dose the more likely the drug reaction.

It also matters a great deal by which route the chemical substance first reaches the skin. For instance, surface applications produce a contact dermatitis, which is mediated by delayed sensitivity. This can be illustrated well by the old-fashioned mercury sensitivity due to applications of mercury ointment. However, if in such a patient the mercury happened to be given internally a generalized exfoliative dermatitis would occur which might well puzzle the clinician because it might be the first exposure to the drug given internally. The table shows some of the common skin sensitizers which may induce a generalized exfoliative state when certain drugs are given by mouth.

We are now aware of a number of substances which can penetrate the skin and yet which cannot be distinguished by the body from drugs normally used internally. One of the most intriguing is Tetmosol or monosulphiram. This, when used as an

<i>Topical Sensitizer</i>	<i>Systemically Administered Drug</i>
Caladryl lotion (diphenhydramine)	Mandrax (methaqualone and diphenhydramine)
Neomycin sulphate	Streptomycin, kanamycin
Aromatic benzenes of the para-amino group	Sulphonamides
Hair dyes	Local anaesthetics
	Aminobenzoic acid
	Chlorothiazide and hydrochlorothiazide
	Tolbutamide and chlorpropamide
Hydrazine hydrobromide	Isoniazid, Apresoline (hydralazine), Nardil (phenelzine)
Balsam of Peru	Cinnamon
Mercury and mercurial compounds	Mercurial diuretics, calomel (mercurous chloride)
Ethylenediamine (widely used in industry); many anti-histamines are ethylenediamine derivatives	Aminophylline, antihistamines (Antistin, Phenergan, Pyribenzamine citrate, etc)

Table *Common skin sensitizers*

application in the treatment of scabies if followed by alcohol, makes the patient feel very ill, since the body cannot distinguish it from disulphiram, Antabuse, used in curing alcohol addiction. I have had a number of patients who after treatment of scabies, have had a stiff drink which has made them feel very odd and go bright red all over.

The level at which the substance is placed in the skin may also alter the reaction. In this colourful example a youth developed a dermal reaction to the red areas of his tattoo. Histology showed a lymphocytic granuloma which surrounded the fragments of mercury oxide and the condition subsided with treatment by local steroids which penetrated the skin. Unusually we were unable to demonstrate an epidermal sensitivity by patch tests but one wonders what would have happened if mercury had been given internally. A somewhat similar situation exists in those who are sensitive to nickel and in whom metal prostheses are buried. A few develop a generalized eczematous reaction after they have had a hip replacement.

It has always fascinated me that the so-called exanthematous eruptions which make up the largest group of drug eruptions produced by the common drugs such as barbiturates, sulphonamides, and

numerous others mimic so closely the naturally occurring exanthemata. Thus we talk about a scarlatiniform eruption which commonly occurs with chloral and looks like scarlet fever, and one tends to get a more morbilliform eruption with sulphonamides though it is true that the reverse can occasionally occur.

Urticarial reactions to drugs are all too familiar, particularly after penicillin, but we know that many are not the result of an allergic response but probably a histamine-release phenomenon (Moore-Robinson and Warin, 1967; Champion, Roberts, Carpenter, and Roger, 1969). This is especially so of the urticarial eruptions produced by aspirin. It is a commonplace happening that the patient is prone to urticaria and has been taking antihistamines to control it, and after a headache takes an aspirin and has a severe flare up of the urticaria.

In recent years other compounds such as the food preservatives (benzoic acid) and an azo dye (tartrazine) have been shown to have the same effect (Juhlin, Michaëlsson, and Zetterström, 1972). Thus golden orange juice which contains sunset yellow may produce severe urticaria. Thirty-nine of 52 patients with urticaria have been shown by Michaëlsson and Juhlin (1973) to give reactions to azo dyes, aspirin, or benzoic acid. I think it is a little unwise of one of the pharmaceutical firms to incorporate in the capsule around their antihistamine an azo dye as thus the patient may develop sensitivity not to the drug itself but to the coloured capsule which surrounds the drug.

A growing number of compounds can increase damage done to the skin by sunlight. Even this may be affected either by surface application or by internal medication.

Antiseptics such as the halogenated salicylanilides and bithionol used in soaps and cosmetics can produce a severe sunlight sensitivity. Of the light reactions caused by drugs taken internally there are two main types. First the phototoxic reaction which is really an exaggerated sunburn and shows itself as an erythema on the areas exposed to sun and is sometimes of sufficient severity to damage the nails. A common example of the drug that will produce this are the tetracyclines especially demethylchlortetracycline. Not only are these cases dose dependent but dependent also on the degree of sunlight, and it is not uncommon for patients on photosensitizers such as naladixic acid to remain reasonably well until perhaps they have a day at the seaside when they will develop a bullous eruption on the areas exposed to sun, particularly the feet and legs (Birkett, Garretts, and Stevenson, 1969). This bullous eruption persists for several months after the drug has been stopped and may lead to a sus-

picion that one is not dealing with a drug eruption but a true light sensitivity such as porphyria (Ramsay and Obreshkova, 1974).

Photoallergic eruptions which resemble the naturally occurring light-induced eczemas are very much more difficult to solve as a problem, since once the drug has been excreted from the body the light sensitivity often remains. The worst offender amongst the drugs which are capable of producing prolonged light sensitivity are the phenothiazines, particularly chlorpromazine. This can produce persistent light sensitivity either when in contact with the skin in individuals such as mental nurses or in those who take the drug internally. There are still people who were treated in the last war with sulphonamide powder in their wounds who continue to have a light sensitivity due to sulphonamide photoallergy. Whilst on the subject of light sensitivity one should also mention that the metabolic fault in porphyria may remain completely concealed until revealed by alteration of liver enzymes by oestrogens contained in the contraceptive pill (Dean, 1965). Two types of inherited porphyria, the variegata type and porphyria cutanea tarda, may be activated in this way, and once more the metabolic upset once started may continue even though the oestrogen is discontinued.

Another problem produced by the pill is that the naturally occurring chloasma of pregnancy can be imitated (Carruthers, 1966). It has been estimated that 8% of dark-skinned people such as Puerto Ricans may show this side effect which is merely the result of stimulation of melanocytes by oestrogens plus sunlight.

The cause of lichen planus, a not uncommon naturally occurring skin disorder, remains unknown. An identical eruption, only differing in its explosive onset and perhaps in the profuseness of the lesions, can be produced by a variety of drugs. Gold, the antimalarials, Mepacrine and Chloroquine, and *para*aminosalicylic acid are the common causes, but here again the drug need not necessarily be taken internally and lichenoid eruptions may have occurred as a contact sensitivity to a chemical used in colour photography allied to paraphenylenediamine (Buckley, 1968). Lichen planus in a small proportion of patients occurs only in the mouth and equally this may happen with drugs (Dinsdale, Ormerod, and Walker, 1968). The latest drug to be blamed for lichenoid eruptions is methyl dopa (Almeyda and Levantine, 1971; Burry and Kirk, 1974). It may in addition produce a generalized eczematous eruption indistinguishable from naturally occurring seborrhoeic eczema (Church, 1974).

It has been known for some time that the drug chloroquine could precipitate a generalized attack

in a patient with psoriasis (Baker, 1966). In recent weeks, however, we have been made aware (Felix, Ive, and Dahl, 1974) that the long-continued high dosage of practolol is capable of producing a variety of skin eruptions one of which can imitate psoriasis very closely. Not only does it produce chronic scaling plaques on the limbs, and particularly the hands, but it can produce nail changes which, I must confess, I have been completely taken in by, believing that they were due to psoriasis. The histology of these lesions due to practolol appears different from that of psoriasis and resembles more closely lichen planus in that the basement membrane is damaged. Twenty-four per cent of the series of Felix *et al* (1974) demonstrated antinuclear factor in serum so that an autoimmune mechanism may be responsible.

Erythema of all kinds can be produced by drugs but absolutely classical erythema nodosum can be caused by drugs as well as by infection. We have long known that the sulphonamides were capable of this but only recently has the contraceptive pill been incriminated too, and the erythema nodosum will persist for years if the patient remains on the pill.

Some of the most dramatic naturally occurring eruptions, such as the mucous membrane variety of erythema multiforme known as the Stevens Johnson syndrome, can be precipitated by virus infections. Equally, it may be triggered off by drugs and the common ones are the sulphonamides and phenobarbitone. Once the disease process has been set in motion it appears to run in cycles just the same way as it does after a virus infection, but stopping the drug does not produce immediate benefit.

Perhaps the drug reaction we fear most is that of the toxic epidermal necrolysis of Lyell (1956). This has now been ascribed in the young to staphylococcal infections (Lyell, 1967) but in the adult may be produced by drugs such as phenylbutazone and its analogues or the long-acting sulphonamides. It also has been ascribed to a naturally occurring phenomenon and even to measles vaccination (Schoss and Rayhanzadeh, 1974).

There are an ever-increasing number of drugs which are blamed for precipitating the phenomenon of systemic lupus erythematosus. What we do not know is whether the drug induces the disorder in the healthy or merely acts as an exciting agent in a patient already suffering from a disorder of immunity. Certainly in any patient suffering from systemic lupus erythematosus the possibility of drug reaction must be carefully considered and excluded. This last point is a difficult one since patients either by design or merely from forgetfulness tend to deny that they are taking drugs. Perhaps the only time when one can be absolutely certain that one is dealing with a drug eruption, despite the patient's denials, is when

one comes across a fixed drug eruption. This oddity, which affects particularly the mucous membranes, the genitals, and localized areas of the skin, cannot be explained satisfactorily on our present immunological ideas of drug reactions. If one sees a patient with bizarre purplish red areas which may blister from time to time one can be sure that one is dealing with a fixed eruption as there appears to be no naturally occurring disease which is comparable. A recent report listed the following drugs as common causes of fixed eruption (Savin, 1970): barbiturates (7 patients), tetracycline (3 patients), phenolphthalein (5 patients), chlorthalidone (2 patients), oxyphenbutazone (3 patients), and acetylsalicylate (2 patients). However here we are again in the realm of the food additive, since I had a patient whom we were quite unable to prove was taking any drugs but who was absolutely certain that the cause of her drug eruption was a proprietary brand of dried coffee.

I have attempted in this very short and incomplete communication to alert you to the necessity of considering a drug aetiology in virtually all the pathological processes seen in the skin. It is fascinating that bacteria and viruses and drugs can produce what appear to be identical changes. Only constant surveillance of new drugs will keep us aware of new dangers.

References

- Almeyda, J., and Levantine, A. (1971). Drug reactions. XVI. *Brit. J. Derm.*, 85, 604-607.
- Baker, H. (1966). The influence of chloroquine and related drugs on Psoriasis and Keratoderma Blennorrhagicum. *Brit. J. Derm.*, 78, 161-166.
- Birkett, D. A., Garretts, M., and Stevenson, C. J. (1969). Phototoxic bullous eruptions due to nalidixic acid. *Brit. J. Derm.*, 81, 342-344.
- Buckley, W. R. (1958). Lichenoid eruptions following contact dermatitis. *Arch. Derm.*, 78, 453-457.
- Burrows, J. N., and Kirk, J. (1974). Lichenoid drug reaction from methyl dopa. (Letter) *Brit. J. Derm.*, 91, 475-476.
- Carruthers, R. (1966). Chloasma and oral contraceptives. *Med. J. Aust.*, 2, 17-20.
- Champion, R. H., Roberts, S. O. B., Carpenter, R. G., and Roger, J. H. (1969). Urticaria and angioedema: review of 554 patients. *Brit. J. Derm.*, 81, 588-597.
- Church, R. (1974). Eczema provoked by methyl dopa. *Brit. J. Derm.*, 91, 373-378.
- Dean, A. (1965). Oral contraceptives in *Porphyria variegata*. *Sth Afr. med. J.*, 39, 278-280.
- Dinsdale, R. C., Ormerod, T. B., and Walker, A. E. (1968). Lichenoid eruption due to chlorpropamide. *Brit. med. J.*, 1, 100-101.
- Felix, R. H., Ive, F. A., and Dahl, M. G. C. (1974). Cutaneous and ocular reactions to Practolol. *Brit. med. J.*, 4, 321-324.
- Hurwitz, N. (1969). Predisposing factors in adverse reaction to drugs. *Brit. med. J.*, 1, 536-539.
- Juhlin, L., Michaëlsson, G., and Zetterström, O. (1972). Urticaria and asthma induced by food-and-drug additives in patients with aspirin hypersensitivity. *J. Allergy*, 50, 92.
- Lyell, A. (1956). Toxic epidermal necrolysis: an eruption resembling scalding of the skin. *Brit. J. Derm.*, 68, 355-361.
- Lyell, A. (1967). A review of toxic epidermal necrolysis in Britain. *Brit. J. Derm.*, 79, 662-671.
- Michaëlsson, G., and Juhlin, L. (1973). Urticaria induced by preservatives and dye additives in food and drugs. *Brit. J. Derm.*, 88, 525-532.

- Moore-Robinson, M., and Warin, R. P. (1967). Effect of salicylates in urticaria. *Brit. med. J.*, 4, 262-264.
- Ramsay, C. A., and Obreshkova, E. (1974). Photosensitivity from nalidixic acid. *Brit. J. Derm.*, 91, 523-528.
- Savin, J. A. (1970). Current causes of fixed drug eruptions. *Brit. J. Derm.*, 83, 546-549.
- Shoss, R. G., and Rayhanzadeh, S. (1974). Toxic epidermal necrolysis following measles vaccination. *Arch. Derm.*, 110, 766-770.