Progress report

Intestinal malabsorption and the skin

The interrelationship between the gut and the skin is complex. It is certainly not a one-way system, and just as the gut can affect the skin so can the skin affect the gut: in fact there are four ways in which diseases of the skin and gut can be interrelated\(^1\), \(^2\) namely, (1) malabsorption can cause a rash; (2) a rash can cause malabsorption; (3) skin abnormalities and malabsorption can have a common cause; and (4) skin disease and malabsorption can be related indirectly.

Group I

In this instance the rash arises as the result of malabsorption and disappears when the malabsorption is corrected. The concept was first formulated by William Hillary in 1759\(^3\) and the idea was kept alive by Whitfield and his 'dermatitis colonica'.\(^4\) The early literature on the subject has been reviewed by Wells.\(^5\) Two groups of physicians\(^6,\) \(^7\) have looked at the incidence of rashes in adults with malabsorption and have quoted figures of 20\(^\%\) and 10\(^\%\) respectively. Conversely, in our dermatology department we have screened over 200 patients with the appropriate rashes (see below) and have not found clinical coeliac disease to be responsible for any of them. We have in the last seven years seen two patients with rashes secondary to coeliac disease but these had bowel symptoms as well as a rash at the time they presented to us. Thus rashes due to occult coeliac disease would appear to be rare.

Rashes occur secondary to tropical sprue and postgastrectomy steatorrhoea as well as gluten-induced enteropathy, but no information is recorded in the case of pancreatic steatorrhoea. One apparent anomaly is the comparative rarity of rashes in coeliac disease of children.\(^8,\) \(^9,\) \(^10\) We have no explanation for the difference in incidence of rashes in adults and children, though duration and severity of disease are possible factors.

The rashes which are consequent upon malabsorption are usually eczematous\(^5,\) \(^11,\) \(^12\) or psoriasiform\(^6,\) \(^13,\) \(^14\) and are in no way specific. Hyperpigmentation\(^12,\) \(^15,\) \(^16\) may occur as it does in other chronic disease and in other inflammatory skin disease. Acquired ichthyosis\(^6\) may occur but we suspect that it is related to the severity of the malabsorption for none of our patients with the coeliac syndrome of dermatitis herpetiformis (see below) have it. Acquired ichthyosis also occurs in other wasting diseases, eg, reticulosis and chronic renal disease, and it seemed possible that in these cases too it was due to malabsorption, but in a study of 10 cases of acquired ichthyosis from various causes\(^17\) only one has shown evidence of a secondary coeliac syndrome\(^18\) or steatorrhoea. Consequently, generalized malabsorption would not as a rule appear to be the mechanism of the production of this skin change.

Our understanding of the mechanism of the rashes produced by malabsorp-
Intestinal malabsorption and the skin

The concept that skin disease could actually produce malabsorption arose out of the much wider concept that changes in internal organs can result from a rash. It is also of course in keeping with observations that malabsorption occurs in diseases of other systems without direct involvement of the small intestine. The term 'dermatogenic enteropathy' was first introduced to describe the steatorrhoea which occurred as a result of a rash. It is a common condition and its features are now well documented. It is most common and most severe in patients with extensive rashes, for its presence and severity are proportional to the extent of the rash. It is in eczema and psoriasis, the commonest skin diseases we see, that most studies have been done but we have also seen dermatogenic enteropathy in patients with lichen planus and pityriasis rubra pilaris: the steatorrhoea is often short lived for it rapidly disappears following response of the rash to topical treatment of the skin: in patients with chronic relapsing dermatoses it is not uncommon for the steatorrhoea to recur in subsequent attacks of skin disease. There is evidence that malabsorption of substances other than fat, namely, d-xylose, iron, folate, calcium, and lactose occurs in some patients with dermatogenic enteropathy, but abnormalities of d-xylose, iron, and folate metabolism are extremely common in patients with skin disease and the precise role of malabsorption and other factors in their production is not fully worked out: abnormalities of vitamin B12 excretion are common but in this case, although the evidence is suggestive, there is as yet no proof that malabsorption occurs: finally, a
number of patients have a protein-losing enteropathy.\textsuperscript{31, 61} Although much of the work on malabsorption secondary to skin disease has been done by our group in Newcastle upon Tyne evidence that skin disease can cause an enteropathy is forthcoming from other centres in this country too\textsuperscript{41, 42, 43} and from San Francisco,\textsuperscript{52} though in this last case the authors themselves interpret their results another way: from Bristol and Stoke-on-Trent the results are particularly interesting as the workers there have shown malabsorption of fat,\textsuperscript{41} folate,\textsuperscript{42} and lactose\textsuperscript{43} to be proportional to the extent of the rash.

Accounts of structural 'abnormalities' in the small-intestinal mucosa in psoriasis and eczema lie in the literature\textsuperscript{28, 53, 54, 55, 56, 57, 58} alongside reports that no structural abnormality can be demonstrated.\textsuperscript{56, 28, 52, 58, 59} The confusion is partly due to the different techniques used by the various workers, partly to differences in terminology, and, in particular, the differences in the use of the terms 'convoluted' and 'normal', partly to the difference in the incidence of a convoluted mucosa, however defined, in different geographical areas of this country,\textsuperscript{28} and partly to the fact that sweeping conclusions have been drawn even when only small numbers of patients have been biopsied. The present position is that a number of patients in Newcastle upon Tyne with psoriasis and eczema as well as rosacea, pemphigoid, lichen planus, pityriasis rubra pilaris, and other dermatoses have a predominantly convoluted mucosa in the upper part of the small intestine.\textsuperscript{28} The overall incidence in these skin diseases is 8\% and there is no significant difference in incidence in the different diseases. In Newcastle upon Tyne 8\% of a 'control' population studied at necropsy in a series of sudden deaths reported to the coroner also had a predominantly convoluted mucosa.\textsuperscript{28} From this we have concluded that there is no stereomicroscopic abnormality of the small-bowel mucosa associated with these dermatoses, although we realize that the use of postmortem material for comparison is far from ideal. Nevertheless, in Oxford the incidence of a convoluted mucosa in patients with psoriasis is similar to that in biopsy material from an appropriate local 'control' group\textsuperscript{58} and this adds support to our own findings. In Bristol, however, a higher incidence of convolutions has been found in patients with psoriasis and other chronic diseases than in a local 'control' group.\textsuperscript{57} No correlation between the presence of a convoluted mucosa and the steatorrhoea of dermatogenic enteropathy has been demonstrated\textsuperscript{28} and numbers are too small for response of the mucosal appearance to treatment of the rash to be assessed.\textsuperscript{2} Thus as far as stereomicroscopic appearances go the question of an abnormality in eczema and psoriasis is still unresolved.

In the 23 patients with psoriasis studied in detail\textsuperscript{55} there was good correlation between stereomicroscopic and histological appearance and patients with convolutions on stereomicroscopy showed histological changes of partial villous atrophy. We now know that the histochemical abnormalities we described in the small-intestinal mucosa in psoriasis\textsuperscript{55} are not specific to psoriasis,\textsuperscript{60} and this may turn out to be true of the enzyme abnormalities others have described too.\textsuperscript{61} The electron-microscopic changes reported\textsuperscript{56} in the small-intestinal mucosa of psoriatics obviously require confirmation.

The cause of dermatogenic enteropathy is unknown. Changes in small-intestinal blood flow, folate and iron status, bacterial flora of the gut, and pancreatic function, as well as specific changes in mucosal enzymes, have been considered\textsuperscript{2, 58} but the evidence so far is that they are not responsible.
Gluten sensitivity as usually understood is not responsible either as the condition has occurred in a patient already on a gluten-free diet.\textsuperscript{2, 38} Further evidence on this point comes from the jejunal biopsy findings in dermatogenic enteropathy for a completely flat mucosa with subtotal villous atrophy has not been reported. We have drawn attention to the similarity of dermatogenic enteropathy to the enteropathy which occurs in patients with chronic wasting diseases.\textsuperscript{38} Whilst there may be a similar mechanism in both, dermatogenic enteropathy differs clinically from the enteropathy of chronic wasting disease in that our skin patients are not wasted. Again dermatogenic enteropathy occurs and recurs throughout a normal life span and presents a different problem from the enteropathy of advanced cancer, for example. Finally, we do not yet know whether malabsorption is a common feature of diseases of other organs as it is of patients with rashes. At the present time, therefore, we must continue to regard dermatogenic enteropathy as a distinct syndrome.

In summary, intestinal malabsorption of fat and other substances is a common complication of extensive skin disease: the question of whether or not mild structural changes occur in the small-intestinal mucosa in dermatogenic enteropathy is still sub judice.

**Group III**

A number of diseases are common to the skin and the intestine either exclusively or as part of more generalized involvement. Of the collagen vascular diseases, systemic sclerosis frequently affects these two organs as well as others. It is well known that the pathological processes which are responsible for the characteristic facies, sclerodactyly, etc., produce also the oesophageal changes which result in dysphagia. Similar changes in the small bowel lead to dilatation, loss of peristalsis, and abnormal bacterial colonization of the upper part of the small intestine with steatorrhoea. Bluestone, MacMahon, and Dawson\textsuperscript{62} examined 21 patients with systemic sclerosis and found symptoms suggestive of small bowel involvement in five, radiological changes in 12, and steatorrhoea in six: in three of these six urinary indican excretion was increased, suggesting that an abnormal bacterial flora was at least in part responsible for the steatorrhoea. We,\textsuperscript{63} like Peachey, Creamer, and Pierce,\textsuperscript{64} have found a temporary improvement in steatorrhoea in this condition after treatment with antibiotics. Bluestone et al\textsuperscript{65} found jejunal mucosal biopsies to be normal as we have done in the seven patients we have examined.\textsuperscript{66} An important feature of systemic sclerosis is the arteritis, and here as in other collagen vascular diseases, including rheumatoid arteritis, we should expect malabsorption to occur as a result of arteritis of the vessels of the bowel, while skin ulceration occurs from arteritis of the skin vessels.\textsuperscript{5, 66} Some of the patients concerned have a normal small-bowel mucosal appearance on biopsy but in some cases there is flattening indistinguishable from that of coeliac disease. The finding of vasculitis with coeliac disease seems to be a bad prognostic sign.\textsuperscript{67} Whether the vasculitis is a complication of the coeliac disease or whether the gut and skin lesions are both due to a primary vasculitis is not known. The presence of hyaline eosinophilic material, probably collagen, in the lamina propria of patients with malabsorption associated with vasculitis and a bad prognosis\textsuperscript{68} does not appear to be specific to this so-called 'collagenous sprue'.\textsuperscript{69} Malignant
atrophic papulosis\textsuperscript{70, 71} is a disease of unknown aetiology in which there is an endovasculitis of small arteries of the small bowel with occlusion of the vessels which leads to perforation of the bowel: in the skin the arteritis is responsible for the unique porcelain-like papules.

The precise relationship of the diarrhoea of acrodermatitis enteropathica\textsuperscript{72} to the rash, alopecia, and nail changes of the disease is not known but the fact that bowel and skin respond simultaneously to treatment with diodoquin\textsuperscript{78} suggests a metabolic abnormality common to both. At one time it was thought that diodoquin was not absorbed from the gut and its action on the skin was an indirect one, but we now know that diodoquin is absorbed and retinitis has been reported as a result.\textsuperscript{74} The nature of the small-intestinal lesion is not known. The changes described in the intestinal epithelium, including the absence of succinic dehydrogenase,\textsuperscript{78} are now known to be non-specific.\textsuperscript{54}

Allergic gastroenteropathy\textsuperscript{78} is a syndrome characterized by eczema and other manifestations of atopy together with oedema, hypoproteinaemia, and a protein-losing enteropathy. The fact that the eczema and the protein-losing state disappear when milk is withdrawn from the diet suggests that there may be a common allergic basis for both.

**Group IV**

There are certain instances in which diseases of the skin and bowel occur together more often than would be expected by chance without there being any direct relationship, as in groups I, II and III above, between them. The most important relationship of this type is that between dermatitis herpetiformis and coeliac disease. Dermatitis herpetiformis is characterized by groups of very itchy blisters and papules, particularly on the extensor surfaces of the body. Histologically there are collections of polymorphs and eosinophils in the dermal papillae, and subepidermal blisters: the rash is made worse by iodides and is suppressed by sulphonamides and sulphones. Our report\textsuperscript{77} that two-thirds of people with this dermatosis have structural changes in the proximal small-intestinal mucosa indistinguishable from those of coeliac disease has been confirmed by others\textsuperscript{78, 79, 80} and a number of other cases of the association have been reported.\textsuperscript{81, 82, 83, 84, 85, 86} The stereomicroscopic and histological appearances of the bowel, the response to gluten in the majority of cases, the fact that the lesion is worse in the proximal small bowel than in the distal small bowel,\textsuperscript{87} the increased incidence of small bowel abnormalities in families of affected individuals,\textsuperscript{88} as well as the development in one of our own\textsuperscript{8} and one other patient\textsuperscript{69} of an abdominal reticulosis, have long convinced us that the enteropathy of dermatitis herpetiformis is indeed coeliac disease, and after an initial dissension from this view\textsuperscript{80, 81} Rubin’s group too are now in agreement with us on this point.\textsuperscript{92} The only ways in which the coeliac disease of dermatitis herpetiformis appears to differ from that occurring in other situations are the large proportion of patients who have no symptoms referable to the small intestine and in some cases no biochemical evidence of malabsorption, and the higher proportion of convoluted/flat mucosae in the untreated cases (14/20 in our personal series at present):\textsuperscript{98} these differences are to be expected from our method of selection of patients, ie, by examination of consecutive cases of dermatitis herpetiformis regardless of whether they have gut symptoms or
not. Severe cases of malabsorption do occur in dermatitis herpetiformis and sometimes the initial presentation is to a gastroenterology clinic.\textsuperscript{94}

Our evidence is that although the enteropathy of dermatitis herpetiformis is nearly always due to gluten, the rash is not\textsuperscript{2, 87} and now that some of our patients have been on a strict gluten-free diet for as long as five years, we believe that we have reasonable proof that gluten withdrawal plays no part in the treatment of the rash of dermatitis herpetiformis. Most instances of complete clearing of the rash while the patient is on a gluten-free diet\textsuperscript{85, 86} can be explained in terms of the natural history of the disease.\textsuperscript{93, 97} There remain the very few patients in whom it has been alleged that the rash itself can be turned on and off by gluten feeding and withdrawal.\textsuperscript{88} Here again the very singularity of the observation and the lack of a clear time relationship to dietary gluten makes it difficult to exclude the unrelated clinical fluctuations which are a feature of the rash. It is a fact of scientific life that positive early findings are more often published than subsequent less happy results: it is essential that the results of further and more critical studies on these few patients are published again in the future. It is unfortunate that premature advice on the use of a gluten-free diet for the treatment of the rash of dermatitis herpetiformis has already appeared in some textbooks. The reported response of a patient with dermatitis herpetiformis and coeliac disease to a milk-free diet\textsuperscript{89} likewise requires amplification.

Just as the rash of dermatitis herpetiformis does not respond to treatment of the enteropathy, the enteropathy does not respond to treatment of the rash, and this difference in response of the skin and gut to treatment is our main evidence that the rash and enteropathy are related only indirectly. What then is the connexion between the two? The finding of a jejunal biopsy abnormality in so many relatives of patients with dermatitis herpetiformis,\textsuperscript{48} as well as the knowledge that the rash occurs in more than one member of a family more often than we should expect to in so rare a disease,\textsuperscript{100} led us to believe that the connexion may be a genetic one, patients with one disease having a ‘predisposition’ to develop the other. Since all the early reports suggested that about one-third of patients with dermatitis herpetiformis had a normal jejunal mucosa it seemed that the presence of coeliac disease was not necessary for the production of the rash. Recently, however, it has been reported that all patients with dermatitis herpetiformis can be shown to have patches of flat mucosa on repeated biopsy.\textsuperscript{101} This strongly suggests that all patients with dermatitis herpetiformis have the coeliac diathesis, and our recent finding of relatives with coeliac disease in two families of patients with dermatitis herpetiformis who themselves have an apparently normal small bowel\textsuperscript{102} lends support to this idea. This would greatly simplify our understanding of the disorder.

Is the factor which precipitates the rash in someone with a coeliac diathesis environmental or genetic? Inorganic iodine will induce or worsen the rash of dermatitis herpetiformis: this appears not to be the factor since we have given iodine to patients with uncomplicated coeliac disease and this does not produce a rash. The increased family incidence of the rash, together with preliminary results in a study of genetic markers,\textsuperscript{103} favour the idea that dermatitis herpetiformis may occur in a genetic subgroup of the coeliac constitution. One interesting and important characteristic of this group is the high incidence of circulating autoantibodies now confirmed by many
workers, and more specifically the deposition of IgA at the dermo-epidermal junction even in normal looking skin.

There remain a number of instances in which the relationship of the gut lesion to the skin lesion is still unknown. In the Canada-Cronkhite syndrome, for instance, it has been suggested that the hair and nail abnormalities are secondary to protein deficiency consequent upon the protein-losing enteropathy: it is equally probable, however, that both skin and gut abnormalities are associated rather than causally related defects.

**Management**

A knowledge of the relationship of the various skin-gut abnormalities to one another is important in deciding on treatment. Obviously if clinical coeliac disease is present it must be treated. The management of the coeliac disease of dermatitis herpetiformis in those cases in which there are no symptoms and no detectable biochemical abnormalities is more difficult. Though a number of patients in this category who have been put on a gluten-free diet have gained weight and have admitted ‘feeling better’ afterwards, for the remainder in whom the disease really is subclinical we must look for advice to our gastroenterological colleagues. One reason for advocating a gluten-free diet would be to reduce the risk of a reticulosis, but while there is some evidence that this is reduced by effective treatment of clinical coeliac disease experience does not extend to those with subclinical structural changes in the bowel. What is quite clear now is that all patients with dermatitis herpetiformis should have a jejunal biopsy and this should be repeated at regular intervals in those in whom it is initially normal: those in whom it is abnormal should have regular clinical and biochemical follow up for evidence of malabsorption. Regardless of the management of the bowel, patients with dermatitis herpetiformis will need dapsone for the skin.

Patients with dermatogenic enteropathy do not need a gluten-free diet as the steatorrhoea will improve with effective treatment of the rash: rarely in severe longstanding rashes they may need replacement of essential minerals and vitamins. Occasionally diagnostic difficulties arise in those with extensive rashes and steatorrhoea, and then the finding of a completely flat jejunal mucosa will differentiate coeliac disease from dermatogenic enteropathy: regression of the steatorrhoea with topical treatment of the skin disease alone will also help to distinguish the two.

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**References**

Intestinal malabsorption and the skin


946 Janet Marks and Sam Shuster


Intestinal malabsorption and the skin

947


