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Small-Bowel Abnormalities in Dermatitis Herpetiformis

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The occurrence of jejunal mucosal abnormalities in dermatitis herpetiformis was first reported by Marks, Shuster, and Watson (1966) and Van Tongeren, Van der Staak, and Schillings (1967). More recently two other studies of small-bowel structure and function have been published (Fry, Keir, McMinn, Cowan, and Hoffbrand, 1967; Fraser, Murray, and Alexander, 1967). In addition, Smith (1966), in his clinical study of 149 cases of dermatitis herpetiformis seen at St. John's Hospital, found two patients who had a malabsorption syndrome.

In an investigation of the jejunal biopsy appearance of patients with rosacea it was noted that in the control series one of the two patients with dermatitis herpetiformis had subtotal villous atrophy (Marks, Beard, Clark, Kwok, and Robertson, 1967). We here report our findings in 29 patients with dermatitis herpetiformis.

Methods

The patients were admitted for investigation. The first part of the jejunum was biopsied with the Crosby capsule under radiological control. The specimens were immediately examined under a Watson dissecting microscope and photographed before being submitted for histological examination. The classification of dissecting microscope appearances is that described by Holmes, Hourihane, and Booth (1961). Fingers and leaves describe the appearance of the villi of the normal jejunum; convolutions, the mosaic pattern; and the completely flat mucosa are regarded as increasing degrees of abnormality. The histological classification used is the accepted one of normal mucosa, partial villous atrophy, and subtotal villous atrophy. Subtotal villous atrophy is the condition associated with untreated gluten enteropathy. Partial villous atrophy is the condition associated with tropical sprue and certain other conditions where the villi are short and blunt and many inflammatory cells are present, some crossing from the lamina propria into the epithelial layer.

We have also used the term "partial focal villous atrophy" to describe a condition in which the villi appear focally shortened but not to the extent seen in partial villous atrophy and where there is an excess of inflammatory cells in the lamina propria and epithelial layer. We have scored this as "normal," though it is possible that it represents early abnormality. We have not scored epithelial cytological abnormalities, as it is intended to compare the biopsies with those taken after treatment with a gluten-free diet and to report these findings later.

In most cases the following haematological investigations were performed: peripheral blood and bone-marrow examinations, serum vitamin B_{12} and folate estimations, and a Schilling test of vitamin-B_{12} absorption. Serum vitamin B_{12} and folate were estimated by bioassay with *Lactobacillus leishmanii* and *Lactobacillus casei* respectively.

Twenty-eight patients had xylose tolerance tests; a 25-g. dose was given to 25 patients and a 5-g. dose to three. The amount of xylose in a five-hour specimen of urine and in the blood was estimated by the method of Roe and Rice (1948), The lower limit of normal for urinary xylose excretion in five hours has been taken as 17% of the ingested dose (4.2 g. for a 25-g. test and 0.85 g. for a 5-g. test). A level of 26 mg./100 ml. at one to two hours after ingestion of the xylose was regarded as the lower limit of normal.

A glucose tolerance test was performed on 24 patients. Blood sugar levels were estimated by a method based on that of Haslewood and Strookman (1939). A rise in the blood sugar level of 30 mg./100 ml. or less over the fasting value has been regarded as abnormal and rises of 30 to 40 mg./100 ml. as equivocal.

Stools were collected to estimate the average daily faecal fat excretion in 25 patients. The collection was made over a five-day period on 18 occasions, over a three-day period on 10

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occasions, and over four days once. Patients were on a normal ward diet during the collections. Faecal fat was estimated by the method of Van der Kamer, Huinink, and Weyers (1949).

Twenty-three patients were studied radiologically by barium-meal examinations. Special attention has been paid to the presence of dilatation, segmentation, the mucosal pattern of the small intestine, and the speed of passage of the contrast medium through it.

Other investigations included chest *x*-ray examination, serum calcium and phosphate estimations, serum alkaline phosphatase activity, serum protein electrophoresis, blood urea estimations, and the empirical tests of liver function.

Results

Clinical Findings

Cases 1 and 2 had had a frank malabsorption syndrome and were investigated before the association of dermatitis herpetiformis and small-bowel disorder was recognized. Seven other patients were found to have diarrhoea (see Table I).

Case 1 was diagnosed as having dermatitis herpetiformis in 1955, but he probably first had the disorder in 1918. In 1961 he was investigated for diarrhoea present intermittently for many years and for recent loss of weight. He was found to have steatorrhoea and intestinal malabsorption. A diagnosis of gluten enteropathy was made and he was treated with a gluten-free diet and folic acid. His diarrhoea stopped and he gained weight. In 1963 he was able to stop taking dapsone without recurrence of skin lesions. At the time of writing he was free of all symptoms and remained on his gluten-free diet.

Case 2 had been treated with dapsone for dermatitis herpetiformis since 1957. During an admission to the Hammersmith Hospital in 1966 for an exacerbation of chronic bronchitis he was found to have a macrocytic anaemia. Further investigation showed megaloblastic change in the marrow and intestinal malabsorption. Idiopathic steatorrhoea was diagnosed and folic acid was given. Attempts at persuading him to persevere with a gluten-free diet have been unsuccessful and when last seen he was cachectic and had multiple ills.

Seven other patients had diarrhoea. Case 3 had suffered from diarrhoea intermittently since 1944. Furthermore, this patient had an enlarged liver (5–6 cm. below the right costal margin) and an easily palpable spleen. Liver biopsy revealed no significant abnormality and the cause of his hepatosplenomegaly remained obscure. Case 7 had moderately severe diarrhoea for the previous three or four years with up to four stools per day. Case 11 had episodes of moderately severe diarrhoea which he attributed to anxiety, persistent jaundice (serum bilirubin in the region of 3 mg./100 ml.), with a reticulocytosis of 7% and splenic enlargement. All other tests of liver function are normal in this patient. Case 12 had had persistent severe diarrhoea for the past one to two years though her weight had not changed and was within 10% of its expected value. Case 20 had also had attacks of diarrhoea for many years. This patient has a brother who for many years had an itchy blistering rash that might be dermatitis herpetiformis (Case 26 had had troublesome diarrhoea for two to three years and Case 27 had had severe explosive diarrhoea of recent onset.

Hepatic cirrhosis was found in Case 21 after investigation at the Royal Free Hospital. This patient also had diabetes mellitus, controlled by diet alone.

The brother of Case 22 had a malabsorption syndrome for many years and recently died at another hospital after operation for small-bowel obstruction. It was suggested that the cause of his obstruction was intestinal lymphosarcoma. The youngest patient in our series (Case 23) had what was termed "folate deficiency" anaemia 10 years before developing his skin disease, and had been treated for this up to the age of 11.

Other Findings

Jejunal Biopsies.—The results of the jejunal biopsies are given in Table II; it will be seen that 18 of the 26 (70%) are unequivocally abnormal. Thirteen showed the picture of par-

TABLE I.—*Summary of Findings*

Case No.	Age	Sex	Duration of D.H. (years)	Treatment at Investigation	Jejunal Biopsy	Xylose Test: 5-hour Urinary excretion (G.)	Xylose Test: Plasma Level of Xylose	Faecal Fat excretion (G./day)	Maximum Glucose rise in G.T.T. (mg./100 ml.)	Schilling test (percentage of dose excreted)	Marrow	Clinical Comments
1	61	M	42	Dapsone	—	2·9	—	20·8	24	13·1	Normoblastic but few macronormoblasts	Malabsorption syndrome. Diarrhoea
2	66	M	9	„	P.V.A.	2·3	—	5·5/9·8	15	—	Intermediate megaloblastic change	Malabsorption syndrome
3	46	M	17	„	P.V.A.	5·8	56	8·8/4·7	—	—	Normoblastic hyperplasia. Some macronormoblasts	Hepatosplenomegaly. Diarrhoea
4	53	F	1	„	P.F.V.A.	—	—	—	—	—	—	
5	28	F	1	„	Severe P.V.A.	1·7*	—	8·8	68	—	Normoblastic hyperplasia	
6	64	M	8	Sulphas	P.V.A.	2·9	35	3·9	30	29	Normal	
7	62	M	Many	Dapsone	S.V.A.	3·9	—	1·3	52	—	—	Diarrhoea
8	20	F	6	„	P.V.A.	3·0	54	—	40	15·6	Normoblastic hyperplasia	
9	58	M	9	„	Severe P.V.A.	0·9*	—	5·0	—	—	Early megaloblastic change	
10	23	F	7	„	„	0·4*	—	—	—	—	„ „ „	
11	26	M	9/12	„	„	0·5	20	2·1/1·8	42	19·9	Normoblastic hyperplasia	Splenomegaly. Jaundice. Diarrhoea
12	24	F	6	„	P.V.A.	5·5	39	0·6	26	23·9	„ „	Diarrhoea
13	49	M	19	„	S.V.A.	3·9	30	10·6/6·6	89	17·9	Normal	
14	57	M	4	„	Normal	4·3	46	3·2	19	—	„	
15	18	F	5/12	None	—	4·2	43	1·0	17	18·2	„	
16	59	M	10	„	Severe P.V.A.	6·0	—	2·8	45	—	„	
17	28	M	3½	Dapsone	P.V.A.	5·3	40	4·9	63	—	Normoblastic and macronormoblastic hyperplasia	
18	53	M	7	„	Normal	3·8	39	—	47	—	Decreased iron content	
19	31	F	2½	„	P.V.A.	3·0	36	2·3	81	38·3	Normoblastic hyperplasia	
20	44	M	3	„	Normal	1·7	19	4·4	56	19	Early megaloblastic change	Diarrhoea
21	48	F	15	Sulphas	—	3·8	66	7·2	175	—	Decreased iron content	Cirrhosis. Diabetes
22	68	M	33	Dapsone	S.V.A.	0·3	15	7·3	10	2·6	Moderate megaloblastic change	Brother had malabsorption syndrome
23	16	M	3	None	Severe P.V.A.	3·8	26	0·8	0	13·6	Decreased iron content	Folate deficiency anaemia as a child
24	59	M	2	Dapsone	Normal	5·0	—	3·2	—	35·8	Normoblastic hyperplasia	
25	58	F	2	„	S.V.A.	5·3	45·7	1·0	52	18·8	„ „	
26	27	M	13	„	Normal	5·3	26	1·4	88	18·3	„ „	Diarrhoea
27	50	F	2	„	S.V.A.	13	46·7	1·5	62	21·2	Early megaloblastic change	„
28	47	M	8	„	Normal	4·0	53	0·7	34	30·2	Normoblastic hyperplasia	
29	48	F	4/12	None	P.F.V.A.	4·2	38	4·6	20	17·1	Normal	

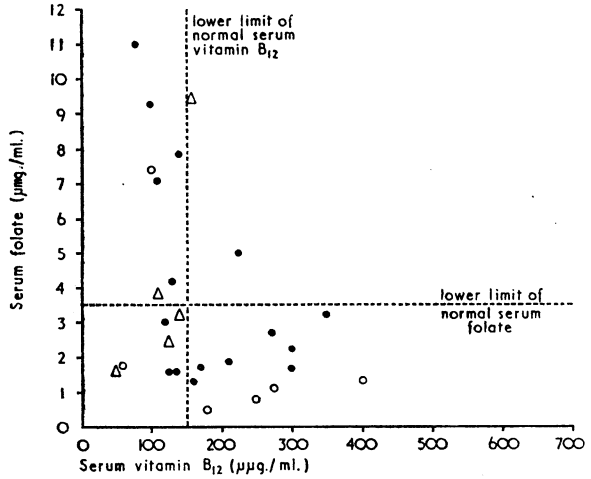
* 5 g. dose of xylose. P.F.V.A. = Partial focal villous atrophy. P.V.A. = Partial villous atrophy. S.V.A. = Subtotal villous atrophy. Sulphas = Sulphamethoxypyridazine.

tial villous atrophy and five the more severe condition of subtotal villous atrophy. There seems to be a poor correlation between the anatomical abnormality and any functional disability or the presence of symptoms (see Table I).

TABLE II.—*Results of Jejunal Biopsies*

	Normal		Abnormal			Total
Dissecting microscope	Fingers and/or leaves		Convolutions	Mosaic pattern	Flat	
No.	8		13	2	3	26
Histology	Normal	P.F.V.A.	P.V.A.		S.V.A.	
No.	6	2	13		5	26

Haematological Findings.—The results of marrow biopsies and Schilling tests are given in Table I. The correlation between serum folate and serum vitamin B_{12} is illustrated in the Chart, which shows that only one of the patients not receiving dapsone had normal levels of both in the blood. Eleven patients receiving dapsone showed normoblastic hyperplasia of the marrow. The peripheral blood of patients taking dapsone showed reticulocytosis with the presence of distorted spherocytes, Heinz bodies, and poikilocytosis. Six patients showed mild or intermediate megaloblastic changes in the marrow. Four of these six patients showed a serum folate lower than normal, and a normal serum vitamin B_{12} level, and were on dapsone treatment. Case 22 had an abnormal Schilling test, and in Cases 1 and 23 the Schilling tests were marginally abnormal.



Correlation between serum folate and serum vitamin B_{12} (27 patients). O=Early megaloblastic change. △= No dapsone treatment.

Faecal Fat.—The average daily faecal fat was estimated in 25 patients and found to be more than 5 g./day in seven. These seven are among those most severely affected.

Glucose Tolerance Tests.—Eight patients had maximum blood sugar rises of less than 30 mg./100 ml. at one hour, and three showed blood sugar rises between 30 and 40 mg./100 ml. A plateau type of glucose tolerance test did not correlate with any other feature—biochemical, haematological, or clinical.

Xylose Tolerance Tests.—Four patients had both an abnormal urinary excretion and depressed plasma levels of xylose. In Cases 1, 2, and 10 the urinary excretion alone was measured, and was found to be considerably below normal. These seven patients are among those most severely affected.

Radiological Studies.—Seven of the 23 patients who had a barium-meal examination showed changes associated with malabsorption. In Case 22 the passage of barium through the gut was extremely slow and there were changes suggestive of adhesions. Two cases showed some mild dilatation and segmentation only, and were classed as equivocal. Cases 1 and 2 showed thinning of the bones.

Serum Calcium, Serum Alkaline Phosphatase.—No patient has shown a persistently lowered serum calcium. Case 21 had an alkaline phosphatase of 19.7 i.u./100 ml., and this was probably due to her liver disease.

Serum Proteins.—Only one of the 28 patients who underwent this investigation had a low serum albumin (Case 13—3.1 g./100 ml.). Case 21 had a diffuse increase in gamma-globulins—probably due to her liver disease.

Discussion

In these patients 70% of those who had jejunal biopsies had either partial villous atrophy or subtotal villous atrophy. The proportion of patients affected is similar to that found by Marks *et al.* (1967) and Fraser *et al.* (1967).

It is well recognized that there is a poor correlation between jejunal mucosal abnormality and small-intestine function as determined by the conventional laboratory tests, including small-intestinal barium meal (Frazer, 1962 ; Cooke, Fone, Cox, Meynell, and Gaddie, 1963). Our results similarly show this lack of correlation between structure and function. Thus of the 18 patients with abnormal jejunal biopsies, only six had an increased faecal fat excretion. It follows that functional abnormality of the gut does not necessarily depend on an easily detectable morphological change and that marked deviations from normal morphology may provoke surprisingly little functional deficit. We hope to shed some light on this problem by more detailed cytological as well as histological studies when re-biopsies after treatment are compared with these pretreatment biopsies. In addition, the patients with biochemical evidence of malabsorption and with abnormal biopsies were often free of bowel symptoms—for example, Cases 13 and 22. Similarly the eight patients with diarrhoea showed no consistent features, though five of the seven who had a jejunal biopsy showed abnormalities (see Table I).

Dapsone is known to cause a mild haemolysis in most patients, and as 23 of our patients were receiving this drug the haematological results are difficult to interpret. Fürst, Möller, Rorsman, and Tryding (1964) found reduced levels of serum vitamin B_{12} and folate in some of their patients with dermatitis herpetiformis being treated with dapsone, and they attributed this to the drug-induced haemolysis. Fry *et al.* (1967) similarly found that many of their patients with dermatitis herpetiformis had a lowered serum folate concentration. However, three of our patients had depressed levels of both vitamin B_{12} and folate and were not receiving dapsone treatment. Three patients had an abnormal Schilling test, and it seems that the lowered serum vitamin B_{12} and folate and the consequent megaloblastic changes in some patients may be due in part to the intestinal lesion.

It seems that in some cases of dermatitis herpetiformis the intestinal lesion is of considerable importance and is associated with a malabsorption syndrome (Cases 1 and 2). Seven other patients had diarrhoea of varying severity but did not seem to have any other clinical evidence of malabsorption. In addition one patient (Case 23) had had what was described as a "folate deficiency" anaemia of childhood, and we suggest that this may have been an early manifestation of the small-bowel lesion. The brother of Case 22 had a severe malabsorption syndrome, and it can be seen from Table I that this patient had biochemical evidence of malabsorption, though, apart from being 18% underweight, he seemed to have none of the clinical sequelae.

The steatorrhoea and jejunal mucosal changes seen in some patients with widespread skin disease, especially psoriasis and eczema, are now well documented (Shuster and Marks, 1965 ; Fry, McMinn, and Shuster, 1966 ; Shuster, Watson, and Marks, 1967). It should be emphasized that patients with dermatitis herpetiformis rarely have widespread skin involvement of comparable extent, and when controlled by dapsone

have but few if any skin lesions. Thus it is not likely that the same mechanisms are involved as in the dermatogenic enteropathy of Shuster.

In addition, jejunal mucosal changes in dermatitis herpetiformis occur in a much higher proportion of patients than in dermatogenic enteropathy and they tend to be of a more severe nature. Two of the four patients who were investigated before starting dapsone therapy had jejunal mucosal abnormalities, and one patient on sulphamethoxypyridazine also had this abnormality. It therefore seems unlikely that dapsone itself is responsible for the changes that are seen.

The relation between the jejunal lesion and the skin disorder remains unsolved. Certainly in one of our patients (Case 23) the bowel lesion may have antedated the skin disease. Rarely in the course of ulcerative colitis a dermatitis-herpetiformis-like skin disease is seen (Forman, 1966). It is therefore possible that the abnormality of the small intestine precedes the skin disease, though we are inclined to the view that both the skin and the gut disorder are caused by a common agent.

It is difficult to explain the presence in this series of one patient with proved cirrhosis (Case 21), one with an enlarged liver and spleen of unknown origin (Case 3), and one with splenomegaly and jaundice (Case 11). The patient with cirrhosis had taken dapsone for 12 years before her treatment was changed to sulphamethoxypyridazine. Case 3, the man with hepatic and splenic enlargement, had been taking dapsone for 12 years, while Case 11, the man with splenomegaly and jaundice, had been taking dapsone for a few months only. We are now considering the possibility that in some patients dapsone may be hepatotoxic, though we are aware of no other patient with abnormal liver function.

In conclusion, it appears that in nearly three-quarters of our patients with dermatitis herpetiformis there were jejunal mucosal abnormalities and in some cases intestinal malabsorption. One patient appears to have been relieved of both his malabsorption syndrome and skin disease by a gluten-free diet, as was one patient of Van Tongeren *et al.* (1967), and we are investigating the effect of a gluten-free diet on many of the other patients in this series. In view of the many patients with abnormally low serum folate and vitamin B_{12} levels and some with megaloblastic changes in the marrow we are now giving our patients folic acid and vitamin B_{12} supplements when this measure is indicated.

Summary

Twenty-nine patients with dermatitis herpetiformis were investigated by jejunal biopsy and tests of intestinal function. Twenty (70%) of the patients were found to have jejunal mucosal abnormalities on biopsy. Two suffered from a malabsorption syndrome, one of whom was treated with a gluten-free diet and whose skin and gut disorder subsequently remitted. Many patients were found to have a low serum vitamin B_{12} and folate and six had megaloblastic changes in the marrow. The possible clinical outcomes are emphasized.

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