Anaemia and skin disease

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ANAEMIA and skin disease are both common and it is to be expected that often they will be found together in the same patient. In some instances this will be a chance association, but in others it will be the result of some special relationship. We do not intend to give an account of all situations in which anaemia and skin disease are associated, but merely to describe a few examples chosen either because we consider them to be important, or because we have some special knowledge of them.

General changes in skin, hair and nails in anaemia

The pallor of the skin seen in all types of anaemia, the jaundice found in anaemia in which there is a haemolytic element, and the visible capillary pulsation seen in the skin in patients with anaemia severe enough to produce a 'high output state' are obvious examples of such changes. Hyperpigmentation is a common skin manifestation of anaemia in which there is haemolysis or in which long-term treatment by blood transfusion is required: the pigments are haemosiderin and melanin. Telogen effluvium may follow an acute anaemia—usually that of sudden blood loss. In this situation, as in others in which it occurs, the hair loss is usually noted, not while the patient is seriously ill, but during the phase of recovery. The prognosis is almost invariably good. Changes in the hair are found also in chronic anaemia associated with both iron and folate deficiency states: iron deficiency is one of the known, though rare, causes of diffuse alopecia, and both pregnant women (Hibbard & Hibbard, 1968) and folate deficient sows (Cartwright *et al.*, 1948) may develop lustreless hair which returns to normal after the administration of folic acid. Koilonychia appears to be associated with anaemia only if there is a co-existing iron deficiency: the mechanism of the production of the nail changes is unknown and, although the iron content of nails is reduced in people with iron deficiency (Jacobs & Jenkins, 1960), the relationship of nail iron content to koilonychia is not known.

Leg ulcers in patients with haemolytic anaemia

These have been reported to occur in sickle-cell anaemia, thalassaemia, hereditary spherocytosis and other forms of haemolytic anaemia (Dacie, 1962; Rook, Wilkinson & Ebling, 1968) but have not been seen in several hundreds of cases of hereditary spherocytosis examined in this country, and there is doubt whether they occur in the acquired haemolytic anaemias either (Thompson, 1970, personal communication).

Sickle-cell anaemia serves as an example of a haemolytic anaemia in which leg ulcers are common for they occur in about 60% of patients. It is generally believed that changes in blood viscosity are a major factor in the production of the ulcers but infection and trauma no doubt play a part in some patients, and venous stasis in the legs is presumably a factor in determining their predilection for the front of the shins. The inherited abnormality is in the formation of the β -chain of the haemoglobin molecule so that a haemoglobin other than the usual adult haemoglobin HbA is found. The common variety of sickling is associated with the presence of HbS which is less soluble than HbA: the solubility is further decreased at low oxygen tensions when semi-crystalline bodies called tactoids are formed and there is gelling inside the erythrocytes. These physical changes result in the formation of sickle-shaped cells and an increased blood viscosity: there is, in consequence, a decreased rate of blood flow through small vessels leading to further deoxygenation with more marked sickling, more increase in viscosity, further decrease in blood flow, blockage of vessels and infarction.

Micro-angiopathic haemolytic anaemia syndrome

A type of haemolytic anaemia due to red blood cell fragmentation occurs in a number of diseases and in some of them, for example thrombotic thrombocytopenic purpura and polyarteritis, it is associated with purpuric lesions in the skin. Animal work supports the idea that the fragmentation of the

erythrocytes is due to strands of fibrin in the blood vessels (Bull *et al.*, 1967) and the fibrin deposition must be a factor in the production of the skin lesions also.

Anaemia due to eczema and psoriasis

Anaemia may be caused by eczema and psoriasis and in consequence is seen more commonly in patients with these dermatoses than in the general population.

In patients with erythrodermic eczema and psoriasis a special situation exists in that the increased plasma volume found in these patients (Shuster & Wilkinson, 1963; Fox *et al.*, 1965) causes a haemodilution anaemia which, as would be expected, is usually normocytic (Shuster & Marks, 1967).

In patients with less extensive eczema and psoriasis, in which we have no reason to believe the plasma volume is increased, anaemia appears to be more common than in the general population. We find, for example, that in Newcastle upon Tyne, 13% of patients admitted to hospital with non-erythrodermic eczema have a blood haemoglobin concentration of less than 12 g/100 ml (Shuster & Marks 1967), and Kaimis, Summerly & Giles (1970, personal communication) find that 16% of patients with non-erythrodermic eczema and psoriasis admitted to hospital in Stoke on Trent are anaemic. Sometimes this anaemia is normocytic, sometimes it is megaloblastic and sometimes it is microcytic: although on occasions it may be due to co-existing disease of other organs in other cases it is due to the rash.

Megaloblastic anaemia occurring in skin disease is due to folate deficiency and although abnormalities of vitamin B₁₂ excretion occur in patients with this disease (Shuster & Marks, 1970) and, although vitamin B₁₂ deficiency might be expected to occur, especially in patients with dermatogenic enteropathy (Shuster & Marks, 1965), we have found a reduced serum vitamin B₁₂ concentration in only one of our patients with the megaloblastosis of eczema or psoriasis. Patients with these dermatoses sometimes become folate deficient as was suggested by early studies of formimino-glutamic acid (FIGLU) excretion after an oral dose of L-histidine (Knowles, Shuster & Wells, 1963), and later confirmed by measurement of serum (Shuster, Marks & Chanarin, 1967) and red cell (Marks, Chanarin & Shuster, unpublished observations) concentration of folate. There are several reasons why folate deficiency may occur in these dermatoses.

Firstly there may be malabsorption of folate. An increased excretion of fat in the faeces is common in patients with eczema and psoriasis, especially when the rash is extensive (Shuster & Marks, 1965; Marks & Shuster, 1970) and although not all patients with

a low serum folate concentration have steatorrhoea or other evidence of malabsorption (Shuster *et al.*, 1967; Shuster & Marks, 1970) we cannot exclude the possibility of a lone defect of folate absorption in such patients. Kaimis *et al.* (1970, personal communication) found that the increase in serum folate concentration after an oral dose of folic acid was less than normal in patients with erythroderma and also in patients with less extensive eczema and psoriasis and this suggests decreased folate absorption in these patients.

Secondly, there may be increased utilization of folate. The rate of turnover of epidermal cells is increased about ten-fold in the lesions of patients with psoriasis, and is increased to a lesser extent in the skin between the lesions in these patients (Porter & Shuster, 1968). Furthermore, the basal metabolic rate is increased in patients with eczema and psoriasis (Fox *et al.*, 1965) even when the rash is of limited extent (Shuster, 1967). Thus it is to be expected that folate demands will be increased in patients with skin disease, and folate deficiency may occur from increased need as it does, for example, in pregnancy and in patients with haemolytic anaemia (Chanarin, Bennett & Berry, 1962).

Thirdly, folate deficiency may be secondary to iron deficiency (Chanarin, Rothman & Berry, 1965) and, although true iron deficiency is rare in patients with skin disease (see below), it does occur: nevertheless our work shows that not all patients who have a low serum folate concentration also have a low serum iron concentration (Shuster *et al.*, 1967).

In the majority of patients with skin disease who have been found to be folate-deficient it is likely that more than one of the factors discussed above contributed.

The microcytic anaemia we find in patients with eczema and psoriasis may be associated with a decreased serum iron concentration, but hypoferraemia occurs also in patients with skin disease who are not anaemic (Marks, 1967; Marks & Shuster, 1968). The hypoferraemia caused by skin disease is, like the hypoferraemia of chronic infection, usually associated with a normal or decreased total iron-binding capacity, a normal iron turnover and the presence of stainable iron in the bone marrow: in such cases there is no true iron deficiency, in that total body iron is not decreased, and iron loss does not exceed iron intake. The decreased concentration of iron in the plasma and rapid clearance of injected ⁵⁹Fe from the plasma in such a metabolic hypoferraemia appear to result from failure of the cells of the reticulo-endothelial system to release iron in a normal fashion (Freireich *et al.*, 1957). A few patients with skin disease do develop a true iron deficiency (Marks & Shuster, 1968) as might be expected, for

increased iron losses occur from the skin and the bowel in some.

Patients with extensive scaly dermatoses lose excessive amounts of iron from their skin. For example, we have shown that one of our patients with psoriasis was losing 7.3 mg iron in her scales each day (Marks, 1967; Marks & Shuster, 1968), which represents a huge iron drain when compared with the normal daily iron loss from all sources of less than 1 mg/day, and Reizenstein, Skog & Stigell (1968) have shown that some of their patients with erythrodermic psoriasis lost iron from the skin at about seven times the normal rate.

A large number of patients with eczema and psoriasis, especially if it is extensive, have dermatogenic enteropathy and in some of these patients we have found co-existing malabsorption of iron (Marks & Shuster, 1968). In addition a number of patients with extensive rashes have a protein-losing enteropathy (Shuster, 1967) and iron may be lost together with its carrier protein by this route.

In summary, anaemia due to eczema and psoriasis may be normocytic, megaloblastic or microcytic: the megaloblastic anaemia is due to folate deficiency, and the microcytic anaemia is associated with iron deficiency. Usually the only treatment necessary is treatment of the rash and when this is under control the anaemia will improve as a result. If folate deficiency, indicated by megaloblastic erythropoiesis and a decreased blood folate concentration, arises as it may, especially in patients with long-standing, extensive rashes and dermatogenic enteropathy, it must be treated. Similarly, if iron deficiency arises as indicated by hypoferraemia with a raised total serum iron binding capacity and the absence of stainable iron in the marrow, this too may require treatment. The simple metabolic hypoferraemia of skin disease does not respond to oral iron and in any case calls for no further measures than treatment of the rash. In management of these patients with anaemia attributed to a rash it is of course important to make sure that the anaemia does in fact respond to treatment of the skin, and if it does not, a cause other than the skin disease must be sought.

Anaemia in the collagen vascular diseases

More than half the patients with disseminated lupus erythematosus are anaemic (Dubois, 1966). This anaemia may be identical with the normochromic anaemia seen in other chronic illnesses, but hypoplastic anaemia due to vasculitis of the capillaries supplying the marrow (Burkhardt, 1965) and autoimmune haemolytic anaemia also occur. The haemolytic anaemia is important not least because it may be the presenting feature of the disease. It is more often associated with the presence of 'warm' antibodies than 'cold' antibodies (Dacie, 1962) in

spite of the common occurrence of Raynaud's phenomenon in lupus erythematosus.

In systemic sclerosis anaemia may result from involvement of the gastrointestinal tract. Bleeding may occur from an oesophagus inflamed by acid regurgitation as a result of connective tissue changes at the gastro-oesophageal junction, or from inflamed diverticula of the large bowel. Megaloblastic anaemia may arise as in the 'blind loop' syndrome, for the defective peristalsis consequent upon the connective tissue changes in the small bowel results in contamination of the upper jejunum by bacteria not normally present there, and in malabsorption.

Anaemia and skin changes in malignant disease

Various infiltrative diseases which give rise to anaemia by marrow replacement may cause skin changes by deposits in the skin, by production of 'id' reactions, by haemorrhage into the skin from a concomitant thrombocytopenia, or from skin infection as a result of a coexisting altered immune reaction.

Skin disease associated with anaemia due to gastrointestinal bleeding

Examples of inherited skin conditions which may be associated with bleeding from the gastrointestinal tract and other sites include hereditary haemorrhagic telangiectasia, hereditary capillary purpura, pseudo-xanthoma elasticum and the Peutz-Jeghers syndrome. In some of these diseases the appearances of the skin are specific and provide an important clue to the cause of what might otherwise have been a mysterious bleed or anaemia. Acquired conditions of the skin which also may be associated with gastrointestinal bleeding and anaemia include anaphylactoid purpura and scurvy.

Skin disease, anaemia and malabsorption

Skin disease and anaemia commonly occur in malabsorption. The anaemia results from the malabsorption and may be due to deficiency of folic acid, vitamin B₁₂ or iron. The rashes caused by malabsorption in 'idiopathic' steatorrhoea and tropical sprue, though rare in dermatological practice, are well known (Cooke, Peeney & Hawkins, 1953; Badenoch, 1960; Wells, 1962). Dermatogenic enteropathy (Shuster & Marks, 1965; Marks & Shuster, 1970), in which the steatorrhoea is produced by the rash, rarely gives rise to anaemia but may do so in patients with long-standing extensive eczema or psoriasis. Dermatitis herpetiformis is an important diagnosis to be considered when skin disease and anaemia are found together for two-thirds of patients with this dermatosis have a coeliac syndrome (Marks, Shuster & Watson, 1966; Fraser, Murray & Alexander, 1967; Fry *et al.*, 1967) which, although it is mild in some cases, is severe and occurs with all its

complications in others. The rash of dermatitis herpetiformis is extremely itchy and consists of grouped blisters which on histological examination are sub-epidermal: characteristically there is a therapeutic response to dapsone. The anaemia of malabsorption due to systemic sclerosis has already been mentioned.

Pernicious anaemia, vitiligo, alopecia areata and autoimmunity

There is a significant association of both vitiligo (Cunliffe *et al.*, 1968) and alopecia areata (Cunliffe *et al.*, 1969) with pernicious anaemia and other organ-specific autoimmune diseases, and this indirect evidence supports the idea that both vitiligo and alopecia areata are themselves autoimmune diseases. The mechanism of the premature greying of the hair in pernicious anaemia is unknown but it may be related.

Skin lesions and anaemia in erythropoietic protoporphyria

Erythropoietic protoporphyria is of great interest in that both the skin lesions and the haemolysis which occur appear to depend, at least in part, upon the photochemical properties of protoporphyrin. This is a photosensitizer with maximal absorption at 400 nm which coincides with the action spectrum for the skin lesions (Magnus, 1969). Haemolysis occurs *in vitro* when red cells from patients with erythropoietic protoporphyria are exposed to radiation of 400 nm (Fleischer *et al.*, 1966) and presumably photohaemolysis occurring in superficial vessels contributes to the anaemia which may be found in these patients.

Anaemia due to treatment of skin disease

Anaemia is one of the undesirable side-effects of the use of cytotoxic drugs in the treatment of such conditions as skin reticuloses and psoriasis. Usually the anaemia is part of a more general marrow depression, but a megaloblastic anaemia due to folate deficiency may arise when folic acid antagonists are used. The treatment of dermatitis herpetiformis with dapsone or sulphonamides may result in haemolytic anaemia, though the mechanism of its production is different in the two cases. Dapsone produces haemolysis with a shortened red-cell life in nearly everyone taking the drug, though clinical anaemia is unusual in patients taking the dose of dapsone normally required to control the rash of dermatitis herpetiformis: there is no evidence that glucose-6-phosphate dehydrogenase activity is abnormal (Pengelly, 1963). Sulphonamides on the other hand produce haemolysis only in susceptible individuals and in some of these there is evidence of glucose-6-phosphate dehydrogenase deficiency (Dacie, 1962).

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