The gut and the skin

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A CONSIDERABLE amount of work has been carried out on the relationship between the small intestine and the skin in various disorders during the past decade and this article will be concerned with the small intestine rather than the whole of the alimentary tract.

The exact relationship between the small intestine and skin disease has posed many problems in the past and how one organ may influence the other is still unknown in the majority of instances. Methods for investigating the small intestine have improved during the last few years particularly with the advent of per-oral small intestinal biopsy. When a patient has 'disorders' both of the small intestine and skin it is important that the 'primary' disease is established and appropriate treatment given and for this purpose it has to be appreciated which investigations for the small intestine should be performed, and what are the limitations of these investigations, in association with skin disease.

At the present time the association of small intestine and skin disease may be considered under the following subgroups.

1. A non-specific relationship in which: (a) primary disease of the small intestine causes non-specific changes in the skin, (b) primary disease of the skin produces non-specific changes in the small intestine.

2. A specific relationship. A particular disease-entirety of the skin is associated with a particular disorder of the small intestine.

3. A generalized disease process which affects both the skin and the gut but which is not necessarily confined to these two organs, e.g. systemic sclerosis or polyarteritis nodosa. Since these disorders are not primary disorders of the skin or gut they will not be discussed in this article.

Skin changes due to primary disorder of the small intestine

Pigmentation of the skin has been described in tropical sprue (Manson-Bahr & Willoughby, 1930)

and in coeliac disease (Badenoch, 1960). The pigmentation may occur on the oral mucosa and be indistinguishable from that found in Addison's disease. The pigmentation on the skin may be generalized but is more likely to occur in light-exposed areas and as post-inflammatory hyperpigmentation if there is associated eczema. The palms, however, tend to be spared (Cooke, Peeney & Hawkins, 1953).

Dermatitis has been described in association with coeliac disease by several authors, and the incidence has been stated as seven out of fifteen patients (Bennett, Hunter & Vaughan, 1932), 20% of patients in a series of 100 reported by Cooke *et al.* (1953) and 10% in a series reported by Badenoch (1960). In a number of patients the skin disease may be severe and be the presenting symptom of the small intestinal disorder (Badenoch, 1960; Wells, 1962; Friedman & Hare, 1965).

The appearances of the dermatitis are variable and non-specific. It has been described as desquamating, psoriasiform, and frequently pigmented (Cooke *et al.*, 1953). Wells (1962) in his series of six patients with malabsorption described discoid eczematous lesions, generalized eczema (erythroderma) and prurigo nodularis. In the four patients described by Friedman & Hare (1965) the eczema was generalized in three and consisted of only dry scaly patches in the other one. The eczema is, therefore, not always widespread.

Acquired ichthyosis. A dry scaly skin has been reported in association with coeliac disease (Thaysen, 1932).

Hair changes. Premature greying of the hair has been described in coeliac disease (Cooke *et al.*, 1953) and the hair is invariably of a fine texture. The hair tends to grow poorly: in men shaving may only be necessary two or three times a week, and in some patients axillary hair is lost.

Nail changes. Clubbing of the nails may occur in coeliac disease, and koilonychia may be present due to iron deficiency. Brittle nails with transverse

grooves have been described in coeliac disease and attributed to hypocalcaemia (Simpson, 1954).

Purpura. Purpura occurred in ten of the 100 patients described by Cooke *et al.* (1953). The condition is thought to be due to prothrombin deficiency due to malabsorption of vitamin K.

Apart from the purpura due to vitamin K malabsorption there is as yet no satisfactory explanation for the skin changes (described above) seen in primary malabsorptive states. Dent & Garretts (1960) described a patient with hypocalcaemia and steatorrhoea whose eczema improved when the serum calcium was raised with AT 10. Hypocalcaemia has also been reported to exacerbate psoriasis, and correction of the serum calcium improves the skin disorder (Vickers & Sneddon, 1963). However, hypocalcaemia was not present in the four patients with probable coeliac disease and eczema reported by Friedman & Hare (1965). These patients' skin condition improved with a gluten-free diet, and when gluten was re-introduced to the diet in one patient the skin condition relapsed within 2 hr suggesting a possibly hypersensitivity reaction to gluten. The possibility exists that the changes in the skin are not due to any specific deficiency but to a combination of multiple deficiencies. Dryness of the skin, acquired ichthyosis, defective hair and nail growth, and pigmentation are also seen in malnutrition from causes other than coeliac disease.

Effect of skin disease on the small intestine

Shuster & Marks (1965) coined the term dermatogenic enteropathy in their report of ten patients with extensive eczema or psoriasis. Nine of the ten patients had steatorrhoea (faecal stearic acid excretion above 5 g daily). On treatment of the skin disease with topical measures only, the faecal fat excretion fell in seven patients, and it fell below 5 g per day in four patients. However, intestinal biopsies were not performed before and after treatment in any one patient. As a result of these findings Shuster & Marks suggested the gut changes were due to the skin disease. In a subsequent study of forty-six patients with psoriasis, Shuster, Watson & Marks (1967) reported steatorrhoea in approximately 50% of the patients studied and found a correlation between the extent of skin involvement and the steatorrhoea; the more extensively the skin was involved, the more likely the patients were to have steatorrhoea. In addition, in twelve of the twenty-four patients in whom intestinal biopsy was performed, some structural abnormality of the small intestinal mucosa was found but the abnormality was not severe in that none had a flat biopsy macroscopically (subtotal villous atrophy histologically). Unlike the steatorrhoea there was no connection between the extent of the skin disease and the gut abnormality.

However, the high incidence of small intestinal abnormality and steatorrhoea due to skin disease reported by Shuster and his colleagues (Shuster & Marks, 1965, Shuster *et al.*, 1967) has not been confirmed by other reports. In a study of sixteen patients with eczema and three with psoriasis (Fry, McMinn & Shuster, 1966) structural abnormality of the small intestinal mucosa was found in only three patients with eczema, one patient had a macroscopically flat biopsy and was subsequently shown to have gluten-sensitive enteropathy by response to a gluten-free diet, and the other two patients had a convoluted appearance of the small intestinal mucosa. Faecal fat excretion was not measured in the patients reported by Fry *et al.* (1966) and the patients with eczema were investigated because the condition was extensive and/or chronic, and those with psoriasis because the condition was extensive. In another study Doran, Everett & Welsh (1966) performed intestinal biopsies in four patients with extensive eczema and estimated faecal fat excretion in three patients, but found no abnormality in either of these investigations. Correia, Esteves & Brandao (1967) investigated fifteen patients with psoriasis; the faecal excretion was normal in all, and the jejunal biopsy was normal in fourteen of fifteen patients. However, no information was given as to the extent of the psoriasis in these patients.

At the present time it is not known if the small intestinal changes described in eczema and psoriasis (by Shuster & Marks, 1965, and Shuster *et al.*, 1967) revert to normal after treatment of the skin (Shuster *et al.*, 1967), but apparently the steatorrhoea does regress (Shuster & Marks, 1965).

The significance and cause of the steatorrhoea and structural abnormality of the small intestine in eczema and psoriasis are speculative. The structural changes described by Shuster & Marks (1965) and Shuster *et al.* (1967) have been described in control subjects by Baker *et al.* (1962), but these were Asians and the changes were not found in European subjects by Girdwood *et al.* (1966). However, Townley, Cass & Anderson (1964) have suggested that a 'leafy' and convoluted appearance in the upper small intestine does not necessarily mean a disease process, as the changes can be brought about by hydrochloric acid. Thus the stomach contents may be important in determining the appearances of the small intestine. It could well be asked why, if the structural changes of the small intestine are significant in psoriasis, are they not related to the extent of the disease, as is the steatorrhoea? Shuster *et al.* (1967) suggested that the small intestinal changes seen in psoriasis were mild compared with those in coeliac disease, but similar to those found in tropical sprue. However, it is unlikely that these small intestinal mucosal changes are produced by

folate deficiency which can occur in psoriasis (Shuster, Marks & Chanarin, 1967; Hild, 1969) as these changes are not present in nutritional folate deficiency.

Like the small intestinal structural changes the cause and significance of the steatorrhoea is not known. It is known that altered blood supply to the intestine (Shaw & Maynard, 1958) can cause structural changes and steatorrhoea, and the increased skin blood flow in extensive skin disease may just possibly affect the blood supply to the intestine.

Distinction between coeliac disease and dermatogenic enteropathy

If it is accepted that coeliac disease can cause dermatitis and if extensive skin disease can affect the small intestine, then it is important to be able to distinguish between the two conditions so that the correct treatment can be given to the appropriate organ. The distinction can be made if the following investigations and clinical points are considered:

Intestinal biopsy. In untreated coeliac disease the macroscopic appearance of the small intestine is either flat or convoluted. A flat biopsy has not been described in dermatogenic enteropathy (Shuster & Marks, 1965; Shuster *et al.*, 1967), thus if the intestinal biopsy is flat the patient is likely to have coeliac disease. If the biopsy is convoluted other criteria will have to be employed to establish the diagnosis. In coeliac disease the small intestinal mucosa is often heavily infiltrated, particularly with plasma cells, as yet this has not been reported in dermatogenic enteropathy.

Faecal fat excretion. This would appear to be an unsuitable test, as it may be increased in both conditions, and may even be normal in coeliac disease (Dawson, 1964).

Xylose absorption. The measurement of the urinary excretion, after an oral loading dose of xylose, is of no value in skin disease because of increased plasma volume and impaired renal excretion. (Fry, Shuster & McMinn, 1965). However, the measurement of plasma xylose at 1 and 2 hr after a loading dose may be of some help in distinguishing between the two conditions. Xylose absorption is often impaired in coeliac disease (Chanarin & Bennett, 1962), but not in patients with widespread skin disease (Fry *et al.*, 1965; Doran *et al.*, 1966). In the five patients with psoriasis studied by Shuster *et al.* (1967) only one had a low plasma xylose.

Folate absorption. It is known that patients with coeliac disease and widespread eczema and psoriasis may be folate deficient (Shuster *et al.*, 1967; Hild, 1969; Fry & Hoffbrand, 1970). However, folate absorption is usually deficient in coeliac disease (Chanarin & Bennett, 1962), but not in skin disease (Hild, 1969; Fry & Hoffbrand, 1970).

Globulin deficiency. One third of patients with coeliac disease have a deficiency of γ M globulin. This is not known to occur in psoriasis or eczema.

Clinical response. Finally if there is still doubt as to whether the patient has coeliac disease or dermatogenic enteropathy, a therapeutic trial of a gluten-free diet or the topical treatment of the skin disease alone may help to solve the problem. If the steatorrhoea clears with topical treatment alone, then it is likely that the patient has dermatogenic enteropathy. If the small intestinal lesion and the skin (Freidman & Hare, 1965) improve with a gluten-free diet and relapse with the re-introduction of gluten, then the patient almost certainly has coeliac disease.

Specific relationship between skin and small intestinal disease

Dermatitis herpetiformis. Dermatitis herpetiformis has specific clinical and histological features and responds empirically to dapsone, the eruption recurring when the dapsone is stopped. Until 1966 it was thought that dermatitis herpetiformis was not associated with any other disorder, and that the patients only suffered from a skin disease. However, Smith (1966) mentioned two patients with malabsorption in a retrospective study of 150 patients with dermatitis herpetiformis and Marks, Shuster & Watson (1966) reported a high incidence of small intestinal structural abnormality in patients with this disorder. Marks, Shuster & Watson (1966) found that nine of the twelve patients they investigated had either a flat or convoluted macroscopic appearance of the small intestine, and in addition faecal fat excretion was raised in four of the patients in whom it was estimated. Marks *et al.* (1966) did not come to any conclusion as to the cause of the small intestinal abnormality. In the following year there were three further reports of small intestinal abnormality in dermatitis herpetiformis (Fraser, Murray & Alexander, 1967; Fry *et al.*, 1967; and van Tongeren, Van der Staak & Schillings, 1967). Neither Fraser nor van Tongeren and their respective colleagues came to any conclusion as to the nature and cause of the small intestinal abnormality. However, Fry *et al.* (1967) suggested the possibility that the intestinal abnormality was due to gluten-sensitivity because in addition there was a high incidence of increased faecal fat excretion, of folate, iron and γ M globulin deficiency, of splenic atrophy and of a serum-agglutinating factor to *lactobacillus casei*—all features of coeliac disease. The suggestion that the small intestinal lesion was due to gluten-sensitivity was subsequently confirmed by the fact that it improved in the majority of patients treated with a gluten-free diet (Fry, McMinn, Cowan & Hoffbrand, 1968; Shuster, Watson & Marks, 1968; Marks & Whittle, 1969). Further evidence that the

small intestinal abnormality was due to gluten was provided by Fry *et al.* (1969) who reported improvement in the macroscopic appearance of the intestine, height of the intestinal villi, surface epithelial cell height, faecal fat excretion and serum and red cell folate with a gluten-free diet for a year, and reversal on re-introduction of gluten. In addition Shuster, Watson & Marks (1968) found that the small intestinal mucosa was not so severely affected in the lower small bowel compared with the upper jejunum, suggesting a dietary cause for the enteropathy. That the dietary cause was probably gluten was further established in two patients by the fact that administration of gluten produced a focal subacute inflammatory reaction, in the upper small intestinal mucosa, which was not present in the biopsy specimens before gluten administration (Shuster *et al.*, 1968).

The incidence of structural abnormality of the small intestine in dermatitis herpetiformis has been found to be similar in most of the reported series to date (Fraser *et al.*, 1967; Fry *et al.*, 1967; Shuster *et al.*, 1968). In all these reports the incidence was found to be 70–80%; the question therefore arises whether in fact all patients have a gluten-sensitive enteropathy or whether 25% of patients with dermatitis herpetiformis do not have sensitivity to gluten. Certainly in untreated coeliac disease there is some degree of variation in the changes of the small intestinal mucosa produced by gluten (Booth *et al.*, 1962). In dermatitis herpetiformis there may be an even greater variation in the small intestinal changes produced by gluten. Since only few of the patients reported had any overt symptoms and signs of malabsorption, despite the fact that the small intestinal mucosa was severely affected, it may well be that in a number of patients the sensitivity to gluten was slight and therefore not manifested by routine histological studies and the macroscopic appearances. Thus whether the 25% of patients with no obvious structural change of the small intestinal mucosa have gluten sensitivity or not will only be answered in the future by more elaborate investigations and when there is a better understanding of how gluten produces the changes in the small intestine in certain individuals.

Effect of gluten-free diet in dermatitis herpetiformis

Clinical. The majority of patients presenting with dermatitis herpetiformis in a skin clinic do not have severe symptoms or signs of malabsorption (if they did they would probably have presented to a general medical clinic). However, a number of patients with dermatitis herpetiformis are underweight (Fraser *et al.*, 1967; Fry *et al.*, 1967). In some of these patients, but not all, the weight increases with a gluten-free diet (Fry *et al.*, 1968; Shuster *et al.*, 1968). There was subjective improvement in four of the seven patients

reported by Fry *et al.* (1969) after 1 year on a gluten-free diet.

Intestinal biopsy. The effect of a gluten-free diet on the small intestinal mucosa has already been referred to above. Shuster *et al.* (1968) reported improvement after 9 months in the macroscopic appearance of two of their four patients studied, and a significant improvement in the epithelial cell height in two patients. Fry *et al.* (1969) investigated seven patients after 1 year on a gluten-free diet and found improvement in the macroscopic appearance in three patients in whom it had been abnormal, and increase in the epithelial cell height and villous height. However, one patient showed a deterioration in the macroscopic appearance during 1 year on the diet. On re-introduction of gluten the macroscopic appearance became abnormal in six of the seven patients, and there was a significant fall in the villous height and mean epithelial cell height. Marks *et al.* (1969) reported improvement in the structure of the small intestine in ten of their nineteen patients, after 1 year on a gluten-free diet.

Faecal fat excretion. In the seven patients investigated by Fry *et al.* (1969) there was a fall in the faecal fat excretion in the five patients in whom it was above normal and slight increase when gluten was re-introduced. Shuster *et al.* (1968) however, found no fall in the faecal fat excretion after 1 year on a gluten-free diet in the three patients in which it was raised.

Folate. Folate deficiency is common in dermatitis herpetiformis. Low serum levels were found in ten of the twelve patients and low red cell folate levels in seven of the twelve patients reported by Fry *et al.* (1967) and low serum levels in eighteen of the twenty-nine patients reported by Marks *et al.* (1968). With a gluten-free diet both serum and red cell folate levels rose in six of the seven patients studied and fell when gluten was re-introduced with the diet (Fry *et al.*, 1969).

Skin lesions. The reports on the effects of a gluten-free diet on the skin lesions of dermatitis herpetiformis are conflicting. Fry *et al.* (1969) reported that three of their seven patients were clear of their skin disease after a year's diet and all required dapsone again on re-introduction of gluten. Another three patients required less dapsone whilst on a gluten-free diet and two of these had to increase their dose of dapsone on the reintroduction of gluten. Marks & Whittle (1969) studied twenty-nine patients for periods over 8 months and found nine patients required less dapsone for control of their skin disease, and three more required no dapsone at all. On re-introduction of gluten only one of their patients relapsed. Shuster *et al.* (1968) however found no improvement in the skin disorder in five patients studied for periods of 6 months or more. Van Tongeren *et al.* (1967) reported one patient whose

skin lesions cleared with a gluten-free diet, and another who derived no benefit.

Reasons for failure to respond to a gluten-free diet. It will be seen from the above results that not all the patients improved with a gluten-free diet, whether it be assessed on the small intestinal structure, faecal fat excretion, folate levels, or the response of their skin lesions. If it is accepted that the enteropathy is due to gluten-sensitivity then an improvement should occur in the structure and function of the small intestine. However, there are three possible reasons for failure to respond to a gluten-free diet:

(a) Not all patients with coeliac disease respond to a gluten-free diet (Pink & Creamer, 1967).

(b) The patients do not keep strictly to the diet, knowingly or unknowingly, and some authorities consider this the most common cause for failure to improve with a gluten-free diet.

(c) The time of the studies so far reported has been too short. It is known that the small intestine will go on improving after a year (Stewart *et al.*, 1967) and therefore, if these patients are studied for longer periods, a higher incidence of improvement may be obtained.

The question has been raised whether there is in fact a direct relationship between the small intestine and the skin in this disorder and whether if there is improvement in the small intestine the skin will also improve. As will be seen from above the clinical results as far as improvement of the skin lesions is concerned, are conflicting. However, the failure of the skin lesions to improve may be explained by a failure of the gut to respond adequately to a gluten-free diet for the reasons above. Certainly in none of the patients reported by Shuster *et al.* (1968) did the small intestine revert to a normal structure, as happened in the patients report by Fry *et al.* (1969). In the patient reported by Fraser, Ferguson & Murray (1968) in whom skin lesions of dermatitis herpetiformis developed whilst the patient was on a gluten-free diet for coeliac disease, the small intestine had not shown any structural improvement with the diet. However, Marks & Whittle (1969) did not find any relationship between dapson requirements and structural improvement of the small intestine mucosa. If the small intestinal abnormality can influence the skin to develop the lesions of dermatitis herpetiformis in some individuals the mechanism can only be speculative at the present time.

Is a gluten-free diet indicated in dermatitis herpetiformis? If a patient with dermatitis herpetiformis is found to have a structural abnormality of the small intestinal mucosa, then ideally he should be given a gluten-free diet. Sheldon (1969) considered a gluten-free diet should be life-long in coeliac disease, because of deficiencies that were present in untreated coeliac patients even if there were no overt

clinical symptoms. Certainly deficiencies of folate and iron are severe in patients with dermatitis herpetiformis and this may account for ill-health, and for the corresponding subjective improvement with a gluten-free diet. In addition control of the skin disease does appear to be easier in some patients with a gluten-free diet (Fry *et al.*, 1969; Marks & Whittle, 1969). In addition there is a high incidence of malignancy of the small intestine in coeliac disease (Gough, Read & Naish, 1962) and treatment with diet may well prevent this complication. More recently Morris, Adjukiewicz & Read (1970) have found that female patients with untreated coeliac disease may be infertile, and on treatment with a gluten-free diet they are able to conceive, so this should be borne in mind with young female patients who have dermatitis herpetiformis. However, the practical and social problems of adhering to a gluten-free diet for a life-time have to be taken into consideration and as with any treatment for any disease each patient should be considered individually.

Acrodermatitis enteropathica

Acrodermatitis enteropathica was first described by Danbolt & Closs (1942) when they reported two children with diarrhoea, periorificial dermatitis, alopecia and apathy. Margileth (1963) reviewed sixty-five published cases of acrodermatitis enteropathica and found that routine biochemical and haematological studies were normal. Steatorrhoea has been reported, but only in a small number of patients, and the cause of the diarrhoea is as yet unknown. Deficiency of succinic dehydrogenase has been described in the small intestinal mucosa in one case (Moynahan, Johnson & McMinn, 1963), but no other histological or structural abnormality of the mucosa has been found. The deficiency of succinic dehydrogenase is unlikely to be the primary or specific defect of the disease as it has been described in several other disorders of the small intestine (Fry & McMinn, 1966).

The skin lesions in acrodermatitis enteropathica were originally thought to be due to *Candida albicans*, and that is why di-iodohydroxyquinolone was first used by Dillaha, Lorincz & Aavik (1953). However, it is now realized that the *Candida* was a secondary invader. The mechanism of action of di-iodohydroxyquinolone is not known but it is a specific cure in this disease. Since the drug is not absorbed it must act on the surface of the small intestinal mucosa or on the contents of the gut. Bloom (1960) considered acrodermatitis to be an example of another disease due to an 'inborn error of metabolism'.

Rosacea

Rosacea is a fairly common skin disorder characterized by erythema, telangiectasia, papules and occasionally pustules on the face. In addition there is

a high incidence of 'flushing attacks'. Watson, Paton & Murray (1965) found a group of sixty patients with rosacea to be underweight compared with a control group; twenty of their sixty patients had some abnormality of their small intestinal mucosa on biopsy and they considered that four of their patients had definite coeliac disease. They postulated that there was a high incidence of small intestinal disease in patients with rosacea and suggested there may be a hereditary basis for this disease. However, the findings of Watson *et al.* (1965) were not confirmed by Marks *et al.* (1967) in a study of sixty-two patients with rosacea. These workers did not find any difference in the incidence of gastrointestinal symptoms or weight of their patients compared with sixty-two control subjects, and there was no difference in the incidence of abnormality of the small intestinal mucosa in subjects with rosacea and in a control group; they considered that an abnormal small mucosa was present in three of the thirty-four patients with rosacea and in six out of thirty-four 'control' subjects. However, their 'controls' were subjects with other skin disease including psoriasis and dermatitis herpetiformis where small bowel changes have been reported, and so the findings in rosacea may possibly be significant.

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