REFRESHER COURSE FOR GENERAL PRACTITIONERS

DRUG ERUPTIONS

BY

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The term "drug eruption," or dermatitis medicamentosa, refers to any eruption attributable to the action of a drug which reaches the skin by way of the blood stream, irrespective of the method by which it has been administered. The term does not apply to any local reaction which may occur as a result of direct contact of the drug with the skin from the outside, but it does include eruptions attributable to drugs which have been absorbed through the skin into the blood stream, whether or not this process is accompanied by a local reaction at the point of entrance.

Introduction

Drug eruptions present the most varied clinical manifestations, and all the primary skin lesions—erythema, papules, bullae, etc.—may result from drug action. These lesions can be regarded as being primarily vascular in origin. Some are merely transient neurovascular reactions, while in others the inflammatory process may be associated with structural changes in the skin which, depending on their degree, may be of long duration. A true eczema reaction is seldom seen in dermatitis medicamentosa even though a large number of drugs can produce it in susceptible individuals when brought into external contact with the skin. In a few instances a visible change may be caused when the drug is deposited in the skin; but such examples of cutaneous drug action cannot be classed as eruptions, and the same may be said of the alterations in epidermal growth produced by drugs such as arsenic.

The characteristic lesion of an eruption due to a given drug may be totally different in one individual from that in another. Factors intimately connected with the reacting tissue must therefore operate in determining the nature of the response. There are thus two types of individual variation in response to drugs; one involving susceptibility to the pharmacological action, and the other the variation in the incidence of untoward phenomena including skin eruptions, and so far as is known there is no correlating link between these two variables.

As the capacity of the skin to vary its reactions to noxious agents is limited, the lesions presented by drug eruptions are similar to those seen in other skin diseases due to infections and intoxications or of unknown origin. In drug eruptions the disposition of the lesions with regard to each other, their course, and their duration differ in detail from that seen in other forms of skin disease. In spite of this there is not infrequently a close similarity between drug eruptions and other dermatoses, and differential diagnosis may at times be difficult. It is possible that some of the eruptions which appear during the administration of a drug are due not to the direct effect of the drug on the skin but to the action of some toxin which has been liberated from the site of the disease under treatment or from some latent focus of infection. This mechanism is referred to as biotritism, and it would account for the close similarity

between some eruptions attributed to drugs and those due to infections—for example, the erythema nodosum reactions.

Drug eruptions have the following peculiarities with regard to their mode of production. As already emphasized, they are unusual effects of drug action and, even in the type associated with prolonged structural alteration of the tissue, the threshold dose may be minute. So far as is known, and with the exception of phenylethylhydantoin, it is not possible to produce drug eruptions at will. In the case of inorganic arsenic there is, however, some relation between cumulative dosage and alteration in skin growth. The individual susceptibility to develop an eruption is usually specific for a given drug or chemical group, it is seldom polyvalent, and it is never a universal cutaneous hypersensitivity in which the skin reacts to all drugs. Drug eruptions therefore possess some of the characteristics attributed to allergic phenomena, but, as some of the criteria of allergy are lacking, it might be more appropriate to call them idiosyncratic rather than allergic. For instance, it is not possible to demonstrate by means of scratch or intradermal tests a capacity to react after injection or parenteral administration, and no antibodies can be demonstrated in the blood by passive transfer experiments. That the factors immediately responsible for the cutaneous response are localized in the skin would appear to have been proved by grafting experiments in fixed drug eruptions.

With therapeutic doses the possibility of producing an eruption seems to vary with the type of drug. The frequency and comparative incidence of eruptions due to different drugs must, however, depend to some extent on the size of the population to which the respective drugs are administered. For instance, eruptions due to phenobarbitone are often seen, while those due to digitalis are rare, but the number of people who ingest these drugs is very different, and the percentage incidence of eruptions due to phenobarbitone is probably low. In the case of the organic arsenicals and gold, which are administered only to a small percentage of the population and which are notorious producers of skin eruptions, repeated administration may even appear to induce cutaneous hypersensitivity, though this could be explained on the assumption that the drug must accumulate to a critical concentration in the cutaneous tissue before a reaction develops.

General Characteristics

Drug eruptions present general characteristics which should lead to their presence being suspected. They are for the most part extensive and symmetrical in distribution; they are usually of short duration, disappearing almost immediately the drug is withheld; and the degree of itching associated with them is variable, complete absence of itching often being observed. There are, however, notable exceptions to these common

findings. For instance, the eruption due to a heavy metal may persist for many months after the drug has been discontinued. With other drugs, the eruption may be limited to a restricted area where recurrence takes place with any subsequent administration.

Drug eruptions are seldom associated with general symptoms, but on occasion they may be accompanied by fever, collapse, blood changes, and asthma, all of which can be regarded as idiosyncratic responses comparable in nature to the eruption itself. In rare instances a grave systemic upset in association with skin manifestations may prove fatal—for example, with organic arsenical preparations.

It is not possible to give a comprehensive list of drugs which have been reported as having caused eruptions; it would be more appropriate to state that, with the exception of vitamin preparations and normal saline, the administration of any medicinal substance may produce skin lesions. The same types of eruption are seen today with new drugs as were noted fifty years ago with drugs now seldom if ever used, such as copaiba and cubebs; on the other hand, new drugs have been found to cause eruptions of a type and course not previously described.

While a large number of common drugs produce eruptions which are identical in appearance and which have no distinguishing feature to suggest that this or that drug is the cause, the eruptions produced by a small number of drugs present features which permit a fairly accurate guess to be made of the actual drug which has caused them. Such drugs usually produce skin lesions other than simple erythema. These tend to have an unusual distribution; sometimes they pursue a prolonged course after cessation of the drug and present some similarity to classified skin diseases not due to drugs. Distinctive eruptions of this type due to drugs at present in common use merit detailed consideration.

Distinctive Eruptions

Phenobarbitone.—Eruptions caused by this drug usually take the form of a transient itchy morbilliform or punctate erythema. Occasionally, however, a severe generalized eruption develops, beginning as an erythema-multiforme-like rash affecting the limbs and mouth and

proceeding to a generalized scarlatiniform erythema sometimes associated with superficial subcorneal bullae. This eruption may persist for a few weeks and may be associated with considerable constitutional disturbance (Fig. 1).

Opium and its Derivatives.—An urticarial eruption is often caused by such preparations. It differs from ordinary urticaria in the persistence of the weals and the absence of the usual periodic freedom from lesions. The weals are asso-

ciated with brilliant or dusky surrounding erythematous to a much greater extent than is usually found in ordinary urticaria, and they may be almost entirely free from itching. Apart from their administration for their analgesic effects these substances occasionally cause a rash of this type when used in cough mixtures and antipyretic mixtures.

The Sulphonamide Group.—These preparations when administered by mouth may produce scarlatiniform, morbilliform, purpuric, erythema-multiforme-like or bullous eruptions (Fig. 2). In some cases the rash may persist for a number of weeks and be associated with fever.

Erythema nodosum lesions sometimes develop during administration of these drugs and they may be indistinguishable from those associated with tuberculosis and other infections.

Sulphonamides may give rise to hypersensitivity to sunlight, and while this may occur as a result of oral administration it is much more likely to develop if the drug has been absorbed through a skin lesion or from a wound. In the latter case direct contact with the skin will take place almost inevitably, and it would seem that photosensitivity develops to a much higher degree when there is a combination of cutaneous contact with concomitant or subsequent absorption. The development of photosensitivity is attested by the sudden appearance of an acute eczematous dermatitis on uncovered areas within a few hours of exposure to sunlight.

These effects of the sulphonamides on the skin are produced by varying amounts of the drug, and while the manifestations attributable to the sulphonamide alone are transient the state of photosensitivity produced by it may persist for at least two years, and in rare cases the areas repeatedly affected by sunlight may become atrophic and resemble in appearance an x-ray atrophy with telangiectasia and pigmentation. For this reason, and quite apart from the fact that a contact eczema may also be produced, the use of sulphonamide preparations as local applications to the skin should be avoided. These preparations may also cause eruptions of the fixed type.

Gold Salts, Organic Arsenical Preparations, and Metallic Mercury.—These may all produce a severe generalized simple dermatitis (non-eczematous) which lasts for months after their administration has been stopped. The eruption may develop after one or several therapeutic doses, or following a course of treatment which seems to have been well tolerated initially. The first cutaneous manifestations may be apparently insignificant localized patches of scaly erythema which later become generalized, or the entire body surface may become suddenly erythematous associated with swelling of the face and extremities. As a

FIG. 2.—Erythema multiforme-like eruption due to a sulphonamide.

FIG. 1.—Severe generalized erythema, with mucous membrane involvement, due to phenobarbitone.

result of cutaneous oedema superficial bullae may develop under the stratum corneum, and when these rupture a persistent weeping surface is produced. After a short time exudation becomes negligible and a state of dry scaly erythroderma gradually becomes established, characterized by more or less leathery thickening of the skin and scaling.

In the case of gold salts this hypertrophic process progresses to the formation of circumscribed plaques, or large areas, closely studded with small hard nodules and papules which bear a striking resemblance to those of lichen planus both in contour and in colour (Fig. 3). As

FIG. 3.—Lichenoid eruption due to gold, six months' duration.

time passes the melanogenic function of the skin becomes extremely active, so that deep brownish pigmentation is super-added to the erythroderma. This capacity to stimulate cutaneous pigment formation is common to all the heavy metals. As the eruption persists the hair falls out. With all three drugs intense itching accompanies the eruption, and in the early stages there may be fever, constitutional upset, prostration, and evidence of damage to the liver and kidneys. Although gold, organic arsenic, and prolonged mercurial therapy is given to comparatively few the incidence of skin manifestations is high and must be constantly watched for, as they are often the most severe and dangerous of all drug eruptions. At the first sign of an erythema the drug must be stopped.

In contrast to metallic mercury and inorganic mercurial preparations the recently introduced mercurial diuretics, even when administered for long periods, seldom produce skin rashes, and when they do so the eruption is a non-characteristic erythema which quickly subsides on cessation of the drug.

The cutaneous manifestations due to inorganic arsenic are totally different from those caused by the organic preparations. Oedema of the conjunctiva may occur after small amounts of inorganic arsenic or after prolonged ingestion. Melanin pigmentation of exposed areas and pressure points and further darkening of areas already pigmented occur. In skin diseases treated with arsenic residual pigmentation of the lesions is a frequent and annoying feature. Gross hyperkeratosis of the palms and soles may develop. Localized keratoses and cutaneous horns, both of which may become carcinomatous, may appear on exposed areas, the action of light seeming to play a part in this process. Prolonged erythroderma such as is produced by organic compounds is not seen with inorganic arsenic.

Iodides and Bromides.—The eruptions produced by these drugs are almost identical, and apart from the macular erythema and purpuric types they are characteristic. The commonest is probably a deep-seated papular eruption affecting the face and often the trunk

and limbs as well. The papules become necrotic in the centre, thus resembling pustules, and the eruption is described as acneiform. The lesions are not necessarily situated at follicle mouths, are not associated with comedones, and of course the eruption is not limited to the period of puberty. Apart from these considerations the lesions are more solid, more deeply seated, and larger than ordinary acne lesions and in fact may be so nodular in character as to suggest a syphilide. Another type of nodular eruption which may develop on a circumscribed area, in the region of the nose, elsewhere on the face, on the limbs, or the trunk, consists of a nodule, or group of nodules which coalesce, and which enlarges to tumour size, ulcerates, and fungates. These nodular manifestations of iodide or bromide intolerance persist for a long period after cessation of therapy, as they are produced by a massive granulomatous type of infiltrate which will obviously require some time to dissolve. Iodides may cause an eruption resembling erythema nodosum. Both drugs, but more especially iodides, may give rise to a persistent bullous eruption resembling dermatitis herpetiformis (Fig. 4), and the administration of iodides to cases of true dermatitis herpetiformis may cause an exacerbation of the lesions in some cases. All of these eruptions may be accompanied by fever and prostration, and may prove fatal.

FIG. 4.—Bullous eruption due to iodide.

The Antibiotics.—Penicillin, streptomycin, and "aureomycin" are all capable of causing skin eruptions, and it would seem that streptomycin does so more often and aureomycin less often than penicillin. The rashes take the form of widespread urticarial lesions, erythema, or erythema-multiforme-like lesions, all of which appear during the first ten days of a course or after a single injection. There may or may not be a reaction at the site of injection. The eruption may be accompanied by fever and swelling of the joints and tendon sheaths. These manifestations persist for days, and may recur after a period of quiescence even though the drug has not been readministered. In the case of penicillin it has been noted that the presence of cutaneous fungus infections seems to increase the possibility of a skin eruption and such infections may themselves be aggravated by its administration. The drug reaction may take the form of cheirpompholyx, and it is possible that the latter may in fact be due to absorption from an existing fungus lesion which has been activated by the penicillin. It has been suggested that the penicillin eruptions may be true allergies, the tissues having been previously sensitized by contact with moulds encountered naturally. Impurities in the penicillin are undoubtedly the irritants in some cases. Erythema has been noted during chloramphenicol administration.

It has been found possible to desensitize to penicillin by administering it orally, and that eruptions due or attributed to streptomycin may disappear in spite of the administration of the drug being continued.

Some of the antibiotics, notably aureomycin and chloramphenicol, cause glossitis and cheilitis. These are due to a profuse growth of monilia. In ordinary circumstances the growth of these organisms is inhibited by the normal bacterial flora of the mucous membrane. The antibiotics, by reducing or abolishing the growth of these bacteria, permit the growth of monilia to proceed unchecked. Interference with the absorption and metabolism of vitamin B, owing to interference with the natural flora of the gut, has also been suggested as the cause of the mucous membrane lesions, but their onset is too rapid to be explained on the basis of a vitamin deficiency.

Phenytoin and Methoin.—These recently introduced anticonvulsant drugs for the treatment of epilepsy seem to produce morbilliform erythematous eruptions with some frequency, and hypertrophy of the gums often accompanies their administration. They are chemically related to phenylethylhydantoin, which was recommended in chorea, but is now seldom used, and which gave rise to an erythema on the ninth day of administration in almost every case. The hydantoin eruptions seemed to be directly related to dosage and might almost be regarded as forming part of the pharmacological action of the drug.

Mepacrine.—In addition to producing a generalized yellow discoloration of the skin this drug may cause curious and characteristic skin lesions which usually do not appear until it has been administered regularly for from three to six months. The hands, feet, neck, face, eyelids, and pressure points on the trunk are the areas commonly affected, either together or singly. To begin with, the lesions are vesicular and pseudo-eczematous in character. They may remain in this state for some time, but are usually followed or accompanied later by the appearance of slate-blue areas of discoloration which may become psoriasiform or bullous in character and which are followed by the development of hypertrophic papules or nodules resembling lichen planus. These lesions persist for months, and healing may be accompanied by scar formation and pigmentation. Dryness and follicular hyperkeratosis may be a feature of the skin not affected by an active eruption.

Biological Preparations.—With the exception of the erythema of nicotinic acid, which is constant and can be regarded as a pharmacological effect, skin eruptions do not seem to be produced by purified vitamin fractions. Generalized erythema and urticaria have been ascribed to oestrogen and insulin therapy, but must be extremely rare. A local urticarial reaction at the site of injection is, however, common with insulin. The acne of androgen therapy can be regarded as physiological.

Antihistamine Preparations.—Most curious of all drug eruptions are the few apparently fully authenticated eruptions attributable to "benadryl." These are erythematous and pruritic in nature. In view of their occurrence and the fact that, with the exception of the urticarial type of reaction, drug eruptions do not appear to be much influenced by the administration of antihistamine preparations, it would seem doubtful if histamine plays a frequent part in their development.

Fixed Eruptions

Certain drugs produce what are known as fixed eruptions. By this term is meant that the eruption always recurs on the same area—that is, it is the site which is fixed; the duration of an attack may vary within wide limits. Phenazone (antipyrin), phenacetin, arspenamine, quinine, sulphonamides, and particularly phenolphthalein are the drugs which most often cause fixed eruptions.

The usual lesion is a clearly demarcated erythematous plaque of varying size and duration which appears on any part of the body shortly after the ingestion of the drug (Fig. 5). The eruption often leaves residual pigmentation, and it recurs on the same site if the drug is again administered. There may be one or several plaques, and if repeated recurrence takes place new sites may develop lesions

FIG. 5.—Fixed eruption due to phenolphthalein.

in addition to the old. Occasionally the lesion is urticarial or bullous. The reaction takes place only after ingestion of the drug, and testing the "fixed site" with the drug produces no response. It has been found possible to transplant the reactive skin to other areas. It is curious that the sensitivity appears to be strictly localized, and such eruptions are interesting from the point of view of the general problem of distribution in diseases of the skin.

Diagnosis

A perusal of detailed lists of drugs and the eruptions which have been noted to occur in association with them reveals the fact that an erythema—scarlatiniform, morbilliform, or purpuric—is common to them all, and that in only a few are additional types of lesions seen. In most cases an initial diagnosis of toxic erythema is all that is possible, and thereafter an investigation of possible "toxins," including drugs, is initiated. The history of drug ingestion leads to the suspicion of a drug eruption, and the withholding of the drug and the subsequent disappearance of the eruption strengthen it. In the case of a commonly used drug previous experience of this kind tends to confirm the suspicion to some extent. Unfortunately no form of skin test can be relied on to demonstrate cutaneous hypersensitivity to a drug administered internally, and it is only when the eruption is deliberately reproduced by the re-administration of the suspected drug that the association is satisfactorily proved. While such proof is desirable it may be extremely dangerous to attempt to obtain it in view of the possibility of the development of a reaction of much greater severity than the initial one. It is not a procedure to be lightly undertaken in every case, and is to be avoided absolutely when such drugs as the heavy metals or iodides are suspected.

The history of recent ingestion of a drug may not be forthcoming in suspected cases, owing to the patient's memory being unreliable, to false denial, or to the drug

having been unwittingly ingested in the form of a food preservative, a flavouring, or a colouring agent.

Drug eruptions may simulate classified skin diseases fairly closely, but there is always some feature which is atypical. To appreciate this, considerable experience of the appearances of the classified skin diseases may be necessary. The erythema is usually florid in type and its mode of extension, duration, and regression erratic, and this taken in conjunction with extracutaneous symptoms and biological tests serves to distinguish it from the eruptions of the infectious fevers and syphilis. The administration of the heavy metals carries with it the responsibility of being on the alert for the development of skin eruptions. Bromide and iodide eruptions may be mistaken for acne vulgaris and dermatitis herpetiformis, and in their localized form for gummata or manifestations of reticulosis.

Treatment

Extensive eruptions such as those due to gold, organic arsenical preparations, and some types of sulphonamide eruption should be treated in hospital when possible. Prolonged rest in bed, careful nursing, and extensive local treatment are necessary, and the fluid intake must be well maintained. Local applications are directed towards the relief of itching and the restoration of altered skin structure to normal, and mildly astringent lotions and bland pastes or creams are suitable. In the presence of lichenoid lesions, which are usually persistent in character, crude gas tar applications and superficial x-ray therapy are useful.

Dimercaprol ("B.A.L.") is most useful in organic arsenical eruptions; it seems to check extension and

hasten recovery, and is superior in its effect to intravenous injections of sodium hyposulphite. In gold dermatitis dimercaprol tends to relieve the intense itch but does not appear to have a marked effect on the skin changes. It is administered by intramuscular injection as a 5% solution in oil as follows: 2 ml. three times daily for the first 24 hours, and for the succeeding seven to ten days 2 ml. once or twice daily depending on the severity of the eruption. Antihistamine drugs may relieve itching, but with the exception of urticarial reactions they do not benefit the eruption greatly, and it must be remembered that eruptions have been attributed with good reason to the antihistamine preparations themselves. Severe symptoms of collapse, dehydration, and blood dyscrasias, and psychotic manifestations may accompany the eruption and call for appropriate measures.

As a rule attempts at desensitization have met with failure, but in the case of penicillin and the sulphonamides some success has been claimed from gradually increasing the dosage from an initial minute amount.

Conclusion

In conclusion it is safe to forecast that as new drugs are introduced it will be found in due course that the majority, if not all, will cause eruptions in some proportion of the population to which they are administered. It will continue to be a question not of whether the new drug is capable of producing an eruption but whether a skin lesion which has appeared during its administration is being caused by it, and the list of drugs recorded as having produced a rash will probably be lengthened by each addition to our stock of remedies.

PRINCESS TSAHAI MEMORIAL HOSPITAL

The Princess Tshahi Memorial Hospital is being erected in memory of the daughter of the Emperor Haile Sellassie, who trained for five years as a nurse in this country and died in Ethiopia at the age of 22 while attempting to introduce British standards of nursing into her own country. A partially constructed hospital was kindly offered to the Memorial Council by the Emperor, and the central building with accommodation for 92 patients is rapidly nearing completion. Four additional wings have been planned, and these should bring the total number of beds to 250. A two-story out-patient department has been built for medical, surgical, obstetrical, and gynaecological patients, and in addition there are special departments to deal with eye, ear, nose, and throat complaints, dentistry, venereal disease,

and antenatal work. The dispensary is also located here. An annexe has been built at the back of the main building consisting, on the ground floor, of a kitchen department with electrical equipment, and, on the floor above, two operating theatres and an x-ray department, an anaesthetic room, a dark-room, and other facilities necessary to such a surgical unit. There is a corridor linking this annexe to the main building, and an electric lift for both passengers and beds.

Future Training School

It is hoped in time to build a pathological laboratory and also to obtain a building in the neighbourhood to house class-rooms, a reference library, and other facilities for

The Out-patient Department of the Memorial Hospital under construction.