CONTINUING MEDICAL EDUCATION

ADVERSE REACTIONS TO DRUGS
(Diagnosis and Management)

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In days gone by, syphilis was the great imitator—almost all skin diseases and eruptions could be closely mimicked by 'the Great Pox'. I have seen a world famous professor of dermatology at a large clinical meeting gravely scratching at a scaly psoriasiform secondary syphilitic rash with his finger nail in a vain attempt to demonstrate Auspitz's sign as proof of psoriasis. He was somewhat embarrassed when the true diagnosis was revealed. Whether this episode accounts for his subsequent rather splendidly exhibitionistic behaviour, I do not know. But the lesson was plain for all to see—even the very brightest and best of us can be fooled by the Great Imitator.

But now, in my country, the Great Imitator has been deposed and its place taken by young upstarts. So young and new indeed that the human organism can never before have encountered them in its long aeons of evolutionary history. So that sometimes, by their very novelty drug molecules throw large spanners in the biochemical and immunological works which either produce an inappropriate response, or none at all in return.

Drug induced disease is now a serious problem of modern medicine and it is a vulgar misconception to hold that the skin is the only, or even the chief target in drug reactions. Polyarthropathy, LE-syndromes, polyarteritis nodosa, fevers, renal disease, blood dyscrasias (of red cells, white cells or platelets), liver disease, psychoses, a variety of organic neurological syndromes, cardiovascular dysfunction (including collapse under general anaesthetic)—in sum, drug-induced disease may effect any system and reproduce almost any syndrome peculiar to that system. Neither should you be deceived into thinking that only new drugs, or those prescribed by orthodox practitioners, cause such reactions. Some drugs which feature in the oldest pharmacopoeias such as arsenic, mercury, may produce dire effects at times. And so-called "natural medicines" whether homeopathic, allopathic or herbal may contain chemicals just as immunogenic or in some other way noxious, to an ill-fated few.

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Mechanisms of Drug-Induced Disease

In our speciality, it is probably an academic concept to suggest that any drug should be considered as a possible cause of any rash—and certainly diagnostically unhelpful, but it may well be true. What is certainly not true is that all such rashes are allergic in their mechanism; indeed only a few have been adequately established as having any immunological basis whatever. It is much more likely that skin reactions have similar mechanisms to those shown to be important in reactions affecting other organs. Briefly, these may be classified under six headings :

(a) Idiosyncrasy. This is based on abnormal enzyme make-up of certain individuals. This is operative in cases of prolonged apnoea following the administration of muscle relaxants of the suxamethonium type, and

is associated with low levels of pseudocholinesterase in the blood (this is the enzyme which breaks down suxamethonium and similar compounds). Such an enzyme deficiency is of course inherited, and similar genetic polymorphism is illustrated by the different speeds with which individuals break down isoniazid and phenelzine; here deficiency of liver acetyl transferase may lead to what is effectively an over-dosage of these drugs in patients given the normal dose.

(b) Effective over-dosage may also occur in patients with renal and liver failure for obvious reasons, but with drugs like streptomycin the toxic effects may be very serious, in this instance causing permanent deafness and vestibular damage.

(c) Interference. This is a principle only recently recognised as being important. Monoamine oxidase inhibitors (MAO inhibitors), used extensively in psychiatry, inhibit also the enzymes responsible for breaking down or detoxifying such diverse substances as pethidine, phenothiazines or the tyramine found in many strong cheeses. Failure to remove these substances at the normal rate may lead to severe and dangerous effects —again basically a relative over-dosage.

(d) Displacement. Many drugs are transported by plasma albumin in an inactive form. Displacement by a substance more avid for albumin may lead to an effective overdosage of the now free drug. Thus, warfarin may be displaced by phenylbutazone, and produce excessive bleeding in a patient previously well controlled on this anti-coagulant.

(e) Secondary effects are well known : candidosis with antibiotics, and teratogenicity with thalidomide are good examples.

(f) Allergic. Usually there is no reaction on first exposure (i.e. during the first few days of treatment) unless there has been a previous exposure (and sensitization) to a similar chemical. Thus, neomycin may cause topical skin hypersensitivity, but because of certain common chemical groupings, subsequent treatment of the patient with streptomycin or kanamycin may lead to a generalised reaction; similarly the notorious p-amino group may cause clinical havoc via a number of drugs, such as sulphonamides, p-aminosalicylic acid, and local anaesthetics (but not xylocaine/lignocaine). Strangely this cross-sensitivity principle does not necessarily extend to stereoisomers —e.g. quinidine and quinine may not cross-react.

Clinical Presentation in Dermatology

Generally, drug eruptions are of sudden onset and of symmetrical distribution. Morphologically they may be erythematous, urticarial, purpuric, bullous, pustular, eczematous, granulomatous or polymorphic. Apart from skin manifestations, any unexpected or bizarre pattern of disease which becomes superimposed on the original complaint should be suspected of being drug induced.

Anaphylaxis. The rate of absorption affects the clinical picture; it is rare to see anaphylaxis save after parenteral injections though occasionally cases occur after enemas, inhalants or orally administered substances. Some years ago, Dr. Cunliffe and I described a case of anaphylaxis after absorption of bacitracin from a varicose ulcer, and this route of absorption should, perhaps be borne in mind more than hitherto in view of this and similar cases.[1] Penicillin has now replaced animal sera as the foremost cause of human anaphylaxis. Of course in anaphylaxis, the cutaneous manifestations may be minimal (apart from the signs of shock), but urticaria and serum sickness syndrome may follow the acute emergency.

Urticaria is probably the commonest cutaneous result of drug hypersensitivity and penicillin (and all its derivatives), aspirin and antitetanus serum are probably the commonest causes. With

both penicillin and serum, localised urticaria at the injection site may precede the general eruption by a few days. Often, the general rash occurs seven to fourteen days after the first dose, but the interval is less on subsequent treatment. A puzzling and disturbing feature of penicillin urticaria is its persistence long after apparent exposure has ceased. This may be due to delayed excretion, hidden sources of penicillin in milk and other foods (e.g. cheese) or possibly the production of penicillin-like compounds by fungal organisms in the skin.[2] Joint swellings and pain may occur and be severe; when accompanied by lymph gland enlargement and fever, the classical serum sickness syndrome is produced. Renal damage may also occur. Occasionally, a more prolnged course and a greater degree of renal involvement may herald the development of polyarteritis nodosa syndrome

Erythema multiforme is not uncommon as a drug reaction with vesicles and bullae, urticaria and purpura—often with the characteristic iris or target lesions. This reaction may also be accompanied by nephritis.[3] Where there are urticated, erythematous lesions, with pustules and few or no vesicles, the term toxic urticated erythema is used to distinguish it from classical erythema multiforme. Since cases in between these two types occur fairly frequently it is probably not a valid distinction.

Purpura. It is flattering to the dermatological ego to be expected to diagnose at a glance the drug responsible for the rash of a patient who just happens to be taking seven or eight different preparations. Doubtless this misplaced confidence has been engendered by the splendid (I almost said negligent) ease with which we can identify some of these rashes, unquestionably the most faith-inspiring of which is carbromal purpura. Here a bronzed slightly-scaly eruption appears, generally at first on the lower legs. It is composed of innumerable tiny purpuric spots, is itchy, and so distinctive that a fairly firm diagnosis can be made on morphological grounds alone. Very occasionally, other drugs may produce it, such as meprobamate or barbiturates. There is no apparent damage to the blood platelets, whereas the chemically similar Sedormid (once a popular hypnotic) caused thrombocytopenia and gross haemorrhages into the skin and other organs. A number of other drugs such as chloramphenicol, sulphonamides, quinidine and iodides may also cause purpura, with or without obvious platelet damage. They do not produce the characteristic carbromal type of purpura.

Erythema nodosum may be produced by iodides and sulphonamides, differing little in appearance from that provoked by streptococcal infection or sarcoidosis.

Bullous and pustular drug eruptions were much commoner in the days when iodides and bromides were frequently prescribed; pustular iodide and bromide eruptions may resemble acne vulgaris but there are no comedones and the rash is more florid and erythematous; in addition, vegetating masses of pyodermatous tissue may form.

Eczematous rashes may be induced by drugs administered systemically. Such reactions have been described following treatment with quinine, penicillin, arsenic and salicylates. A suggested mechanism is excretion of the drug onto the skin surface in the sweat, which is known to occur with these and other drugs.[4] Rashes produced are typically eczematous, symmetrical and of sudden onset in patients known to be taking such drugs. There may be a history of previous sensitization by contact (ointment, contraceptive creams for example) and patch-testing should be positive.

Erythroderma and exfoliative dermatitis are fortunately not commonly produced by drugs; the effects upon cardiovascular, thermoregulatory and intestinal functions are now well-documented.[5] Drugs known to cause such a picture include gold, mercury and arsenic. However, any severe eczematous reaction may

progress to erythroderma especially if neglected or maltreated, so that the range of possible causative drugs is wide, and includes drugs causing at first a strictly localised contact dermatitis.

Lichen-planus-like rashes have been caused by gold, mercury, antimalarials (mepacrine), and more recently amiphenazole.[6] The eruption is often very acute and may also involve the mucous membranes.

Photosensitivity rashes may be seen after either topical application of certain substances (such as the tetrachlorsalicylanilide incorporated into certain well-known soaps in the past) or following systemic administration of for instance sulphonamides, demethylchlortetracycline and antihistamines. In addition, prophyria may be precipitated by certain drugs (e.g. sulphonamides, barbiturates) and this condition may itself produce symptoms of photosensitivity, sometimes with the formation of blisters in light-exposed skin.

Fixed drug eruption is characteristically seen with phenolphthalein, iodides, barbiturates and sulpha drugs (including the sulphones). The rash recurs at the same site each time the drug is taken. Initial redness, itching and swelling are followed by pigmentation, and eventually more and more fixed sites are affected—including sometimes the mucous membranes.

Diagnosis

In general, once suspected, the drug should be discontinued. Unfortunately, and all too frequently, the patient may be on several or many different drugs and it is uncertain which (if any) is responsible. In this case the likeliest drug as judged by time-relationships and clinical picture should be stopped; ideally all should be discontinued but this is not always practicable. The most certain way to confirm the diagnosis is to restart the suspected agent once the clinical reaction has settled—but with reactions such as urticaria, erythroderma or anaphylaxis the risks of such challenge are very real and in many cases quite unacceptable. Nevertheless, we must consider also the risks to the patient of failing to make a firm diagnosis; we cannot always in good conscience simply relinquish this responsibility by advising him forever after to avoid say all of the five or six drugs he is taking, some of which are not only necessary for his proper treatment but also quite innocent of the drug reaction we are aiming to avoid.

History-taking is so obvious a part of the clinical routine that it is a frequently skipped or badly conducted part of the diagnostic process. It may take considerable skill, time and effort to extract a complete drug history from some patients, particularly if they are elderly or have been subjected (or subjected themselves) to polypharmacy. But accurate history taking in this context is more important and more trustworthy than any laboratory test at present developed, and may be considerably cheaper.

Occasionally, the physical signs are themselves so characteristic of a particular drug rash that the astute doctor can ask critical leading questions, e.g. in the case of rashes due to carbromal, arsenic, or fixed drug eruptions. But even here there may be pitfalls. Witness the lady who persistently denied a history of carbromal ingestion to the O.P. doctor, the ward house physician, the registrar, the senior registrar and finally the consultant. But the rash was typical and the questioning continued. Finally, on the 6-7th time of asking (her resistence beginning to crumble) she admitted that although no doctor had prescribed the drug, she "borrowed" one now and again from her neighbour "when she felt nervy."

Another patient had classical arsenical keratoses and cancers of the skin but swore that she have had only one bottle of the Fowler's solution, at one time purveyed to all and sundry by a local pharmacy in my home town. Now we knew from our own studies and the literature

that a single bottle of Fowler's solution could not have produced the florid and advanced disease she portrayed and we pressed her hard. Every ward round we would insist that surely she must have had more than one bottle of the poison (for such it was) but each time she looked us straight in the eye and was adamant that she had had only the one bottle. This of course set all our theoretical calculations awry and the minimal carcinogenic dose of inorganic arsenic was about to be set at a much lower level in the literature than ever before published when one day my colleague Professor Sam Shuster quizzed her for the last time and without so much as batting an eye-lid the lady said 'yes', she had only one bottle but she had it refilled many, many times over the years and had carefully cleaned it out before the next lot of medicine was dispensed! These cases illustrate how meticulous we must be in taking a drug history, and how important is the precise phrasing of the questions we put. How much more readily can we be deceived in cases where we do not know or suspect which drug or agent has caused the clinical picture; more difficult still where lack of education, or a language barrier exist.

Another, and I hope rarer variety of diagnostic hurdle must be surmounted when information is deliberately withheld from the doctor. Some years ago, I saw a young girl of 16 years in the clinic, who presented with a painful, swollen area of well-defined bright red skin around the eyes. Pus developed, and she was clearly unwell,with fever, rigors and leukocytosis. The diagnosis of erysipelas or a virus infection was suspected, but full investigations revealed no organism—smears, cultures, blood cultures and electron microscopy were all negative. Fortunately the whole clinical picture resolved surprisingly quickly within 3-4 days, only to relapse several times over the next few months. The swelling always occurred in the same place, and because of this, fixed drug eruption was suspected but the patient denied taking any drugs. Eventually as a diagnostic test, in between attacks, she was given a small dose of phenolphthalein by mouth. Within hours the whole clinical picture was reproduced. When confronted with this, the girl finally 'remembered' that occasionally she took a dose of 'Agarol' (a mixture of liquid paraffin and phenolphthalein) for constipation but still denied taking any before her 'spontaneous attacks'. We did not believe her, told her mother what we considered to be the cause, and no further attacks occurred. She was, on reflection, a slightly odd girl, and was probably using the phenolphthalein reaction deliberately to escape situations at school and home, and to obtain sympathy and concern from her parents and physician.

This combination of fixed drug eruptions and dermatitis artefacta has not I believe been described other than by myself and the patient was demonstrated to the North of England Dermatological Society in 1970.

So much for the perils and pitfalls of listening to (or failing to listen to) the patients' story. What other diagnostic techniques can help us in unravelling these sometimes very knotty problems ? Before moving off to the cloistered silence of the laboratory, let us stay in the clinic or at the bedside a little longer, and see if more can be accomplished with in vivo techniques.

Patch testing has proved its worth in contact eczema—can it help us here ? And what about prick, scratch and intradermal skin testing ? In my opinion skin testing, properly conducted, can be of value in elucidating some cases of drug-induced disease. After much thought and experiment I have developed a fairly strict protocol for skin testing in such patients. This is primarily based on safety since even the minute amount of drugs requird for skin testing may in very hypersensitive patients be lethal if injected. Beware particularly of patients whose history suggests an anaphylactoid reaction. Because

of the potential hazard I always begin skin testing by using patch tests since least drug is absorbed by this route. Most cases will give negative results using 1-10% concentrations in yellow soft paraffin, though positive findings may be expected in cases of drug-induced eczema and some cases of fixed drug eruptions. For example in the case of fixed drug eruption due to sulphadimidine described by David Porter and myself[7] we were able to demonstrate positive patch tests in the affected skin, and also in exchange auto-grafts, thus proving donor dominance in this case. The reaction at the patch test site may not be eczematous, and here it was urticated and erythematous. Likewise, with prick testing, the next step in skin testing, a positive reaction may not be the wheal and flare of histamine release. Thus in one of my patients,[8] prick testing produced a classical patch of eczema (in duplicate) at 24 hours, though the clinical reaction was anaphylactoid, on two separate occasions. This illustrates two important points, (1) that the clinical reaction in allergic hypersensitivity may depend on the route by which the allergen is administered; (2) that a positive skin test should be heeded even if it is of an unexpected type. Further similar examples are the cases of anaphylactoid, urticarial and eczematous reactions to nickel from nickle containing infusion needles.[9] I have seen several such cases myself and these patients have suffered sometimes severe, indeed life-threatening reactions to the intravenous challenging dose of nickel.

In performing prick tests, use ten-fold increasing concentrations, but if negative and therefore proceeding to the next stage of intradermal testing, drop your concentration at least 100-fold, and probably 1000-fold, otherwise disaster may ensue. Squire showed a long time ago that the smallest volume of intradermal histamine (say 0.02 ml) was equivalent to a prick test using 1000 x concentration.[10]

Do not be put off by the unexpected—in this area of medicine we should expect the unexpected ! Even corticosteroids may produce allergic reactions both topically and when given parenterally.

Thus, in a case of my own, "who developed a severe generalised urticated erythema after her arthritic knee was injected with a prednisolone acetate suspension extensive investigations proved beyond a shadow of a doubt that she was truely allergic to corticosteroids and not to any adjuvant or contaminant. You might ask why did she not react to her own endogenous steroids. The answer is that allergic reactions are quantitative phenomena and occur in response to a certain minimal or threshold dose of antigen, which was not reached in her own tissue fluids by her endogenous hydrocortisone. We see similar phenomena with thyroid and insulin antibodies which are by no means invariably associated with the clinical states of myxoedema or diabetes.

False positive and false negative reactions may occur with skin as with other tests. Too high a concentration of some drugs may produce irritant reactions and ideally this should be looked for in a battery of 10-12 control subjects. With some drugs this has been well worked out, and also the actual antigenic determinants discovered, as with penicillin allergy. Here penicilloyl compounds as well as the ordinary penicillin G molecule must be tested. False negative reactions occur for several reasons. One is that quite often the drug itself is not responsible, but a metabolite or complex with body proteins. Another is that hapten inhibition may occur locally in the skin, due to a relatively large concentration of the drug being used in the skin testing solution. For these and other reasons strenuous attempts have been made over the years to take the testing procedure away from the patient and into the relatively controlled conditions of the laboratory. Unfortunately, in vitro tests have proved if any-

thing more capricious than the live patient. The basophil degranulation test described by Walter Shelley[12] was difficult to reproduce but after a period in the doldrums its basic principles have been confirmed, and a number of research groups have found it useful, certainly in the direct form of the test using human basophils. Histamine release from basophils,[13] from chopped lung mast cells[14] and serotonin release from blood platelets[15] have also been used with varying success in Type-I allergic reactions. Lymphocyte transformation has proved helpful in certain types of allergic reactions (usually Gell & Coombs Type 4, as would be predicted).

The more recent radio-immune technique using specific IgE antibodies is perhaps the biggest advance and is most helpful in IgE mediated Type I reactions. It has been used extensively and successfully by Lennart Juhlin of Uppsala in Sweden, working with the discoverer of IgE, Dr. Johannsson.[16]

All these tests are time consuming, expensive, and not as yet generally available. Nevertheless, they point the way to the future and even now may be very helpful in selected cases.

Finally we must discuss the ultimate test—that of deliberately challenging the patient with a dose of the suspected drug. This should only be undertaken by experienced physicians who have full resuscitation equipment available and personnel expert in its use. My own procedure is to admit such cases to the Intensive Care Unit, set up a central venous line, and have pre-loaded syringes of adrenaline, chlorpheniramine and hydrocortisone at my side. I certainly would not attempt this in the clinic or ordinary ward. This of course applies most forcefully to cases where anaphylactoid reactions have occurred, or in people such as bad atopics who may easily develop a high level of IgE.

To end this survey of drug-induced disease I will leave you with two thoughts, (1) that drug induced rashes probably occur very commonly in the liver, kidneys, gastro-intestinal tract and indeed in every organ. As more and more endoscopic procedures are performed, I look forward to reading the first description of fixed drug eruption of the stomach, or the bladder, or the colon. (2) Drug-induced disease is both common and underdiagnosed. We diagnose only what we know and what we are aware of. For your patients' sake, have a high index of suspicion and be vigilant.

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