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Iron Metabolism in Skin Disease

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The ancient Greeks used iron as a local remedy in a variety of dermatoses (Gunther, 1959) and iron is still given to patients with skin disease, some of whom have a decreased serum iron concentration (Marks and Shuster, 1966a). There is, however, no evidence that these patients are helped by iron, and practically nothing is known about their iron metabolism. We have recently been investigating this, and a full report of the work will be described elsewhere (Marks and Shuster, 1967).

Anaemia occurs in patients with skin disease and is sometimes hypochromic (Marks and Shuster, 1966a; Shuster and Marks, 1967). The part played by folic acid deficiency has previously been described (Shuster *et al.*, 1967a) and is outlined in this JOURNAL by Dr Chanarin (1967) but this is unlikely to be the only cause of the anaemia, and abnormal iron metabolism must also be considered. There is no other clinical evidence of iron deficiency in patients with uncomplicated skin disease, and, for example, koilonychia and dysphagia from a post-cricoid web are not seen.

A serum iron concentration of less than 60 mg/100 ml was found in just over a quarter of 100 consecutive admissions (50 male and 50 female) to our skin department and occurred most frequently among the 37 admissions for extensive eczema or psoriasis. While patients in the group as a whole were unselected and might have had a coincidental cause for their low serum iron concentration, the patients with extensive skin disease were not, as far as it

was possible to tell, suffering from any other disease that might have affected the serum iron concentration. In these patients at least the hypoferraemia must have been associated with the skin disease.

Not all patients with a low serum iron concentration are iron deficient. For example, patients suffering from infection, inflammation, malignant disease, rheumatoid arthritis, chronic renal disease, myocardial infarction, and scurvy may have a low serum iron concentration in the absence of iron deficiency (Bothwell and Finch, 1962). Where deficiency exists there is always a reason for it. It can arise only as a result of decreased iron intake or excessive iron loss. Our patients with skin disease from whom dietary histories were taken were found to have an iron intake of more than the 15 mg/day normally needed for the maintenance of iron balance. However, normal dietary intake may be inadequate in the presence of the malabsorption that is known to occur in patients with skin disease (Shuster and Marks, 1965; Shuster *et al.*, 1967b). The absorption of iron salts has been measured in seven of our patients by giving them ferric citrate labelled with ^{59}Fe and counting the radioactivity in the stools over the next eight days (after Dubach *et al.*, 1948). In the seven patients examined iron absorption was increased in three, normal in three, and decreased in one. This last patient, suffering from atopic eczema, is the only one in whom we have found evidence of possible decreased iron intake. He had no steatorrhoea and, as far as we know, his inability to absorb iron was his only absorption defect.

The sources of excessive iron loss to be considered in patients with skin disease are the skin and the gastro-intestinal tract. Protein-losing enteropathy has been described in patients with extensive skin disease (Shuster and Wilkinson, 1963; Marks and Shuster, 1966b) so it is possible that, quite apart from malabsorption, excessive amounts of iron together with its carrier protein could be excreted in the faeces. We have, however, found no evidence of this in our patients. The amount of iron that can be lost through the skin is still a matter of some debate. Excretion of iron in sweat was thought at one time to be a factor in the production of tropical hypochromic anaemia (Foy and Kondi, 1957). There now seems little doubt that most of the iron lost from the skin is in desquamated cells rather than cell-free sweat (Adams *et al.*, 1950). Patients with desquamating skin disease, particularly those with psoriasis in whom epidermal cell turnover is increased (Rothberg *et al.*, 1961) are consequently liable to lose excessive amounts of iron through the skin, and we have found one patient who was losing 7.3 mg iron/day in her scales. This is considerably in excess of the normal skin iron excretion of less than 1 mg/day (Bothwell and Finch, 1962).

Thus, two groups of patients with skin disease have reason to be in negative

iron balance, those with intestinal malabsorption and those with widespread scaly rashes of long duration. Further studies of our patients in these two groups, however, provided no evidence of iron deficiency at the time of investigation, despite the possibility that it might develop.

There is no single test available for the diagnosis of iron deficiency and, in particular, results of some of the tracer studies are difficult to interpret even when the newer high specific-activity iron isotopes have been used. Theoretically, one of the best ways of telling whether a patient with a decreased serum iron concentration is iron deficient or not is by measuring plasma iron turnover. All iron moving from place to place in the body passes through the plasma and so, from measurement of the total amount of iron entering and leaving the plasma each day, it is possible to estimate the body's iron turnover. This turnover is calculated from the total amount of iron in the plasma and the rate at which injected radioactive iron is cleared from the plasma (Loeffler *et al.*, 1955). In normal people 0.38–0.77 mg iron/100 ml whole blood enter and leave the plasma each day (Bothwell *et al.*, 1957). Plasma iron turnover is usually increased in patients with iron deficiency (Bothwell *et al.*, 1956), which is to be expected, because, when total body iron is reduced, that which remains has to turn over more rapidly to do the same work and renew the same volume of red cells. However, in iron deficiency anaemia, in which red cell mass is reduced, there will be a tendency for plasma iron turnover to be reduced too, and a normal or low turnover may then result. Plasma iron turnover has not been found to be increased in patients with skin disease and a low serum iron concentration and, as these patients had a normal haemoglobin concentration and, therefore, presumably a normal red cell mass at the time they were studied, the implication is that they were not iron deficient.

Although radioactive iron injected into a vein disappears rapidly from the plasma over the next few hours, it reappears in the blood over the next few days as a result of its incorporation into erythrocytes.

If the percentage of injected iron present in the erythrocytes each day is plotted in normal people and in patients with skin disease, similar curves are obtained (*see* Fig. 1). Despite the fact that some of our patients with skin disease have been anaemic, in none of them have we found a curve with the rapid rise and fall usually seen in iron deficiency (Lajhta, 1961). The percentage of the dose of radioactive iron present in the erythrocytes on the fifth day varied from 48 to 99 per cent in patients with skin disease and a low serum iron concentration, and from 60 to 95 per cent in those with a normal iron concentration.

Total serum iron-binding capacity or the plasma concentration of transferrin or iron-binding protein is increased in patients with iron deficiency

Fig. 1. Uptake of ^{59}Fe by erythrocytes.

for a reason that is not understood. We have failed to find such an increase in patients with skin disease in whom plasma transferrin concentration is often lower than normal. This, together with our finding of iron in the bone marrow of patients with skin disease and a decreased serum iron concentration, is further evidence that they are not iron deficient.

Of the conditions, other than iron deficiency, that result in a low serum iron concentration, most work has been done on iron metabolism in infection and inflammation where changes in iron metabolism may occur as little as 48 hours after the onset of the disease (Cartwright and Wintrobe, 1949). In our patients, too, changes in serum iron concentration occurred rapidly, certainly too early in the disease for iron deficiency to have developed as a result of malabsorption or excessive skin loss of iron. In patients with infection the serum iron-binding capacity is normal or decreased (Cartwright and Wintrobe, 1949). Plasma iron turnover is usually normal but the scatter is considerable (Bothwell and Finch, 1962), and erythrocyte incorporation of iron is normal or slightly impaired (Bothwell *et al.*, 1956). Ferrokinetics are essentially normal but the homeostatic mechanism controlling serum iron concentration is set to keep it at a level lower than normal. Once iron gets into the reticulo-endothelial system there seems to be some difficulty in releasing it (Freireich *et al.*, 1957) and this is one of the reasons why it is present in the marrow of patients with the hypoferraemia of infection. There is no evidence that excessive amounts of iron are present in the inflamed tissue, and we have failed to show excess of iron in affected skin by the crude methods available to us.

The decreased serum iron concentration found in skin disease is therefore explained better by a metabolic abnormality of iron metabolism similar to that seen in infection than by iron deficiency. The patients mentioned earlier

who showed an increased absorption of iron from the gastro-intestinal tract do not at first sight fit in with this hypothesis as iron absorption is usually normal or decreased in patients with infection (Bothwell and Finch, 1962). It is known, however, that it takes very little in the way of blood loss and the consequent increase in erythropoiesis to increase iron absorption (Bothwell *et al.*, 1958), and so the results of our absorption studies carried out in patients in hospital having multiple venepunctures are likely to be misleading.

There is no doubt that we are justified in adding skin disease to the list of causes of a low serum iron concentration, and it should be appreciated that the skin disease does not have to be very extensive to produce this effect. While true iron deficiency may result from skin disease it is usually not the cause of the hypoferraemia. Consequently, the majority of patients with skin disease will not benefit from iron therapy, which should not be given merely on the evidence of a low serum iron concentration.

The abnormality of iron metabolism found in infection does not seem to be important in production of the anaemia of infection (Bothwell and Finch, 1962). There is, however, some correlation between serum iron concentration and blood haemoglobin concentration in patients with skin disease, and so, although altered iron metabolism is obviously not the only factor, it is possible that it does contribute to the anaemia of skin disease.

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Temperature Regulation in Erythroderma

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Man's ability to maintain a remarkably constant deep body temperature depends on thermoregulatory mechanisms that are extremely sensitive and capable of control over a wide range of conditions; a wide control range is essential to cope with the big increase in metabolic heat produced by exercise, as well as the large differences in environmental temperature encountered in everyday life. The skin is the effector organ of the thermoregulatory system, and it is therefore no surprise to find that certain skin diseases that affect a large proportion of the body surface can seriously disturb temperature regulation.

It has long been recognised that the erythrodermic patient 'feels the cold', but it is only quite recently that the thermoregulatory disturbances have been studied in detail and their importance appreciated.

The essential features of body temperature regulation are set out in a simple schematic form in Fig. 1. To maintain thermal equilibrium the rate of heat flow across the skin surface to the environment must equal the rate at which heat is liberated in the body by metabolism. The heat passes into the environment through the thermal exchange avenues of radiation, convection, conduction, and evaporation. For nude individuals at rest in comfortable thermal conditions Hardy and Du Bois (1938) reported partitioning of the losses in the proportions: radiation 50–70 per cent, convection 10–20 per cent, evaporation 20–30 per cent. The amount of heat lost through each avenue is determined partly by the skin temperature and its surface moisture, and partly by the air temperature and the other climatic factors.

If the heat loss exceeds or is less than the heat production, body temperature rises or falls and the physiological mechanisms for promoting heat dissipation