inhibiting test was positive. There remain, however, the single cases described by Somers (1957), by Sédallian *et al.* (1957), and by Galloway and MacBean (1958). However, other authors—for example, Apt (1953–4)—report patients vaccinated without complications. One wonders whether secondary infection could have been a factor in the fatal cases. One is also surprised that Galloway and MacBean state that the overall mortality rate in generalized vaccinia is 90%, which does not agree with our small experience. Nevertheless, in our present uncertain state of knowledge we do not feel that vaccination is a justifiable procedure in the presence of agammaglobulinaemia.

It may be that agammaglobulinaemia is not such an uncommon condition as it seems. Good and Varco (1955) were able to collect six cases in 10 months, and three were seen at the Mayo Clinic in seven months (Hayles *et al.*, 1954). We have on many occasions before and since looked for it in children, who have had several attacks of pneumonia before their first birthday or in whom there is an appropriate family history, without finding a further example. The case of the son of II 4 (see above) suggests that they may go unrecognized at times when bronchopneumonia is epidemic. Obviously the more cases that are investigated the more examples will be found, but there seems nothing in the examination of the child with this condition particularly to draw one's attention to the correct diagnosis.

Margulis *et al.* (1957) have suggested that the chest radiograph may be of potential diagnostic importance when with extensive parenchymal involvement there is a paradoxical absence of hilar lymph-node enlargement. That these features, which are shown by the serial radiographs in Case 2, are not invariable was demonstrated in Case 1. As mentioned previously, his chest radiograph in June had shown a right hilar adenitis, which by the following month was so marked that the radiologist suggested that tuberculosis should be considered. The case described by Elphinstone *et al.* (1956) showed on one occasion "a little enlargement of the right hilar shadow only." His sibling, who also had agammaglobulinaemia, developed enlargement of the regional lymph nodes in response to B.C.G. vaccination.

The normal sedimentation rate of Case 2 at a time when one would have expected it to be markedly raised might in retrospect have been of some diagnostic significance. This was also found by Elphinstone *et al.* and has been commented upon by several other authors. Citron (1957), however, in describing a case of acquired agammaglobulinaemia in a girl of 12, where no gamma-globulin was detectable by paper electrophoresis, states that the sedimentation rate "was moderately raised during infection except in the last few weeks before death, when in spite of much pulmonary infection the E.S.R. was 3 mm. per hour or less." It is, however, not clear from his paper what the time relationship was between the raised E.S.R. and the discovery of the absence of gamma-globulin. It would perhaps be unwise at present to regard the low E.S.R. found in these cases as being due solely to low gamma-globulin, since the rate of sedimentation is known to be influenced also by the alpha-globulin and fibrinogen levels in the plasma.

Summary

Two cases of agammaglobulinaemia are described. Their family history is consistent with a sex-linked recessive mode of inheritance. The problems of diagnosis and the response of these cases to different types of infection are discussed.

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TOXIC EPIDERMAL NECROLYSIS

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The paper by Catto (1959) reporting a case of toxic epidermal necrolysis in a boy aged 3, has directed attention to the syndrome described by Lyell (1956) and by Lang and Walker (1956, 1957), and has again raised the question of aetiology. The available evidence indicates that the characteristic clinical picture is a response to a variety of circulating toxins or allergens, derived from drugs or possibly from foods—for example, snoek liver—but the causative role of the suspected agents has not hitherto been definitely established.

In the cases reported below, known drugs are believed to have precipitated the typical syndrome on more than one occasion in persons who were already sensitive to them : these drugs were phenolphthalein and dapsone.

Case 1

In December, 1959, a deeply pigmented Nigerian woman, aged about 55, was admitted to the Uzuakoli Research Unit Clinic suffering from a widespread papular eruption of four days' duration. The illness had been ushered in by headache, nausea, and general malaise. The temperature and pulse were only slightly raised, and the patient's general condition was good. The skin presented the following picture: a purplish-black discoloration of the whole face, including the lips, but sparing the nose and the periphery ; large macular hyperpigmented areas on the trunk roughly symmetrical in distribution ; a diffuse slate-grey dyschromia of the skin of the limbs. The buccal, nasal, and meatal mucosae and the conjunctivae were unaffected. This hypermelanosis had appeared some months previously ; during the present illness the areas involved had become acutely tender to the touch.

Sedatives and calming applications were prescribed, and prednisolone ("deltacortril" tablets) was given. The subjective improvement was satisfactory, the pruritus and malaise diminishing.

On the fourth day after admission, however, the patient became restless, and the temperature rose rapidly to 104° F. (40° C.). Large areas of skin on all four limbs became detached as if scalded; they could be slid over the subjacent tissue, just as a rubber glove, put on wet, can be slid on the fingers. Nikolsky's sign was positive over adjacent areas of skin not visibly separated. Its elicitation resulted in painful and persistent formication. The temperature remained raised for three days before beginning to return to normal; during this time the patient felt and looked ill. Then, from deltoid to finger-tips and from trochanters to toes, the whole skin peeled off in large sheets, revealing a surface slightly moist and dull pink in colour. The skin of the palms, soles, and pre-tibial regions was the last to separate, but it, too, was shed eventually.

While the skin was peeling, the patient's general condition was very good: the temperature was normal, and she preferred to be ambulant. The underlying skin was soft and supple like that of a newborn coloured baby, but of a more dusky hue than normal. The whole denuded surface repigmented rapidly and uniformly; there was no perifollicular or marginal repigmentation. After three weeks the skin of the limbs had assumed its pre-existing slate-grey colour. Meanwhile the skin overlying the hypermelanotic macules on the face and trunk had desquamated in small flakes, the underlying macules becoming blacker.

Previous History.—Careful interrogation of the patient and her relatives disclosed that two precisely similar episodes had occurred—in 1955 and in June, 1959. The chain of events had been identical: a "fever" for which she had been self-treated on both occasions with aspirin, mepacrine, and proguanil. Shortly afterwards she experienced a generalized irritation, and then the superficial epidermis became detached from all four limbs. The dark areas on the face and trunk appeared; they had faded slightly before becoming darker during the second attack. In the absence of clinical notes, the observations of a son-in-law (a medical auxiliary) have been most valuable, but the "fever" from which she originally suffered cannot be accurately diagnosed in retrospect. The "fever" she remembers most vividly is that associated with the epidermolysis.

Prolonged inquiry failed to incriminate any article of diet, or garment, or skin infection, or contact with plants that might have precipitated the syndrome in all three apparently identical episodes: no hormonal change (puberty, pregnancy, menopause) was operative; the only common factor appeared to be the drugs that she and her relatives admitted she had taken.

Subsequent History

In May, 1960, in an attempt to identify the drug responsible—if such were indeed the case—patch tests were performed in turn with all the drugs she had taken before the occurrence of the epidermolysis. When these tests had proved negative, a small dose of each drug was given by mouth, with negative results. It then transpired that some tablets of sulphathiazole had also been administered by a son as a "tonic"; tests with this product, however, also proved negative.

Some days later, while still under observation, the patient took a proprietary laxative tablet containing 5 gr. (320 mg.) of phenolphthalein. Within 30 minutes she complained of generalized pruritus, and one hour later small papules appeared over the entire skin, closest-set on the limbs. The irritation became more intense, especially in the hypermelanotic areas. The patient affirmed that she felt exactly as she had done on each of the three previous occasions.

That evening the temperature rose to 102.2° F. (39° C.) and the pulse to 88. The urine was normal chemically and microscopically. The total white count was 5,500/c.mm. (22% neutrophils, 54% lymphocytes, 24% eosinophils). The stools were normal, apart from the presence of hookworm eggs. Prednisolone was administered and calamine lotion was applied to the skin. Within 72 hours the temperature and pulse had returned to normal and the irritation had diminished considerably. The prednisolone was gradually reduced.

Seven days after the aperient tablet had been taken, however, the patient complained of all the symptoms of relapse. The temperature rose to 103.2° F. (39.6° C.) that evening, and a degree higher the following evening. The skin of the limbs was tender on palpation, and the superficial layers were beginning to loosen. The temperature and pulse again returned to normal within four days, and the skin irritation and tenderness ceased. The integument became detached in the same situations as before, and in the same sequence. The underlying surface was dull pink in colour and quite dry when the epithelium had become completely separated. The hairs remained intact in their follicles. At no time was there any pus formation or ulceration. No antibiotics or sulphonamides were given. There was no scabbing or scarring.

On subsequent interrogation the son admitted that before each of the three episodes he had given his mother different proprietary laxative preparations each containing phenolphthalein as the active ingredient. When first questioned he had not mentioned this fact, because he did not think that such products were "drugs" or "medicines."

After the patient's recovery, further patch-tests were performed. The site of a hypermelanotic macule showed slight delayed (48 hours) sensitivity to 1% alcoholic phenolphthalein; controls in normal skin, and in the skin of the forearms, showed no reaction.

Comment

In the general population of Eastern Nigeria phenolphthalein in proprietary laxatives is the commonest cause of a fixed drug eruption characterized by hypermelanotic macules, but the incidence of sensitivity to the product is unknown: it is probably very low. In the past 10 months, however, one of us (S. G. B.) has been consulted by 10 persons complaining of a fixed drug eruption that proved on investigation to be due to phenolphthalein, and one of these (Case 1) has developed epidermal necrolysis.

Case 2

A well-built Nigerian woman of about 37 years, and weighing 128 lb. (58 kg.), had been receiving standard treatment with dapsone for tuberculoid leprosy since March, 1956, having first noticed the leprosy lesions about a year previously. She attended, somewhat irregularly, the Kakwagom Leprosy Treatment Centre twice weekly as an out-patient, receiving 400 mg. of dapsone orally at each visit. This maximum dose had been reached in accordance with the dosage schema commonly followed: the initial dose of 100 mg. twice weekly for four weeks was followed by 200 mg. twice weekly for four weeks, then by 300 mg. twice weekly for four weeks, and 400 mg. twice weekly thereafter.

At the end of February, 1960, the patient complained of malaise, "fever," and a generalized papular eruption. Large flaccid blisters made their appearance on the face, trunk, and limbs. She had taken no drug but dapsone.

She was seen by one of us (E. R.) on March 1, and was admitted to Ogoja Leprosy Settlement Hospital. By this time the superficial epithelium in the affected sites had ruptured, releasing a little yellowish fluid. The denuded surfaces were covered by an intact layer of moist epithelium, slightly red in places from punctate capillary exudation, and distinctly blacker than the normal dark-brown skin. The superficial layers of the skin of the arms below the insertion of the deltoid, and of the legs, were almost completely separated from the deeper layers, and could be slid over them. Where no cleavage was apparent to the eye, Nikolsky's sign was present. The pretibial skin was still intact, and Nikolsky's sign could not be elicited here.

Apart from the skin, the patient's general condition was very good. Nothing abnormal was found on routine clinical examination; in particular, the liver was not palpable, and there was no jaundice. The urine contained a trace of albumin.

Dapsone was stopped at once, and antihistamines were given. Calamine lotion was freely applied to the blisters and to the limbs. To anticipate the supposed risk of infection, penicillin was given intramuscularly. The severe degree of anaemia present (haemoglobin, 50%; R.B.C., 2,370,000/c.mm.) was treated with iron. The white blood count showed no abnormal features, apart from an eosinophilia of 10%.

When the patient was examined by both of us on March 10 the only remaining evidence of the flaccid superficial blisters was the presence of hypermelanotic macules on the face and trunk. Except on palms and soles and pretibial region, the skin of the limbs was detached in large continuous sheets, revealing a diffusely hyperpigmented underlying surface.

Prednisolone was given from March 10 onwards for 14 days, decreasing latterly. Apart from the residual hypermelanosis—macular and discrete on face and trunk, and diffuse on the limbs—the patient had completely recovered within four weeks of the onset of the incident. There had been no ulceration, and there was no scarring.

Treatment with dapsone was resumed, with the same cautious build-up as when treatment was begun four years previously. There was no recurrence of pruritus, no papular rash, and no excerbation of the hypermelanosis.

Three months later the patient was again examined at the Leprosy Treatment Centre. She had been taking full doses of dapsone (400 mg. twice weekly) without any untoward symptoms. The hypermelanosis was unchanged, both in extent and in degree.

Previous History.—Interrogation of the patient disclosed the fact that she had previously experienced two similar episodes since she began taking dapsone—the first after about a year's treatment, and the second after two years. On each occasion she had absented herself from attendance at the Leprosy Clinic. She had recovered completely from both attacks, and stayed in her isolated village, 30 miles from the nearest doctor. After the first episode she noticed the black patches on her face and trunk and the general darkening of the skin of the limbs.

It would seem that during the second and third attacks the loss of the superficial epithelium occurred in precisely the same situations—namely, at the sites of the discrete hypermelanotic macules, and, more extensively and superficially, from all four limbs.

Comment

The history of one or more attacks of generalized papular dermatitis, followed by the appearance of the hypermelanotic macules of a fixed drug eruption, is a not uncommon manifestation of sensitivity to dapsone. Sometimes the macules appear *de novo*, with no ascertainable preceding pruritus or exanthem, or suggestion of local inflammation. In some individuals a single tablet of dapsone (100 mg.) has precipitated the condition; whereas in others a period of cumulation seems to be necessary before some threshold is passed and sensitization develops.

The subsequent course of events varies also. Sometimes the hypermelanotic macules behave as a fixed drug eruption, with local symptoms (pain, tenderness, erythema, infiltration, bullae formation, exacerbation of the hypermelanosis) with each subsequent administration of the drug. More often, however, once the initial acute stage is over the patient may continue to take the drug without ill effects. In such a disease as leprosy, in which treatment is imperative, perseverance with therapy without incommoding the patient unduly has revealed different types of reaction that would remain unknown if an optional treatment (like, for example, phenolphthalein given as an aperient) had been abandoned after signs of hypersensitivity had become manifest.

When symptoms persist, or recur with further antileprosy treatment, slow desensitization with aqueous solapsone is often successful.

The fatal dermatitis observed in the early high-dosage dapsone treatment for leprosy seems usually to have been an exfoliative dermatitis (Barnes, 1960, personal communication) or, rarely, an erythema multiforme of the Stevens–Johnson type, associated with jaundice and albuminuria. No cases similar to the present are recorded.

In a total population of 45,035 persons in the Belgian Congo, 160 cases of hypermelanosis were observed in 5,349 patients undergoing treatment for leprosy with dapsone or solapsone by mouth or by intramuscular injection (Browne, 1959). In Nigeria, 19 examples have been encountered in approximately 550 cases of leprosy (Browne, 1960).

Case 2 is the only one in which the intra-epidermal cleavage characteristic of toxic epidermal necrolysis has occurred.

Discussion

The symptomatology and clinical course of the disease in the two patients resemble so closely the findings in published cases of toxic epidermal necrolysis in most respects that detailed comment on this score is unnecessary. In particular, the appearance of the denuded surface, the minimal exudation in the extensive flaccid blisters, and the subsequent absence of pus formation, all indicate the superficial level of the cleavage. The clinical gravity of reported cases appears to vary: three out of 10 cases were fatal; five had recurrent attacks of a similar type.

Several points of interest and importance, however, call for some notice. Firstly, the characteristic syndrome was precipitated by known chemical compounds in subjects whose skin already gave evidence, by the presence of hypermelanotic macules of a fixed drug eruption, of sensitivity to these compounds. It is noteworthy that a similar manifestation of sensitivity in the two patients should be followed by the same syndrome of epidermolysis involving the same areas of skin. A similar hypermelanotic fixed eruption has been observed in Nigeria in connexion with mepacrine, "acetylarsan," thiacetazone, diphenylthiourea, and dithio-*iso*-phthalate; and similar cutaneous lesions have been observed after a contact dermatitis associated with photosensitivity and caused by unidentified purgatives of vegetable origin. No case of toxic epidermal necrolysis has been observed in these patients.

Secondly, the epidermolysis in these two cases appears as a superimposed manifestation of sensitivity to such drugs. In the case of both phenolphthalein and dapsone, cutaneous reactions may show wide variations: erythrodermia, papulo-erythematous eruptions, erythema bullosa, and the Stevens–Johnson syndrome. The commonest eruption is a localized erythema, followed by a discrete or diffuse hypermelanosis; more rarely, there is a severe generalized exfoliative dermatitis which may prove fatal (Lowe, 1950; Allday and Barnes, 1951; Barnes and Barnes,

1951). Cases have been seen by both of us in phenolphthalein-induced and dapsone-induced fixed eruptions showing small bullae; when the epithelium has been removed by scratching, a sky-blue macule remains, which later becomes slate-grey when the pigmented basal layer is reconstituted (Browne, 1959). In such cases the bullae are set deep in the dermis and are tense with fluid.

Thirdly, in both cases reported above, administration of the drugs resulted in an exacerbation of the pre-existing hypermelanosis caused by the same drug, and this exacerbation was accompanied not only by a recurrence of the generalized papular eruption but also by the characteristic intra-epidermal cleavage in the areas of predilection. In the first case each known administration of the drug was followed by the syndrome, whereas in the second case irregular twice-weekly ingestion of dapsone resulted in three distinct but similar episodes. The diffuse slate-grey pigmentation of the limbs indicates a widespread deposit of melanin, mainly in the papillary layer of the dermis—a post-inflammatory phenomenon.

Fourthly, these cases seem to furnish a clinical link between the epidermolysis occurring in apparently healthy persons and the varieties of toxic erythemata. The actual cutaneous manifestations in a given individual depend on the precise level of skin predominantly affected: at one time the cutaneous target is superficial, leading to cleavage in an intra-epidermal plane; at other times the target is deeper, becoming apparent clinically as a hypermelanosis or as a bullous eruption. The present cases conform to the published descriptions in that there was superficial denudation of very extensive areas of integument, in contrast with the commoner type of recurrent fixed drug eruption in which discrete deep-seated bullae occur in an erythematous skin. Why the target for the toxic onslaught in any one patient should be the superficial layers of the epidermis at one moment and the deeper layers at another, or both simultaneously (as in the first case report), is a matter for speculation.

The virtual absence of constitutional symptoms (after the initial pyrexia and generalized malaise) in both patients while they were undergoing the loss of extensive areas of skin is in striking contrast with the shocked condition of cases of scalding in which comparable areas are involved, or of cases of Stevens–Johnson syndrome in which severe toxic absorption from involved mucosae and infected denuded skin occurs. The fatal published cases of the syndrome appear to have been complicated by this type of infection.

Fifthly, the sequence of events in the last episode in Case 1, particularly the rise in temperature from the 7th to the 10th days after ingestion of the incriminated agent, strongly suggests that the mechanism is allergic, and similar to such conditions as the seventh-day rise in temperature not infrequently noted during sulphathiazole treatment, photosensitization by sulphonamides, and second-week penicillin reactions.

It may be that the early generalized papular eruption is precipitated by the unaltered drug, while the epidermolysis seems much more likely to be a response to an allergen, possibly proteose- or protein-conjugated. In Case 2 the mechanism may also be toxo-allergic, sensitization being in some way induced by dapsone taken over a prolonged period, but manifesting itself with dramatic suddenness.

Photosensitization seemed not to play a determinative part: for the nose was spared in the hypermelanosis, and covered and uncovered parts of the limbs were involved indiscriminately.

Parallergic sensitivity is a possibility that cannot be absolutely excluded, but no positive evidence exists for the assumption.

The value of the prednisolone administered is uncertain. In Case 1 it may have reduced the fluid exudation from the denuded surface; in Case 2 it was probably given too late in the course of the disease to have any effect.

In conclusion, the occurrence of a virtually identical syndrome precipitated by two compounds widely different in chemical structure is in keeping with the suggestion (Lyell, 1956; Rook, 1957; *Year Book of Dermatology and Syphilology, 1957–58*) that the characteristic clinical appearances are probably a non-specific cutaneous response to a variety of "toxins" (using the word in its widest sense) causing extensive damage to the suprapapillary zone of the epidermis, in the same manner as fixed drug eruptions or papulo-erythematous rashes may be the limited response-pattern to chemically dissimilar products.

In the 10 reported cases of toxic epidermal necrolysis, phenolphthalein has been suspected twice (Lang and Walker, 1957), penicillin once (Lang and Walker, 1957), and phenylbutazone once (Lyell, 1956). One patient had had aspirin and Dover's powder (Lyell, 1956), and another methyl salicylate application and chenopodium oil by mouth (Lang and Walker, 1956); in the latter case the aperient given is not indicated, but the occurrence of hyperpigmented macules on the trunk and a slate-grey pigmentation of the soles suggests a phenolphthalein-induced fixed eruption similar to the first case here reported.

In view of the widespread use of laxatives and sedatives (barbiturates, ureides) that can be freely purchased, the possibility of further cases of toxic epidermal necrolysis must be recognized. On the evidence now adduced, pre-existing sensitization to such products would seem to be an important—perhaps an essential—factor, and residual sensitivity indicates a predisposition to recurrence of the epidermolysis.

Summary

Two typical cases of "toxic epidermal necrolysis" are reported in which phenolphthalein and dapsone were respectively the causative drugs. Both patients had hypermelanotic fixed eruptions caused by the drugs, and both experienced more than one attack of the syndrome, each attack being apparently precipitated by the agent in question and affecting the skin of all four limbs. The mechanism is apparently allergic.

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