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Skin-Gut Relationships

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The skin and the gut have much in common, and associated lesions are certainly observed in clinical practice. This is about as far as accurate reporting can go, for this is a very confused field and much is still inference. Furthermore, the mechanisms of interaction between skin and gut are almost entirely speculative. Because of the breadth of the subject and the limitation of my own experience I propose to refer only to the small intestine, though there are intriguing relationships between the stomach and colon and the skin.

The relation between skin and intestinal disease may operate in different ways. The gut may be the prime mover; it is now widely accepted that certain small intestinal diseases are complicated by skin conditions. Wells (1962) has clearly described the skin lesions of malabsorption, and I can bear witness to their frequency and their response to treatment of the intestinal lesion and the accompanying deficiencies. Secondly, both gut and skin may be implicated by the same process, and here scleroderma is the obvious example. This communication is principally concerned with the third possibility, the

evidence for the skin being the cause of intestinal malfunction or even structural damage.

The small intestine is a highly robust and also a highly dynamic organ. Failure of the small intestine is rare compared with respiratory or renal failure, which probably depends in part on its swift renewal rate. The epithelial cells are constantly being replaced, as in the skin, but with two important differences. Firstly, production is in specialised zones, the intestinal crypts, from which cells migrate up the villi to be shed from extrusion zones at the tips of the villi; and secondly, the rate of turnover is about six times faster in the small intestine where the renewal or turnover time is about four or five days or even shorter. Because it is so dynamic it is also a plastic organ, and the villi can change shape, depending on the balance between production and loss of the adult cell population (Creamer, 1964). In the West, many normal people have finger-shaped villi, projections with a large surface area. It might be expected that these would simply shrink if the number of adult epithelial cells became diminished but, strangely, the result of fewer cells is a remoulding into different shapes. Finger villi are succeeded by leaf-shaped villi that require only a quarter the number of cells, and these are often found in normal people. Fewer cells cause leaves to become convolutions, using only an eighth of the normal number, while with extreme privation of cells the mucosa becomes flat, which utilises only a thirtieth of the normal number. This last state is the coeliac lesion, the flat jejunal mucosa obtained at biopsy, which is the diagnostic sign of the coeliac syndrome.

The mechanics of mucosal abnormalities can be discerned from a study of the crypt: villous cell ratio and the mitotic rate (Creamer, 1964). In a few cases, severe disease with generalised upset causes a diminution of mitotic activity and the whole mucosa shrinks, the crypts shorten, and the villi become leaf-like and stunted. This is analagous to hypoplasia. A situation analogous to haemolysis can also be seen where the intestinal luminal environment is altered so that cells are damaged and lost at an increased rate, as after gastrectomy, in subacute obstruction or with pancreatic disease. Here the crypts hypertrophy in an attempt to keep up with loss but the balance is usually a smaller adult cell population, with the formation of leaves and convolutions. A flat mucosa may be an extreme form of such a 'haemolytic' process or even a situation akin to maturation arrest so that few cells are delivered from the crypts (Creamer, 1962).

The functional assessment of small intestinal mucosa is not so accurate as the structural assessment, but histochemistry and *in vitro* enzyme measurement can help. Gross histochemical changes of enzyme loss are seen in the coeliac lesion but minor ones also occur. The disaccharide enzymes can also be

measured to demonstrate a specific biochemical lesion with which there is often a clinical syndrome of pain and diarrhoea that will respond to withdrawal of the appropriate disaccharide. At the moment, measurement of malabsorption, the end result of mucosal malfunction, is a better index of functional change in the epithelial cells. These are the ways in which the small intestine's responsiveness to skin disease might be manifest, and examples of all these have been recorded.

A functional upset, malabsorption, secondary to skin disease, has been reported by Shuster and Marks (1965) and termed dermatogenic enteropathy. In a series of 10 patients with generalised psoriasis or eczema 9 were found to have elevated faecal fats. In 3 out of 4 of these patients the jejunal biopsy specimen was normal, and the fourth showed only a mild abnormality, so presumably the steatorrhoea was on a functional basis and, in support of this, the steatorrhoea disappeared as the patients improved. The xylose test is used frequently in assessing small intestinal function but it has been found unreliable in extensive skin disease as there appears to be an abnormality of renal handling (Fry *et al.*, 1965).

Minor structural abnormality and a moderate deficiency of succinic dehydrogenase has been found in several cases of skin disease (Fry *et al.*, 1966); in particular Brocq's ichthyosiform erythrodermia, ichyosis vulgaris, and acrodermatitis enteropathica showed these changes. Similar findings in acrodermatitis enteropathica were recorded by Moynahan *et al.* (1963) who suggested that the intestinal lesion was the primary event. However, these cases did not show malabsorption. Such a lack of correlation between histology and malabsorption when both are in a minor key is one of the difficulties in this field.

The carbohydrate intolerance and flatulent symptoms of rosacea have suggested that these patients might have specific disaccharidase deficiencies. However, a careful search by Paton *et al.* (1966) in twenty patients failed to reveal any case of alactasia, although the lactase levels, in general, were rather lower than the controls.

The changes described so far are all minor and reversible and are probably the result of serious disease and systemic upset in the sensitive small intestinal mucosa. They are similar to changes found in other generalised diseases and not specific to skin disease. The next gut lesion to be considered is the coeliac syndrome alias idiopathic steatorrhoea or adult coeliac disease. The lesion here is a major one and the appearances on jejunal biopsy are specific. This is probably the commonest malabsorption state seen in this country and it is frequently accompanied by skin manifestations such as pigmentation, acquired ichthyosis, and eczema (Wells, 1962; Friedman and Hare, 1965).

However, there are two major difficulties in the relation of this syndrome to skin disease. Firstly, the onset of malabsorption is almost impossible to date, as it may be manifest by only minor ill-health and occasional bowel upset for years before a definite clinical state develops. Secondly, the coeliac syndrome in adults is not a single disease and may develop secondary to other conditions such as generalised diseases, infestations, and drugs (Collins, 1965). The question in the present context is, can skin disease similarly be the cause of a secondary coeliac syndrome? There are now several case reports of generalised dermatitis being followed in time by the coeliac syndrome, and we have seen two such cases (Hindle and Creamer, 1965). It is noteworthy that in four out of five of the series reported by Wells (1962) the skin lesion antedated the malabsorption by two to ten years. Eczema, rosacea, dermatitis herpetiformis, Sjörgren's syndrome, and other collagenoses have been observed in this relationship.

In view of the difficulties of dating the onset of the gut lesion these reports must not be taken as proof that the skin disease is the causal event. I think a coeliac syndrome can be accepted as secondary only under two conditions: firstly, if the incidence of the association is higher than would be expected by chance, i.e. epidemiological proof; or secondly, if the gut lesion reverts to normal with treatment only of the primary disease or with natural remission of the primary lesion. If these criteria are applied then most of these instances are not proven. In two of the diseases mentioned an association has been reported. Rosaceas in Glasgow appear to have an incidence of the coeliac syndrome of over 10 per cent but the report suggests that some were already attending hospital for idiopathic steatorrhoea (there is a high risk of fortuitous associations in hospital practice). The second disease is dermatitis herpetiformis, and two series have shown a remarkable association with the coeliac syndrome. Marks and her colleagues from Newcastle (1966) found 9 definitely abnormal jejunal biopsies out of 12 cases, while Van Tongeren and his colleages from Holland (1967) had 4 similar biopsies out of 9 cases. However, in some of these cases the gut lesion persisted in spite of successful treatment of the skin with dapsone, and in one other the skin improved on a gluten-free diet and relapsed again when the patient returned to a normal diet. Once again the case for the skin lesion causing the coeliac syndrome is not proven and it can only be suggested that coeliac patients are very susceptible to dermatitis herpetiformis.

Finally, in the true dermatological tradition, I want to describe a unique example of small intestinal upset secondary to skin disease (Creamer and Pink, 1967). The patient, a middle-aged man, has been under the care of Dr Wells with recurrent episodes of pustular psoriasis. In each episode he

becomes ill and has diarrhoea, while biochemical tests show steatorrhoea and hypocalcaemia (Copeman and Bold, 1965). A jejunal biopsy taken in remission was normal, and a second, in an attack, showed a more leaf-like and convoluted appearance. Histology showed shorter crypts with an almost complete absence of mitoses but the striking finding was the complete absence of Paneth cells, which had been normally present in remission. These cells are present in the intestinal crypts throughout the small bowel and clearly secrete a glycoprotein into the bowel lumen. Their function is quite unknown although it has been suggested recently that they are nutritional cells keeping constant the luminal environment of the small intestine (Creamer, 1967). It is known that the amino-acid concentration of the lumen stays remarkably constant in spite of dietetic variation or fasting (Nasset, 1964). Whatever the mechanism, it seems that the disappearance of Paneth cells in this patient coincides with a marked functional upset in the small intestine.

This survey may seem to make a difficult subject more difficult. However, the whole question of the systemic effects of skin disease is a fascinating one, and the small intestine is an important site. The questions raised will be answered only by careful studies of associations (with an appreciation of the bigger risk of chance associations in hospital practice as opposed to the whole population) and the opportunistic investigation of unusual patients.

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