Neuman and Neuman (1957) have implied a process of ion exchange whereby calcium ions can enter the extracellular fluid only if the bone crystal takes up other cations—for example, Mg^{++}—to maintain electroneutrality. In the presence of magnesium deficiency this exchange process may be inhibited. Correction of the deficiency would allow mobilization of calcium ions from bone.

The absence of a significant change in serum phosphate levels during these infusions suggests that the effect of magnesium in restoring normal plasma ionized calcium levels is not directly mediated through the parathyroid gland. However, it is possible that magnesium deficiency causes blunting of end-organ—for example, bone—responsiveness to parathyroid hormone.

The magnesium deficiency tetany syndrome in man has been described by Vallee *et al.* (1960). We would suggest that the tetany occurring in this syndrome is due to low plasma ionized calcium levels, despite apparently normal total calcium levels. The rise in plasma ionized calcium to normal levels during magnesium infusion explains why magnesium therapy will relieve tetany in these patients.

It would appear that the tetany seen with hypomagnesaemia is not attributable to magnesium directly but as a result of magnesium deficiency causing depression of ionized plasma calcium levels. Hypomagnesaemia without lowering of plasma ionized calcium levels has not been reported; this hypothesis awaits confirmation.

SUMMARY

Plasma levels of ionized calcium were measured before and after intravenous infusion of magnesium in two patients with tetany and hypomagnesaemia. The tetany reported in association with hypomagnesaemia seems to be a consequence of low plasma ionized calcium. The nature of the defect is uncertain, but evidence is consistent with inhibition of release of ionized calcium from the exchangeable bone pool as a result of magnesium deficiency.

We thank Dr. J. A. Owen, Director of Biochemistry, and his staff for invaluable advice and assistance, and Dr. T. E. Lowe and Dr. D. Coventry for permission to investigate the second patient. Plasma total and ionized calcium levels were measured by one of us (W. G. N.).

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Medical Memoranda

Toxic Epidermal Necrolysis Caused by Skin Hypersensitivity to Monosulfiram

Brit. med. J., 1968, **1**, 623–624

This paper records a peculiar and dangerous complication of treatment with the antiscabetic preparation monosulfiram, which caused an eruption that was diagnosed as toxic epidermal necrolysis of Lyell (1956), and made the patient very ill. Later, on patch-testing, she was found to have had a previously acquired skin hypersensitivity to one of the common rubber vulcanizing accelerators, tetramethylthiuram disulphide, a substance very similar in composition to monosulfiram.

CASE HISTORY

A housewife aged 47, a scabies contact, was admitted to hospital as an emergency case with a three-day history of a rash that had developed three and a half hours after applying diluted Tetmosol (monosulfiram) solution to her body below the neck. She had not taken any alcohol at this time. In 1940 she had consulted the late Dr. Henry MacCormac about rubber dermatitis on her hands which had developed while working in a munition factory. Since then she had been unable to wear certain rubber-containing garments, and after blowing up balloons at Christmas she got an itchy rash on her face. Examination showed that a diffuse erythema with considerable dermal oedema affected all of her body, though initially it was less severe on the face and neck.

On her admission the red areas were rapidly becoming covered by large numbers of small pustules which were coalescing to form lakes of subcorneal pus. The horny layer now started to disintegrate and to be shed in vast sheets—the one below her right knee like a stocking in one piece. The pustules were distributed diffusely, and not in groups or in rings. Mucous membranes were unaffected. She had a fever and was severely ill. Toxic epidermal necrolysis was diagnosed as due perhaps to the methyldopa and hydrochlorothiazide with which her hypertension was being treated, or to a systemic effect of monosulfiram absorbed through the skin.

Investigations.—A cytological smear from the pustules showed a great quantity of polymorph neutrophils but no bacteria. No organisms were cultured. Blood counts: W.B.C. 20,000 (95% neutrophils, 4% eosinophils). Two weeks later: W.B.C. 8,900 (48% neutrophils, 15% eosinophils (1,335 absolute count), 31% lymphocytes, 5% monocytes, 1% plasma cells). The following tests were all normal; haemoglobin, urine (× 3), blood culture, serological tests for syphilis, blood electrolytes, blood urea, random blood sugar, blood uric acid, liver function, serum vitamin B_{12}, and serum folate.

The oedema increased noticeably for the first 10 days; she gained 20 lb. (9 kg.) in weight and had oliguria. Later the jugular venous pulsation was raised to about 6 cm. and the liver became palpable. A larger circulating blood volume from fluid retention and protein loss through the skin rather than cardiac failure was implicated. Chest *x*-ray examination (× 3) showed no evidence of heart failure, and the E.C.G. sinus tachycardia only. The serum proteins totalled 5.0 g./100 ml., but they had risen to 6.3 g./100 ml. two weeks

later, after the diuresis. A 24-hour collection of urine contained only 7.7 mEq of sodium. Serial serum calcium estimations showed a fall to 7.5 mg./100 ml., returning to 9.0 mg. later. Three fractions of her immunoglobulins (IgA, IgG, and IgM) were raised significantly both at this time and two weeks later (Dr. K. B. Cooke). The patient remained severely ill with rigors and fever (101–102° F.; 38.3–38.9° C.) for two weeks, and heat loss from the erythroderma was probably contributory. Fluid loss through the skin was copious.

On the 10th day of illness she was given tab. triamcinolone 4 mg. t.d.s. for two weeks, and from this time her recovery began. The remaining small patches of eczema soon cleared with ung. fluocinolone. There was no scarring of the skin. Then she became bald—a telogen effluvium effect following her serious illness—but three months after the onset of the malady her hair was growing again thickly. She also had deep transverse ridging of the nails, which were later shed and normal nails regrew.

When the eczema had disappeared *patch tests* were done. They were negative to lanolin, parabenz, colophony, balsam of Peru, potassium dichromate, paraphenylenediamine, and nickel sulphate. Two rubber accelerators were tested. Mercaptobenzthiazole was negative, but a positive eczematous response to tetramethylthiuram disulphide was seen 48 and 96 hours after application. Monosulfiram diluted with six parts of water gave a very severe eczematous reaction within three hours of application.

Discussion

There are reasons to justify alternative treatments for scabies, and monosulfiram (Martindale, 1967) is known to be effective. The efficiency of benzyl benzoate, long regarded as the best treatment for scabies (Mellanby, 1943), has recently been questioned (Erskine, 1967; Franklin and Baker, 1967), and Baker *et al.* (1968) have found that some commercial preparations fail to comply with pharmacopoeial requirements. Also, treatment with benzyl benzoate may cause a troublesome dermatitis (Epstein, 1966; Lyell, 1967).

Monosulfiram is a 25% alcoholic solution which is diluted with three parts of water immediately before use. The manufacturers (D. G. Higgins, personal communication, 1967) have no records of an eruption similar to the one described. Monosulfiram is similar chemically to disulfiram (Antabuse), which is used systemically to treat alcoholics and to which eruptions are attributed (Goodman and Gilman, 1965). Monosulfiram is absorbed after application, and systemic toxic effects occur if alcohol is taken (Gold, 1966).

Our patient knew that some rubbers gave her eczema, and these contained the thiuram rather than the benzthiazole group of chemicals (Wilson, 1966). Thus Spandex garments, in the manufacture of which benzthiazole and not thiuram is used as an anti-oxidant (Allenby *et al.*, 1966; Porter and Sommer, 1967), never gave trouble. On patch-testing she developed eczema to tetra*methyl*thiuram disulphide, to which monosulfiram (tetra*ethyl*thiuram monosulphide) has close chemical affinity.

While the nature of toxic epidermal necrolysis may be disputed, the seriousness of a disease with a 30% mortality (Lowney *et al.*, 1967) cannot be questioned.

In infants and children toxic epidermal necrolysis appears to be infective (Jefferson, 1967; Holzel, 1967), and coagulase-positive haemolytic staphylococci may be cultured in many cases (Tyson *et al.*, 1966; Koblenzer, 1967; Holmes *et al.*, 1967; Shilkin, 1967). Sudden recovery may occur spontaneously or after administration of antibiotics, but not with corticosteroids alone. A drug history in neonates is rare, but in the case of one baby, who was born with toxic epidermal necrolysis, the mother had had phenolphthalein during the last trimester (Sweetnam *et al.*, 1964).

Many adults commonly give a history of drug ingestion—sulphonamides, phenylbutazone, penicillin, and phenolphthalein (Lowney *et al.*, 1967). Toxic epidermal necrolysis may be a nonspecific vascular reaction pattern of the skin (Calnan, 1966) precipitated by several factors in the same patient at different times, such as by drug therapy and by infections. The layer of cleavage in the skin may be epidermal or subepidermal. It is not surprising that these patients are compared with cases of erythema multiforme, particularly when the mucous membranes are affected.

The clinical appearance of toxic epidermal necrolysis suggests to some (Lyell, 1956; Beare, 1962) an external toxic agent, perhaps some apparently harmless chemical to which the patient is more susceptible because of an epidermal enzyme defect (*Trans. St John's Hosp. derm. Soc. (Lond.)*, 1967), drug medication, or a virus infection. Walker (1962) even speculated on snoek liver and herbal remedies in South Africa.

It is likely, therefore, that toxic epidermal necrolysis is not a disease entity. That an application can cause an eruption identical with toxic epidermal necrolysis might support the view that this clinical appearance is the result of a number of pathological processes.

I wish to thank Dr. John Franklin and Dr. Peter Samman for their help.

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