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SKIN DISORDERS IN RELATION TO MALABSORPTION*

BY

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In one of his scholarly and thoughtful essays Dr. Parkes Weber (1946) comments on the great reserve power of various organs in the ordinary healthy young adult, who seldom has to call upon the full reserves of heart or brain, for example; but in times of abundance he may sorely tax his alimentary resources and lead the life of a "digestive athlete." One might remark that the skin has plenty in reserve, and functions adequately in most people through a wide range of nutritional and climatic differences. It may not be very obviously affected by indiscretions of diet, and it usually preserves its integrity during severe privation when there is little left but skin and bone. Although the skin remains intact, it may none the less show signs of general malnutrition or of lacking essential food factors both in actual food shortage and where there is disorder of absorption from the gastro-intestinal tract.

In the diseases of malabsorption, with which I am mainly concerned, excess of faecal fat is a characteristic finding, but the term "steatorrhoea" has a much wider meaning and implies variable defects of absorption of all the essential foods, minerals, and vitamins. Associated disorders may be present—for example, loss of protein through the small intestine, or altered gut flora. The subject of steatorrhoea in the adult has been extremely well covered by Badenoch (1960) in his Goulstonian lectures, so that I need say little of the pathogenesis or of the general clinical picture, and I may confine my remarks mainly to changes in the skin.

Sprue

Of the diseases which we now group under the general heading of "steatorrhoea" or "malabsorption syndrome" the first distinct clinical entity was recognized in the tropics. In 1759 William Hillary described a new disease under the tentative diagnosis of "aphthoides chronica." This was a chronic, afebrile, relapsing disease leading to emaciation, and separable from the dysenteries. He described the small vesicles and pustules to be seen on the tongue and round the mouth, which were associated with soreness, so that the tongue became like "a piece of raw flesh." The disease would travel through the gut and was often associated with perianal soreness and irritation. Hillary was struck by "the coldness, dryness and roughness of the patient's skin which usually attends this disease and shows an obstruction and great want of perspiration." This disease came to be known as sprue in Java (Van der Burg, 1880), and it was independently described by Manson (1880) in Amoy. In a more recent analysis

of 200 cases of tropical sprue, Manson-Bahr and Willoughby (1930) drew attention to pigmentation of the skin, which was commonest on the face and abdomen and which they correlated with the anaemia. They also mention eczema in three of their patients and psoriasis in one. In a general statement Manson-Bahr (1960) says, "Dermatitis is a frequent accompaniment of sprue, especially in elderly people with extreme anaemia." He also mentions dryness of the skin and follicular keratosis.

Steatorrhoea occurring in children and in others who had never been in the torrid zone was accurately described by Samuel Gee (1888). He drew attention to the offensive pale stools which were characteristic of the belly sickness or coeliac disease. An important account of idiopathic steatorrhoea (or Gee's disease) was given by Bennett *et al.* in 1932. They described 15 severe cases of adult coeliac disease, and most of their patients had skeletal deformities and tetany. Particular emphasis was put upon skin lesions, which were noted in 7 of their 15 cases. One woman came to hospital because of a very extensive dermatitis which affected mainly the limbs, face, and scalp. The borders of the eczematous lesions were pigmented. This severe and persistent skin eruption cleared as the anaemia responded to treatment with diet and "marmite." Another patient had scaly eczematous patches which were pigmented, and one boy had psoriasis which became very extensive as his general health declined.

Thaysen (1932), in a review of non-tropical sprue, noted dryness and scaliness of the skin, which would commonly start on the finger-tips and palms and spread widely over the body. He found pigmentation in 7 of the 10 cases he reports (Thaysen, 1935). He says that patchy symmetrical pigmentation of the face was so characteristic as to suggest the diagnosis in two of his cases. Snell (1939), referring to 32 patients with tropical and non-tropical sprue, found pigmentation and lacklustre hair and brittle nails to be fairly common. He also mentioned a pigmentary dermatosis of patchy distribution, petechial eruptions, and "pellagrous eruptions." Kaufman and Smith (1943), in an account of six cases of steatorrhoea, noted dryness, inelasticity, and pigmentation of the skin, and made biopsies from which it was clear that the pigment was melanin and not haemosiderin, as was originally thought to be the case by Manson.

Associated Skin Disease

More recent surveys of steatorrhoea emphasize the frequency of associated skin disease. Cooke *et al.* (1953) discussed the diagnostic features of idiopathic

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steatorrhoea with reference to 100 cases selected from a very wide experience of this condition. They drew attention to premature greying and sparseness of the scalp hair and to poor growth of beard and axillary hair. The skin is often parchment-like or scaly, and it may be pigmented. Haemorrhages into the skin are fairly common. Out of 100 patients 20 had desquamative skin disease, of whom 10 had what was called seborrhoeic dermatitis, and in 6 the eruption was psoriasis-like. The psoriasis was seen to get worse with exacerbations of the steatorrhoea. Glossitis and cheilitis were common and some patients had perianal excoriation. Cooke (1952) points out that one patient in five with steatorrhoea may present with a skin disease.

Badenoch (1960) noted pigmentation in many of his patients with steatorrhoea. Of 163 patients, 15 had a dermatitis and in three of these it was the presenting feature of the disease.

It seems that eczema is not particularly common in children with coeliac disease (French *et al.*, 1957) although occasional reports are to be found (Lightwood and Smallpeice, 1937).

Physicians who have had substantial experience of adult idiopathic steatorrhoea recognize this fairly high incidence of erythematous-squamous skin disease, and I understand that the skin condition tends to improve or clear up when the malabsorption is corrected.

How do these patients appear to the dermatologist? A few reports of patients with severe and widespread dermatosis and malabsorption are to be found in the records of the Royal Society of Medicine. Konstam and Gordon (1936) described the case of a man who, at the age of 52, started to get scaling red patches of eczema in which pigmentation was marked, particularly at the borders of the lesions. Some of these patches were vesicular and some were lichenified. After two years macrocytic anaemia and steatorrhoea became apparent. This man recovered on a low-fat diet together with marmite and liver extract, and his skin cleared up. There had been no relapse when Gordon (1938) reported on him two years later and described another case of pigmented and lichenified eczema with macrocytic anaemia, and this man's skin also responded to treatment. Gethin-Jones and Wigley (1949) reported a case of idiopathic steatorrhoea with a chronic pigmentary dermatosis, and Russell (1959) reported erythrodermia with idiopathic steatorrhoea. I would like to say a little more about the last two patients, and then to describe a few more cases of the same kind.

Case 1

A motor mechanic was in good health up till 1946, when, at the age of 39, circumscribed patches of exudative eczema appeared on the flexor aspects of his forearms. This steadily spread until his first admission to hospital in 1947. He then had widespread patchy eczema of the limbs, trunk, and scalp with intense itching. It gradually regressed, leaving pigmentation. It was noted that he had lost weight and had had recurring abdominal pain and occasional loose stools during the preceding year.

He was readmitted to hospital a few months later at the age of 42. He was emaciated, and had a very extensive, deeply pigmented rash which was symmetrical on the limbs and also present on the trunk. There were weeping patches on the arms, areas of lichenification at the wrists and ankles, angular stomatitis, and ulceration in the mouth. A skin biopsy showed lichenified eczema with increase of melanin in the basal layer of the epidermis. He was found to have

a macrocytic anaemia: R.B.C., 2,400,000/c.mm.; anisocytosis and poikilocytosis; mean cell diameter 8.4 μ ; haemoglobin, 10.6 g./100 ml.; C.I., 1.5; W.B.C. 7,300/c.mm. (polymorph neutrophils 42%, lymphocytes 24%, monocytes 9%, eosinophils 25%). His serum calcium was 9.2 mg./100 ml. Stools were unformed and putty-coloured.

A diagnosis of idiopathic steatorrhoea was supported by finding the faecal fat to be 72% of the dry weight. Acute intestinal obstruction due to volvulus of the descending colon was corrected by surgery. He was treated with a low-fat high-protein diet together with crude liver extract and vitamin supplements, and made a good recovery.

He was presented to the Section of Dermatology at the Royal Society of Medicine in 1948 by Dr. Gethin-Jones and Dr. Wigley (1949), to whom I am indebted for these earlier records.

After good control for about two years there was a relapse of his eczema and he was admitted to St. Thomas's Hospital in 1954 (at the age of 47). He then had extensive discoid eczema, the lesions being circumscribed, scaly, and pigmented, and many of them were lichenified.

Barium meal and follow-through showed no gross abnormality of the gastro-intestinal tract, but mild steatorrhoea was still present (faecal fat 41% of dry weight of stool). Haemoglobin was then 12.6 g./100 ml.; R.B.C., 4,200,000/c.mm.; P.C.V., 41%; M.C.H., 30.3 μ g.; M.C.V., 97.8 cubic microns; M.C.H.C., 31%. Serum calcium was 8.9 mg./100 ml., phosphorus 4.3 mg./100 ml. With low-fat diet and calcium and vitamin supplements he again improved.

During the next few years the eczema continued to give trouble, though the steatorrhoea has been fairly well controlled. Another attack of acute volvulus of the descending colon in 1955 required surgery.

During the past two years his health has been good and his skin was scarcely giving any trouble. I am grateful to Dr. Quentin Evans for recent information about him.

Comment.—The eczema in this case has been discoid in pattern, with lesions at times exudative and at times dry, and always very itchy. The period of extensive spread of the eczema with pigmentation can be related to deterioration of his health through steatorrhoea. The pigmentation and lichenification gave to the discoid eczema an unusual appearance. He was thought to be incapable of managing a gluten-free diet, and it is doubtful whether his steatorrhoea has ever been fully controlled.

Case 2

A male clerk first had eczema on the face at the age of 14. It spread on to the limbs and was itchy and persistent. In early childhood he had tuberculous glands of the neck. At the age of 8 he had jaundice. He attended St. John's Hospital for three years with "seborrhoeic eczema." Later he was admitted to other hospitals and spent eight months in one, after the eczema had generalized. At that time his general health was good, and blood counts on two occasions were known to have been normal. After this he became progressively weaker and thinner, and was admitted to the London Hospital in 1954 at the age of 22.

He had generalized exfoliative erythrodermia and marked cutaneous pigmentation, especially on the trunk. Scalp and body hair was sparse. There was ectropion. His tongue was smooth and pale. There was moderate enlargement of lymph nodes. Skin biopsy showed eczematous changes with non-specific inflammatory infiltrate in the corium and marked pigmentation.

He was pale and emaciated (2½ stone (15.9 kg.) below his former weight). His blood-pressure was 150/45; haemoglobin, 2.2 g./100 ml.; R.B.C., 1,060,000/c.mm.; W.B.C., 2,400/c.mm. Sternal marrow showed megaloblastic erythropoiesis. Serum albumin was 3.9 mg./100 ml., globulin 2.1 mg./100 ml. Latent tetany was present. Serum calcium

was 6.6 mg./100 ml., phosphorus 4.8 mg./100 ml. His stools were bulky, pultaceous, and slaty grey in colour. Barium meal and follow-through showed the small-bowel pattern characteristic of steatorrhoea. Test meal showed hydrochloric acid to be present.

After initial transfusion he received a high-protein diet free of gluten together with supplements of calcium, vitamins, and iron. He made an excellent recovery in general health and his skin was greatly improved.

The patient was shown at the Section of Dermatology of the Royal Society of Medicine in 1959 by Dr. Brian Russell (1959), who has kindly let me see the London Hospital case records and allowed me to see the patient recently.

In spite of control of the steatorrhoea on a gluten-free diet and good general health there was relapse of his exfoliative eczema, which required further admission to hospital in 1960.

In August, 1961, he still had ectropion and mild erythrodermia together with diffuse and widespread lichenification of the thighs and buttocks. There was some patchy residual pigmentation on the legs. Some exudative eczema persisted on the extremities. Even at this stage of control of his steatorrhoea, with histidine loading, his urine contained a large excess of formiminoglutamic acid.

Comment.—In this case patchy eczema progressed to generalized exfoliative erythrodermia, which is known to have persisted for at least three years before his general health deteriorated and steatorrhoea with severe malabsorption became manifest. In spite of good control of the steatorrhoea, and improvement in the skin condition, he still gets a good deal of trouble with the eczema. When malabsorption was at its worst his skin was deeply pigmented.

Case 3

A male fitter was first admitted to the Farnham County Hospital in 1948 at the age of 54 with a generalized eczema. He gave a history of malaria and jaundice while serving in India (1914–18) and had had another attack of jaundice in 1943. His eczema seems to have started on the foot or ankle about a year before this admission, and then it spread to the body flexures and gradually generalized. When I first saw him at that time the eczema was red and scaly on the face and trunk and weeping on the forearms, buttocks, and thighs. His general health was good.

With rest and bland applications he improved, but six months later his eczema was as bad as ever and he was readmitted. He was found to have a macrocytic anaemia, and was transferred to St. Thomas's Hospital for investigation. He had had diarrhoea for about six weeks. On the trunk and limbs there was generalized exfoliative erythrodermia and the skin was a dusky purple colour with lichenoid thickening and scaling; at the knees and elbows it was boggy and leathery. In the axillae and groins the skin was red and weeping and hairs were absent. The scalp was scaly and hair was sparse. Itching was severe, angular stomatitis was present, and the tongue was red and raw, and atrophic on the dorsum.

Glands in the axillae and groins were enlarged. Skin biopsy showed chronic eczematous dermatitis, a high proportion of the inflammatory cells being eosinophils. Biopsy of axillary node showed dermopathic changes with pigment in phagocytes.

R.B.C., 3,200,000/c.mm.; anisocytosis and poikilocytosis; haemoglobin, 10.6 g./100 ml.; C.I., 1.2; M.C.V., 103 cubic microns; M.C.H.C., 31.2%; W.B.C., 8,900/c.mm. (polymorph neutrophils 77%, eosinophils 13%, lymphocytes 4%, monocytes 6%). Sternal marrow showed normal cellularity and some eosinophilia, and some of the cells of the normoblast series were larger than normal. Total protein was

4.38 mg./100 ml. (albumin 1.81 mg., globulin 2.57 mg.). Histamine test meal showed free hydrochloric acid. Barium meal and follow-through showed some abnormality of small-bowel pattern that was not diagnostic. Faecal fat was 39% of the dry weight.

On treatment with folic acid and high-protein low-fat diet his diarrhoea ceased, his blood and marrow became normal, and eosinophilia disappeared. His serum albumin recovered and his skin greatly improved.

During the next five years his eczema tended to relapse and his serum albumin dropped to very low figures. In 1954 he was given cortisone, and subsequent attempts at complete withdrawal of steroids led to severe relapses. This occurred in 1956 at the age of 62, and he was treated at St. John's Hospital for Diseases of the Skin.

On this occasion his haemoglobin was 8.2 g./100 ml.; R.B.C., 2,100,000/c.mm.; C.I., 1.3; M.C.V., 106 cubic microns; P.C.V., 34%; M.C.H.C., 25%. There was weeping eczema on the legs, the rest of the skin being dry, scaly, and darkly pigmented. Serum calcium was 9.3 mg./100 ml., phosphorus 5 mg./100 ml.

He improved again on prednisone and has since been in quite good health with only slight skin trouble. When I saw him with Dr. J. Morgan in August, 1961, he was symptom-free. Very little pigmentation remained on the abdomen. There were a few papules of psoriasis on the knees and elbows, and residual lichenification on the right hand. In spite of being on prednisone, folic acid, and "multivite" I found his formiminoglutamic acid test to be positive (moderate excess).

Comment.—Eczema started at the age of 53 and became generalized in about a year. At the age of 55 the general exfoliative eczema became pigmented and lichenified in places, and diarrhoea, macrocytic anaemia, and hypoproteinaemia led to a diagnosis of idiopathic steatorrhoea. After initial recovery on modified diet and folic acid supplement, relapses occurred. Later, steroids controlled these symptoms. The recurring hypoproteinaemia suggests the possibility of some degree of protein-losing enteropathy.

Case 4

A police constable started to have eczema at the age of 32; at first it was mainly intertriginous (groins and axillae). It became very extensive and he was admitted to hospital in 1954 at the age of 37. His general health was good and he had had no previous illness. His eczema regressed with marked pigmentation. A year later he had generalized exfoliative erythrodermia and was treated with prednisone, which has been continued ever since. In February, 1959, he was in hospital for a short time with pneumonia; his weight then was normal and his haemoglobin 91%.

In December, 1959, at the age of 42, his general health started to deteriorate, with loss of appetite and loss of 1 stone (6.4 kg.) in weight, and he was passing an average of three loose stools a day. His tongue became sore with superficial ulcers. He had noticed some nocturia, and his legs were oedematous. He still had a generalized erythrodermia, partly controlled by prednisone, and he was markedly pigmented. His blood-pressure was 95/60. R.B.C., 2,500,000/c.mm.; some anisocytosis and macrocytosis; haemoglobin, 10.6 g./100 ml.; P.C.V., 31%; M.C.V., 119 cubic microns; M.C.H.C., 34%; W.B.C., 6,500/c.mm. (polymorph neutrophils 71%, lymphocytes 28%, monocytes 1%). Sternal marrow showed slight red-cell maturation defect suggestive of vitamin-B₁₂ or folic-acid deficiency. Serum vitamin B₁₂ was 170 µg./ml. (normal 140 to 900); serum calcium 9.2 mg./100 ml. Barium meal and follow-through showed no abnormality of small bowel or stomach. Duodenal biopsy revealed considerable flattening of epithelium, the villi being very inconspicuous. There was some chronic inflammation. These changes were

thought to be characteristic of idiopathic steatorrhoea. Three-day fat excretion was 12 g. of fatty acid a day.

From March, 1960, he was treated with a gluten-free diet, supplemented with folic acid and vitamins. Response was excellent, with rapid recovery of weight and correction of diarrhoea and anaemia. The skin improved, pigmentation had disappeared, and prednisone was being reduced. He was symptom-free on August 31, 1961. At that time his urine showed no excess of formiminoglutamic acid after histidine loading.

Case 5

I first saw this man, a lorry driver, in February, 1960, when he was 44. He had an acute contact dermatitis of the face and neck from using a hair dye containing paraphenylenediamine. This cleared up within a week or so. His health was then good and he admitted to no previous illness or skin disease.

In November he complained of an itchy eczema of the left leg. The eczema extended in patches over the limbs and body, getting progressively worse until he came into hospital in January, 1961. He then admitted to some recent loss of weight. The eczema was in circumscribed patches on the face, limbs, and trunk, and itching was severe. Many lesions were discoid, but larger exfoliative patches were present on the elbows. Most lesions showed coarse lamellar scaling, but some were exudative. There was marked lymphadenopathy in axillae and groins. His tongue was smooth and pale. Biopsy of axillary lymph node showed dermatopathic changes. Red cells showed anisocytosis, poikilocytosis, and polychromasia; haemoglobin, 10.6 g./100 ml.; M.C.H.C., 29%; M.C.V., 116 cubic microns; W.B.C., 2,800/c.mm. (polymorph neutrophils 34%, eosinophils 19%, lymphocytes 41%, monocytes 6%). Sternal marrow showed mild maturation defect as seen in early vitamin-B₁₂ or folic-acid deficiency. Serum proteins: albumin 5 mg./100 ml., globulin 3 mg./100 ml. (raised β and γ globulins). Serum calcium, 10.1 mg./100 ml.; phosphorus 4.5 mg./100 ml. Serum carotene, 48 μ g./100 ml. (low). Prothrombin time, 19.4 seconds (normal). Histamine test meal: no free hydrochloric acid. Three-day faeces: 8.3 g. of fatty acid in 24 hours. Barium meal and follow-through: rapid transit of barium through small bowel; no other abnormality detected. Jejunal biopsy: mucosa showed partial villous atrophy. Xylose absorption test: normal. Schilling test: after oral dose of labelled vitamin B₁₂ 6.2% was excreted in the urine (24 hours) (rather low absorption). After 20 g. of oral histidine, urine in next six hours contained gross excess of formiminoglutamic acid.

During his two months in hospital some relief from itching was provided by applications including hydrocortisone, but the eczema was not materially altered. In March, 1961, treatment was started with iron, vitamin B₁₂, folic acid, and vitamins. His anaemia was corrected, and his skin cleared in the course of about three weeks. Since leaving hospital (six months) he has remained well and his skin has been perfectly clear. He has not fully regained his proper weight, and it is planned that he should have a gluten-free diet.

Comment on Cases 1-5

In this group of five patients the appearance of the eczema is no different from that of other eczemas that we see, where the question of absorption defect does not arise. The discoid and intertriginous patterns of eczema seem to predominate, and pruritus is severe. There is a tendency to lichenify, to pigment, and for the eczema to become generalized.

Biopsies show the histology of eczema, often with eosinophils contributing to the dermal infiltrate; and melanin may be increased in the basal layer and in the papillary corium.

Only one of these patients had hypocalcaemia.

In these cases the eczema has cleared up with treatment of the anaemia and steatorrhoea. In some of them there have been relapses, and in some the control of the steatorrhoea has been incomplete.

Eczema may be present for several years before the symptoms of steatorrhoea become obvious (see Table). During this latent period the patient's weight, bowel

Eczema Becoming Widespread or Generalized

Case No.	Age at Onset of Eczema	Age when Steatorrhoea Manifest
1	39 years	41 years
2	14 ..	22 ..
3	53 ..	55 ..
4	32 ..	42 ..
5	42 ..	42 ..

habit, and general condition may be normal. In two of the above cases normal blood counts were recorded in this period, before macrocytic anaemia developed.

I suggest that the skin changes to be met with in patients with malabsorption might be classified as follows: (1) changes of general malnutrition, (2) vitamin deficiencies, (3) changes related to hypocalcaemia, (4) miscellaneous and incidental, and (5) eczema, exfoliative dermatitis, and psoriasis.

Skin Changes of General Malnutrition

The following changes may be seen in people who are undernourished, but they are also seen in patients with wasting disease and in the malabsorption syndrome: pallor, oedema, dryness of the skin, acquired ichthyosis, follicular changes, defective growth of hair and nails, and pigmentation.

Experience of undernutrition in Europe in 1944-9 indicates that these changes relate to lack of food (particularly protein and perhaps essential fatty acids) rather than to specific vitamin deficiencies.

The following three reports are of great interest in this respect: (a) The composite report on malnutrition and starvation in the Western Netherlands issued by the Dutch Government (Burger *et al.*, 1948). (b) The report of McCance and Barrett (1946) on skin changes in undernourished civilians and repatriated prisoners in the Ruhr town of Wuppertal. (c) The Minnesota experiment of Keys *et al.* (1950) in which 32 volunteers under controlled conditions received a low-calorie diet, similar to the famine diet in parts of Europe at the time of the liberation.

The reasons for pallor and oedema are not so obvious as would appear at first sight, and follicular changes have been the subject of dispute (Stannus, 1945). Of the particular changes listed above I may refer to acquired ichthyosis and pigmentation.

Acquired Ichthyosis.—The skin is dry, partly from lack of sweating and partly from reduction of sebum, as the sebaceous glands atrophy. There is also a kind of acquired ichthyosis—ichthyosis tabescentum (Blum, 1936)—which is found in wasting diseases, whether due to chronic infection, malignancy, or malabsorption. Similar changes are common in old age (ichthyosis senilis) and in undernutrition, where a variety of descriptive names have been used such as "mosaic skin" and "crackled skin" (Platt, 1945). The dry skin surface is hyperkeratotic and often slightly pigmented. Cracks appear in the horny layer and give rise to large scales with polygonal outlines, which gradually separate at their edges. Biopsies show hyperkeratosis with sparse

granular layer, thinning of the Malpighian layer, and flattening of the rete ridges (Keys *et al.*, 1950). The histological appearance suggests that there is delayed shedding of surface keratin and reduced epidermal cell turnover.

Pigmentation.—This is common in idiopathic steatorrhoea as well as in malnutrition generally. It may take on the pattern of chloasma with blotchy symmetrical brownness on the cheeks and forehead as noted particularly by Thaysen (1935). In patients with eczema the pigment may be mainly lesional, in which case the purplish-brown colour is striking. In these sorts of pigmentation there is some temptation to use the term "pellagroid" even though there is no nicotinic-acid deficiency. Finally there is the generalized melanosis which so closely resembles that of Addison's disease. Pigment may even be found in the buccal mucosa on occasion (Lees, 1960). This appearance may be accompanied by emaciation, hypotension, and disturbance of water excretion, in which case the resemblance to Addison's disease can be very close indeed. Pigmentation gradually clears after improvement of the nutritional state. The mechanism of melanosis here is obscure. Lerner and Fitzpatrick (1950) suggest that it might arise from amino-acid imbalance where the sulphur-containing amino-acids are in even shorter supply than phenylalanine and tyrosine. No abnormality of adrenocortical function was found in cases of under-nutrition (Burger *et al.*, 1948) nor in cases of cachexia with pigmentation investigated by Shuster (1960).

Vitamin Deficiency

It has long been recognized (Albright and Stewart, 1940) that all the fat-soluble vitamins may be deficient in patients with steatorrhoea. Although circulating levels of vitamin A and carotene are usually low in these patients, clinical manifestations of vitamin-A deficiency seem to be rare. Lack of vitamin D may indirectly affect the skin through hypocalcaemia. Purpura and ecchymoses may appear in the skin before more serious bleeding occurs. This tendency to bleed in steatorrhoea was found by Fanconi (1938) to be due to failure of prothrombin synthesis through lack of vitamin-K absorption. This is fairly common, and was noted in 17 of 122 patients with steatorrhoea in Badenoch's (1960) series. That this vitamin-K deficiency may be dangerous was emphasized by Shaw (1960). Manifestations of vitamin-C deficiency are not usually encountered in steatorrhoea. This is surprising, since these patients are peculiarly resistant to attempted saturation with ascorbic acid (Boscott and Cooke, 1954). Pellagra is sometimes suggested and may occasionally occur in steatorrhoea (Bean *et al.*, 1944), but more often there is a misinterpretation of the combination of eczema and pigmentation to which I have alluded.

Our field of interest extends to the buccal mucosa and tongue, where the patient with steatorrhoea may show redness, soreness, and ulceration or atrophy. These patients absorb iron very poorly from the gut, and they may also show deficiency of vitamin B₁₂, which it is extremely important to correct. In idiopathic steatorrhoea the absorption defect is mainly in the jejunum, and folic-acid deficiency is common. In these patients folic-acid therapy may make an important contribution to recovery from macrocytic anaemia, to relief of sore tongue, and to improvement of the eczema if it should be present.

Hypocalcaemia

In steatorrhoea the level of serum calcium may be low, and this may give rise to changes in the skin and its appendages. The nails become brittle and crumbly and susceptible to infection with *Candida albicans*. The hair may become sparse, thin, and dry. Learner and Brown (1943) noted a general dryness of the skin as well as seasonal changes in the nails and hair in patients with hypocalcaemia. Attacks of tetany may be followed by transverse ridging of the nails and sudden hair fall (Simpson, 1954). Simpson mentions that the skin may be dry, scaly, and pigmented. Hypocalcaemia may lead to heightened irritability of the skin.

Dent and Garretts (1960) studied four patients with widespread eczema in whom there was hypocalcaemia from one cause or another. In these patients the skin recovered when the serum calcium was restored to normal by more than one mechanism. A similar relationship between low serum calcium and widespread erythematous eruptions was noted by Harrell-Steinberg *et al.* (1957) and by Lachmann (1941). Lachmann possibly overestimated the role of hypocalcaemia in some of his cases—for example, some of those with pustular psoriasis—and it is quite clear that one child (Case 80) diagnosed as a case of "normocalcaemic tetany" was in fact suffering from acrodermatitis enteropathica.

Impetigo herpetiformis is also associated with hypocalcaemia, particularly in pregnancy; but so far as I know it has not been described in patients with malabsorption syndrome.

Miscellaneous

In patients with malabsorption some skin disorders may be irrelevant or so rarely encountered as to be impossible to assess. Simpson (1954) in his series of cases lists a few skin conditions such as urticaria and herpes which may be incidental.

In some patients with malabsorption there is an important alteration of intestinal flora. That this may affect the skin was shown by England *et al.* (1960), who found a patient with Whipple's disease to have porphyria, manifest as a light-sensitivity eruption. The porphyria could be temporarily removed by altering the intestinal flora with antibiotics.

One of our patients (Case 6), who had suffered from prurigo nodularis for seven years, was eventually found to have adult coeliac disease, and when this was treated her skin cleared up and has not relapsed over the last 11 years.

Case 6

A woman was admitted to St. Thomas's Hospital in 1950, at the age of 44, on account of nodular prurigo, which had been continuously present for seven years. She had had atopic eczema on and off since early childhood, and had been subject to recurring attacks of diarrhoea all her life.

There were numerous excoriated lichenoid nodules on the arms and thighs and in the lumbar region. Skin biopsy showed the characteristic histology of prurigo nodularis. She also had diffuse lichenified eczema of the left calf.

While in hospital she developed iliac-vein thrombosis and became rather ill with fever and loss of weight. She was found to have a macrocytic anaemia. Haemoglobin, 7.7 g./100 ml.; R.B.C., 3,300,000/c.mm.; W.B.C., 6,700/c.mm. (polymorph neutrophils 70%, lymphocytes 25%, monocytes 5%, eosinophils 1%); M.C.V., 103 cubic microns; M.C.H.C.,

25%. Sternal marrow was normal apart from increase in plasma cells. Serum calcium, 10.4 mg./100 ml.; phosphorus, 3.9 mg./100 ml. She was found to have pale greasy stools, and faecal fat was 37.7% of dry weight.

The steatorrhoea was thought to be a sign of adult coeliac disease. She was treated with a low-fat diet together with "hepamino" and folic-acid supplements, and this regime has been followed ever since.

During the next few months there was gradual improvement in all respects, and within six months the prurigo nodularis had completely disappeared. There has been no skin trouble since (11 years), and when last seen (October, 1961) she was in good health and her skin was normal.

Eczema, Exfoliative Dermatitis, and Psoriasis

My experience of patients with malabsorption is necessarily small, but so far as it goes it supplements the evidence of Cooke *et al.* (1953) and of Badenoch (1960) concerning a relationship between eczema and idiopathic steatorrhoea—particularly in so far as treatment of the latter favourably affects the eczema.

A high incidence of eczema is found in idiopathic steatorrhoea and sprue, but not in other malabsorption syndromes such as may occur after gastric or intestinal surgery. Nor is eczema or psoriasis common in simple malnutrition. Sefton (1947) commented on the rarity of seborrhoeic eczema among undernourished prisoners of war in Singapore, where conditions of hygiene and climate might have predisposed to it. Loewenthal (1954) states that eczema is not common in the undernourished, and it was less often seen during the time of severe food shortage in the Netherlands than in times of plenty (Burger *et al.*, 1948).

It is, of course, possible for eczema to develop in ichthyotic skin, where irritation may start up in the cracks of keratin—eczema craquelé of Brocq (1907). But this was not the sequence of events in the cases I have just described. In these patients the eczema preceded any overt sign of malabsorption, and at present no explanation of its pathogenesis can be offered.

It has already been noted that the atrophic dry skin of malnutrition and malabsorption appears, histologically, to show a defect of keratin-shedding and reduced epidermal cell turnover. Quantitative information is, however, not available; one difficulty being the low mitotic index of normal human skin, for which Pinkus (1954) quotes widely diverse figures. The researches of Bullough and Lawrence (1960) have shown how many factors conspire to influence the mitotic index of mammalian skin.

What is impressive is the tremendous burst of mitotic activity of which the human epidermis is capable if it is disturbed, as in the keratin-stripping experiments of Pinkus (1954). And certain exfoliative skin conditions show a very lively epidermis.

In psoriasis or exfoliating eczema there is a continuous loss of sulphur-rich protein from the surface. In cases of generalized exfoliative dermatitis Peters (1945) and Pegum (1951) collected scales from the patients' beds, and found the yield of protein to be about 19 g. a day. The amount of scale varies, of course, from one case to another.

This squandering of protein from the surface is accompanied by great mitotic activity, and brings the exfoliating epidermis a step towards those organs which normally have a rapid cell turnover, such as intestinal epithelium or blood cells. An idea of the rate of

continuous cell replacement in the normal subject may be gained from the rough figure of 2.5 g. daily for the red cell mass and of 50 g. daily for the intestinal epithelium given by Professor Witts (1956).

Of many important factors which may be in short supply in the presence of malabsorption, I would like to single out the folic-acid substances for consideration. As is known, they are necessary for nucleic-acid synthesis and for some steps in amino-acid metabolism. The appearance in the urine of an abnormal metabolite (formiminoglutamic acid) was found by Bakerman *et al.* (1951) to be evidence of folic-acid deficiency. An active derivative of folic acid is necessary for the release of glutamic acid from formiminoglutamic acid. This metabolic defect is enhanced if the patient is given 15 or 20 g. of histidine before urine is collected. Formiminoglutamic acid can be identified in the urine by biological assay or, more conveniently, by high-voltage electrophoresis. Luhby *et al.* (1959) found excess of formiminoglutamic acid in the urine to be a reliable indication of folic-acid deficiency. Most patients with idiopathic steatorrhoea—83% according to Doig and Girdwood (1960)—show evidence of folic-acid deficiency. If in addition to malabsorption from the jejunum the skin is exfoliating, this defect is even more likely to be present.

So far we have found the patients with eczema and idiopathic steatorrhoea to have a large excess of urinary formiminoglutamic acid. The defect may still be apparent when malabsorption and anaemia seem to be corrected, as in Cases 2 and 3 described above. We have had negative results in other patients with widespread skin disease and no defect of absorption (with some exceptions which are not yet accounted for). The formiminoglutamic acid test may prove to be of some practical value in so far as a negative result in a patient with extensive eczema or psoriasis would make malabsorption unlikely.

I wish to make it quite clear that idiopathic steatorrhoea is not often found in the background of patients with exfoliative eczema; on the contrary, this association is rare and widespread eczema is common enough. For example, Wilson (1954) reported on 50 patients with exfoliative dermatitis in whom no evidence of gastrointestinal disease came to light. He did mention, however, that a few of these patients "suffered from a severe macrocytic anaemia for which no cause could be found."

However rare it may be, the possibility of malabsorption in patients with intractable eczema should not be ignored, since treatment may be successful. One would wish to be able to discover the absorption defect before obvious manifestations, such as sore tongue, macrocytic anaemia, or loss of weight; and here the new techniques being developed in gastroenterology may help.

Acrodermatitis Enteropathica

The skin disorders that I have mentioned are none of them specific for steatorrhoea, and only a combination of clinical findings would lead one to suspect malabsorption.

In contrast to this I should like to end by mentioning one condition in which the outward appearance is so distinctive as to suggest the diagnosis at once.

I refer to acrodermatitis enteropathica (Danbolt and Closs, 1942). This clinical condition was first recognized

as a familial disease with defective absorption by Brandt (1936). The erosive lesions round the mouth and anogenital region and on the extremities are coupled with complete baldness. These children are subject to recurring attacks of diarrhoea, and they become listless and miserable. In the past they were usually thought to have generalized moniliasis, whereas it is now established that *Candida albicans* is a secondary invader and not consistently present. One of the most remarkable things about these children is their recovery when di-iodo-hydroxyquinoline is given. The first recognized case of acrodermatitis enteropathica to be treated with di-iodohydroxyquinoline was reported by Dillaha *et al.* (1953). Watching the recovery of this little girl was one of my most memorable experiences in dermatology. Di-iodohydroxyquinoline is not absorbed, and must presumably exert its action on the gut or its contents. While it is being taken the skin becomes normal, the hair grows again, and the general health is maintained; and indeed several lives have been saved by its use. Investigations so far have not indicated exactly where the fault may lie, but an inherited defect of absorption from the intestine seems probable. The elucidation of this defect should prove of great interest in terms of the skin's biochemistry.

For this lecture I felt that I might claim a certain licence for the consideration of rare diseases from the founder of this trust, who has contributed so much in this field. May I follow Dr. Parkes Weber in quoting Sir James Paget (1882), who said of rare diseases: "We ought not to set them aside with idle words about 'curiosities' and 'chances.' Not one of them is without a meaning. Not one of them but might be the beginning of excellent knowledge."

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Earlier this year Dr. C. Belfield Clarke, who is chairman of the Ghana Medical Advisory Committee, made a tour of medical institutions, training colleges, and community centres in Ghana, as well as the Universities of Legon and Kumasi. He visited hospitals in Accra, Kumasi, Tamale Bolga Tonga, and Cape Coast, and saw the work of the research units for leprosy, river blindness, malaria, and tuberculosis. Everywhere, he said, he saw devoted men and women, including recruits from Europe, India, and Pakistan, working to build a medical service for Ghana of which everyone could be proud. There was still a great need for doctors, especially general duty medical officers and public health doctors, and public health and community centre nurses. The situation could be eased by the development of a kind of flying doctor service to take serious cases in the outlying areas to the big central hospitals where specialists could be concentrated. The difficulties facing Ghana in every direction, he said, were immense, but it was stimulating to see how they were being overcome. (From broadcast made by Dr. Belfield Clarke in Ghana on May 27.)