The parasites are non-pigmented, inhabit the red blood cells, and may be mistaken for malaria in humans. The disease is familiar to farmers as "redwater" in cattle. Only three human cases have been authenticated, and all, before being infected, had had splenectomies.

Unlike the two previous human cases of babesiosis the Irish patient rarely walked through fields, and no cases of redwater had been reported for years in the neighbourhood of his home. The evidence points to his having acquired the infection in County Galway in mid-August, while on a short caravan holiday. Further weight is added to this belief because three cases of redwater in cattle were reported from that area in that month (MacCon, 1967). A field study beside the caravan was undertaken at a later date (Garnham, Donnelly, Hoogstraal, Kennedy, and Walton, 1969).

In contrasting the haemoglobinuria of babesiosis in cattle with blackwater in humans, Thomson (1924) wrote that the former is always associated with numerous parasites in the peripheral blood, whereas malaria parasites are usually not numerous at the onset of blackwater. Maegraith (1946) stated that malaria parasites are found in the peripheral blood in about half the active cases of blackwater fever. There is a parallel to the redwater of cattle in the blood findings of the human case now reported: Shute (1967), commenting on the latter, pointed out that maximum parasitaemia seems to occur when redwater is at its height. Škrabalo and Deanovic (1957) thought that piroplasmosis should be added to the list of causes of acute haemolytic anaemia in man.

The American patient, who had had a splenectomy for hereditary spherocytosis, was initially regarded as a case of malaria and treated with chloroquine. Perhaps other patients in the past—with or without a spleen—have also been misdiagnosed as malaria, treated as such, and recovered.

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ADDENDUM.—A further case of human babesiosis has recently been reported (Benson, Galdi, Altman, and Fiurmara, 1969). The patient, a 59-year-old woman, who was treated with chloroquine, recovered. This is the first account of babesiosis in a human being with an intact spleen. The parasite is stated possibly to be *Babesia rodhaini*, a rodent species.

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Results of Treatment of Dermatitis Herpetiformis with a Gluten-free Diet after One Year

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Summary: Twenty-one patients with dermatitis herpetiformis initially controlled by dapsone or sulphonamides have been treated with a gluten-free diet and reassessed at intervals for up to 15 months (mean 11·9 months). According to routine histological and dissecting microscope criteria the small-bowel lesion improved in 10, but when mean epithelial cell height was used as a measure 15 patients improved. Five of the patients with diarrhoea improved after withdrawing gluten from the diet but none reverted to completely normal bowel habit. The tests for malabsorption showed little improvement in the treatment period. Twelve patients needed less dapsone to control their skin complaint, the mean dose falling from 144 mg. to a mean of 70 mg. per day; of these three stopped using this drug altogether.

Introduction

The association of disease of the small intestine with dermatitis herpetiformis is now well documented (Marks, Shuster, and Watson, 1966; Van Tongeren, Van der Staak, and Schillings, 1967; Fry, Keir, McMinn, Cowan, and Hoffbrand, 1967; Fraser, Murray, and Alexander, 1967; Marks, Whittle, Beard, Robertson, and Gold, 1968; Bendl and Williams, 1968). The similarities of the jejunal disorder to the coeliac syndrome have raised the question of the effectiveness of a gluten-free diet in dermatitis herpetiformis. There are two ways in which such treatment may be beneficial; the small-bowel disorder could be improved, the skin disease remit, and the need for dapsone be eliminated. Fry, McMinn, Cowan, and Hoffbrand (1968) described the treatment of seven patients and Shuster, Watson, and Marks (1968) the treatment of five patients with gluten-

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free diet. While both groups found improvement in the enteropathy, only the first authors thought that the skin had also improved.

We now report the results of treatment of 21 patients with dermatitis herpetiformis, controlled by dapsone or sulphonamides with a gluten-free diet after one year.

Patients and Methods

Twenty of the patients were among those reported by Marks *et al.* (1968). All had typical dermatitis herpetiformis with an itchy vesicular eruption which initially responded to dapsone or sulphapyridine. The patients were admitted for initial assessments and for follow-up jejunal biopsy examinations at six-month intervals.

Jejunal biopsies were obtained with a Crosby capsule under radiological control. They were examined with a Watson binocular dissecting microscope immediately after retrieval, and photographed. The biopsy specimens were classified according to the method of Holmes, Hourihane, and Booth (1961). "Fingers and leaves" described the appearance of the villi of the normal jejunum and duodenojejunal flexure; convolutions, the mosaic pattern, and the completely flat mucosa indicated increasing degrees of abnormality. The histological classification used was the accepted one of normal mucosa, partial villous atrophy, and subtotal villous atrophy (Fone *et al.*, 1960). We also graded partial villous atrophy into severe, moderate, and mild degrees, according to the condition of the lining epithelial cells, the degree of effacement of the villi, the depth of the crypts, and the amount of inflammatory cell infiltrate. Histological sections were cut at 3μ so that more cytological detail could be seen. The heights of 20 epithelial cells at the sides of the villi were measured in each section by means of an eyepiece graticule. The following tests were also performed, and, if abnormal, were repeated at intervals.

Xylose Tolerance Test.—A 25-g. dose was given and the five-hour urinary excretion and the blood levels after one and two hours were measured. Xylose was estimated by the method of Roe and Rice (1948). The lower limit of normal excretion of xylose in five hours is 17% of the ingested dose (4·2 g. in a 25-g. test). A level of 26 mg./100 ml. in the blood one to two hours after ingestion was regarded as the lower limit of normal.

Glucose Tolerance Test.—A 50-g. oral loading dose of glucose was used. Blood sugar levels were estimated by a method based on that of Haslewood and Strookman (1939). A rise in the blood sugar of less than 30 mg./100 ml. over the fasting value was regarded as abnormal.

Faecal Fat.—Stools were collected over periods of three to five days while patients were on normal diets. Faecal fat was estimated by the method of Van de Kamer, Huinink, and Weyers (1949).

Serum vitamin B_{12} and folate levels were estimated by bioassay with *Lactobacillus leishmanii* and *L. casei*, respectively. The gluten-free diet was instituted and supervised by the dietetic department. Supplements of folic acid (5 mg. b.d.) were given to 14 patients who had a serum folate level of less than 4 ng./ml. Supplements of vitamin B_{12} (1,000 μg./month) were given to nine patients who had a serum vitamin B_{12} level below 150 ng./ml. Both these supplements were continued until the blood levels became normal, and in any case for not longer than four months. Six patients had early or moderate megaloblastic changes in the marrow, which also became normal after this treatment. At each visit the amount of dapsone that had been necessary to suppress the appearance of irritant skin lesions was recorded.

Results

Six of the patients had diarrhoea, five experienced some decrease in frequency of bowel motion, but none reverted to a normal bowel habit. One had no change in his diarrhoea. There was a slight increase in the average weight of the group, but this was not of statistical significance. Some patients said that they felt better, but there was no striking change in the general health of this group of patients as a whole.

Jejunal Biopsy.—Twenty-one patients have been reassessed after periods of 8 to 15 months (average 11·9 months) on the gluten-free diet (Table I). With the histological grade and the dissecting microscope appearance only, it can be seen that 10 patients improved, six remained the same, and three became worse (Table II). Two were normal to start with and remained so. Improvement is more evident if the mean epithelial cell height is examined: 15 patients showed a statistically significant increase. The overall mean epithelial cell height was found to be increased after the gluten-free diet by 1·1μ, and this is also statistically significant $p=0{\cdot}01$). One of the three patients

TABLE II.—*Summary of Findings of Jejunal Biopsies Before and After Gluten-free Diet*

	Before Diet	After Diet
Dissecting microscope appearance:		
Fingers and/or leaves	3	9
Convolutions	15	10
Mosaic	1	2
Flat	2	0
Histology:		
Normal	3	6
Mild P.V.A.	4	3
Moderate P.V.A.	1	2
Severe P.V.A.	9	6
S.V.A.	4	4

TABLE I.—*Results of Serial Jejunal Biopsy in Patients with Dermatitis Herpetiformis Treated with a Gluten-free Diet*

Case No.	Biopsy I				Biopsy II				Biopsy III		
	Dissecting Microscope Appearance	Histology	Mean Epithelial Cell Height (μ)	Months on Diet before Biopsy II	Dissecting Microscope Appearance	Histology	Mean Epithelial Cell Height (μ)	Months on Diet before Biopsy III	Dissecting Microscope Appearance	Histology	Mean Epithelial Cell Height (μ)
1	Con.	Mild P.V.A.	25·1	6	Con.	Mod. P.V.A.	27·5	14	Leaves	N.	29·5
3	Mosaic	Severe P.V.A.	28·5	8	Mosaic	S.V.A.	18·4	—	—	—	—
4	Con.	Severe P.V.A.	25·7	5	Con.	Severe P.V.A.	—	14	Leaves	Mod. P.V.A.	22·4
5	Con.	S.V.A.	22·6	8	Con.	Severe P.V.A.	25·3	13	Fingers and leaves	N.	28·9
6	Con.	Mild P.V.A.	18·9	5	Flat	Severe P.V.A.	—	13	Leaves	N.	26·0
7	Con.	Severe P.V.A.	21·2	6	Con.	Mod. P.V.A.	—	14	Con.	Severe P.V.A.	22·5
9	Con.	Severe P.V.A.	20·7	7	Leaves	N.	—	15	Leaves and Con.	Mod. P.V.A.	24·8
10	Con.	Severe P.V.A.	23·1	6	Con.	Severe P.V.A.	18·8	—	—	—	—
11	Con.	Severe P.V.A.	18·3	6	Con.	Severe P.V.A.	—	13	Con.	S.V.A.	20·3
14	Con.	Severe P.V.A.	20·2	4	Con.	Mod. P.V.A.	—	13	Leaves	Mild P.V.A.	23·3
15	Con.	Mod. P.V.A.	17·4	3	Con.	Severe P.V.A.	19·2	11	Con.	Severe P.V.A.	18·0
17	Con.	Mild P.V.A.	19·2	6	Leaves	N.	22·7	13	Con.	S.V.A.	15·9
18	Fingers	N.	23·8	8	Leaves	Mild P.V.A.	20·1	—	—	—	—
20	Con.	S.V.A.	22·3	5	Con.	Mod. P.V.A.	28·6	13	Con.	Severe P.V.A.	24·5
21	Con.	Severe P.V.A.	17·5	7	Con.	Severe P.V.A.	20·3	12	Con.	Severe P.V.A.	24·7
22	Fingers	N.	21·2	7	Con.	N.	—	13	Fingers	N.	25·3
23	Con.	Severe P.V.A.	17·1	9	Leaves and Con.	Mild P.V.A.	—	13	Leaves and Con.	Mild P.V.A.	17·6
25	Flat	S.V.A.	20·3	5	Con.	Severe P.V.A.	—	12	Con.	Severe P.V.A.	23·3
26	Fingers	N.	21·6	13	Fingers	N.	22·6	—	—	—	—
27	Con.	Mild P.V.A.	25·8	8	Fingers	N.	25·0	—	—	—	—
32	Flat	S.V.A.	—	9	Mosaic	S.V.A.	—	—	—	—	—

Con. = Convol utions. S.V.A. = Subtotal villous atrophy. Mod. P.V.A. = Moderate partial villous atrophy. P.V.A. = Partial villous atrophy. N. = Normal.

TABLE III.—*Results of Serial Tests of Intestinal Function in Dermatitis Herpetiformis Patients Treated with a Gluten-free Diet*

Case No.	Initial Investigation					Final Investigation			
	Daily Faecal Fat Excretion (g./Day)	G.T.T. Max. Rise (mg./100 ml.)	X.T.T. 5-hour Excretion in Urine (g.)	X.T.T. Blood Levels at 1–2 Hours (mg./100 ml.)	Time Between Investigation (Months)	Daily Faecal Fat Excretion (g./Day)	G.T.T. Max. Rise (mg./100 ml.)	X.T.T. 5-hour Excretion in Urine (g.)	X.T.T. Blood Levels at 1–2 Hours (mg./100 ml.)
1	4·7	20	5·8	30	14	4·2	60	4·3	67·0
3	8·8	88	1·7*	—	8	8·2	32	10·8	52·8
4	2·9	30	2·9	35	5	—	66	1·6	33·4
5	1·3	52	3·9/1·35	30	8	3·3	62	5·6	33·3
6	—	40	3·0	54	13	—	66	4·4	46·9
7	5·0	65	0·9*	—	14	2·2	77	5·5	44·5
9	1·8	42	5·0	21	7	4·2	69	5·7	36·2
10	2·0	27	5·5	48	6	—	34	3	13·9
11	10·6/6·6	89	3·9	20	6	6·3	70	5·3	42·4
14	2·8	45	6	44·3	13	—	50	8·3	41·1
15	1·1	63	5·3	41	4	8·8	31	5·2	40
17	2·3	81	3·0	27	6	7·5	18	4·9	40·4
18	4·4	56	1·7	19	8	2·1	50	3·1	45·2
20	7·3	18	0·26	15·8	13	11·5	38	0·94	22·9
21	0·5	0	3·8	26·5	12	0·9	20	3·9	23·2
22	3·2	69	5	—	6	4·4	12	7·3	65·2
23	1·0	52	5·3	33·2	13	1·5	50	3·5	23
25	4·3	71	13·0	46·7	5	6·2	53	4·1	56·7
26	0·7	34	4	44	13	—	—	7·5	47
27	4·6	18	4·2	25	13	7	35	4·6	47
32	0·3	35	4·3	30	9	—	—	—	—

* 5 g. dose of xylose.

whose biopsy specimen indicated a deterioration after the diet by histological criteria was pregnant at the time of final biopsy (Case 3); Case 10 was also pregnant at the time of final biopsy, and her jejunal mucosa showed no change.

Tests for Intestinal Malabsorption.—The results of glucose tolerance test, xylose tolerance tests, and average daily faecal fat excretions are given in Table III and are summarized in Table IV. In some cases there seemed to be a slight functional improvement after the diet.

TABLE IV.—*Summary of Results of Tests of Intestinal Function Before and After Gluten-free Diet*

Dietary Status	Xylose Tolerance Test		Glucose Tolerance Test		Faecal Fat Excretion	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Before G.F.D.	14	5	15	6	15	3
After G.F.D.	15	3	16	4	7	5

Dapsone Requirement.—Twenty patients took dapsone for a mean period of 12 months while on the diet (range 8 to 16 months). The mean dose before starting the diet was 144 mg./day (range 50 to 300 mg./day). The mean dose after the diet was 70 mg./day (range 0 to 120 mg./day). Twelve patients required less dapsone after the diet, including three who were able to stop taking the drug. Case 17 required no dapsone after 16 months' treatment with the gluten-free diet. The skin disease subsequently relapsed two weeks after a normal diet was started, and a daily dose of 100 mg. of dapsone was necessary for control. She then recommenced a gluten-free diet, and after two months needed only one or two 100-mg. tablets a week. Case 3 was able to stop taking dapsone after 10 months on the diet and while pregnant. She started a normal diet and has not needed to take further dapsone in the past year. Case 21 could stop taking dapsone after one year on gluten-free diet. He recommenced a normal diet and needed no dapsone for at least two months before he was lost to follow-up.

Illustrative Case Reports

Case 21

A youth aged 16 had typical dermatitis herpetiformis (histologically proved) for three years, controlled by dapsone 100 mg./day. Weight 158 lb. (71·7 kg.). Jejunal biopsy showed severe partial villous atrophy (mean epithelial cell height 17·5 μ). He was said to have had folic-acid-deficiency anaemia as a child. Xylose and glucose tolerance tests were abnormal (Table III). Serum folic acid and serum vitamin B_{12} levels were 1·7 ng./ml. and 55 pg./ml., respectively (before starting dapsone). Gluten-free diet was started in July 1967. Jejunal biopsy February 1968 showed severe partial villous atrophy (mean epithelial cell height 20·3 μ). Jejunal biopsy July 1968 showed severe partial villous atrophy (mean epithelial cell height 24·7 μ). Some improvement in glucose tolerance test occurred. Serum folic acid and vitamin B_{12} levels subsequently became normal. Weight 166 lb. (75·3 kg.). Dapsone requirement nil. Remained clear on normal diet after two months.

Comment.—The "folic-acid-deficiency anaemia" was probably the result of malabsorption antedating the onset of the skin disease. The severe jejunal mucosal changes were unchanged by a gluten-free diet. The dapsone requirement was reduced to nil after 12 months on gluten-free diet and there was no recurrence on resumption of normal diet.

Case 5

A man aged 63 had typical dermatitis herpetiformis for many years, controlled by 75 mg. of dapsone daily. Weight 146 lb. (66·2 kg.). He had had diarrhoea for the previous six to seven years (four or five loose motions daily). Jejunal biopsy showed severe partial villous atrophy (mean epithelial cell height 22·6 μ). The xylose tolerance test was equivocal and the other tests for malabsorption were normal (Table III). Gluten-free diet was started July 1967. Jejunal biopsy March 1968 showed severe partial villous atrophy (mean epithelial cell height 25·3 μ). Jejunal biopsy August 1968 was normal (mean epithelial cell height 28·9μ). Dapsone requirement August 1968, 50 mg./day. Bowel habit improved but still troublesome on occasion with diarrhoea two to four times a day. Weight 146 lb. (66·2 kg.).

Comment.—This patient had severe jejunal mucosal changes with slight if any change in function after dietary treatment. He had diarrhoea without steatorrhoea. There was improvement in the jejunal biopsy after the gluten-free diet but little reduction in dapsone requirement.

Case 25

A woman aged 50 had a 20-year history of typical dermatitis herpetiformis (histologically proved). Weight 144 lb. (65·3 kg.). Severe diarrhoea had occurred in the previous five years. Dapsone requirement 200 mg./day. The jejunal biopsy in July 1967 showed subtotal villous atrophy (mean epithelial cell height 20·3 μ). Tests of intestinal function were normal (Table III). Serum folic acid and serum vitamin B_{12} levels were 0·5 ng./ml. and 180 ng./ml., respectively. The marrow showed early megaloblastic change. Gluten-free diet started August 1967. Jejunal biopsy July 1968 showed severe partial villous atrophy. Serum folic acid and serum vitamin B_{12} levels, and marrow examination were normal. Weight 144 lb. (65·3 kg.), dapsone requirements 50 mg./day. Definite improvement in diarrhoea occurred but bowel habit did not return to normal.

Comment.—This patient had typical dermatitis herpetiformis with diarrhoea. Severe mucosal changes in small bowel did not show any definite improvement after gluten-free diet. There was a considerable decrease in dapsone requirement.

Discussion

Most patients with the adult type of coeliac syndrome respond clinically to treatment with a gluten-free diet. The mucosal lesion seen in the small bowel also responds to withdrawal of gluten, but the improvement is incomplete as well as lagging behind the clinical response (Benson, Kowlessar, and Sleisenger, 1964 ; McDonald, Brandborg, Flick, Trier, and Rubin, 1964 ; Madanagopalan, Shiner, and Rowe, 1965). There are some patients, however, who do not improve after gluten withdrawal (Pink and Creamer, 1967). In five of our patients the diarrhoea improved (Cases 1, 5, 6, 10, and 25), though in none did the bowel habit revert to normal, and there was no change in their general health. The serial jejunal biopsies did, however, show improvement of the same order as that seen in adult coeliac disease.

Some patients in this series showed early or moderate megaloblastic changes in the marrow, and many had serum levels of folic acid and vitamin B_{12} well below normal when studied initially. For this reason patients were given folic acid 5 mg. b.d. by mouth or vitamin B_{12} intramuscularly 1,000 μg./month when indicated by the haematological findings, or both. These supplements were continued only until the blood levels were normal. Large doses of folic acid have been given in tropical sprue, and slight improvement in the appearance of the jejunal mucosa is said to occur after this treatment (Sheehy, Baggs, Perez-Santiago, and Floch, 1962). The small dose given in this study for short periods of time did not seem to have an appreciable effect on the jejunal mucosa, as biopsies taken after the folic acid had been stopped showed the same trend to improvement.

Our findings indicate that improvement in the intestinal lesions occurs after a gluten-free diet and are in agreement with those of Fry *et al.* (1968) and Shuster *et al.* (1968).

Effect of Gluten-free Diet on Skin Disease.—The decreased dependence on dapsone seen in our patients following dietary treatment has not been the experience of Shuster *et al.* (1968). Our finding is also difficult to explain in the light of the occurrence of dermatitis herpetiformis in the course of the coeliac syndrome treated with a gluten-free diet (Fraser, Ferguson, and Murray, 1968 ; Dyer and Verbov, 1968). None the less, Fry *et al.* (1968) also reported that some dermatitis herpetiformis patients needed less dapsone and that two could stop taking it altogether after a gluten-free diet. The apparent beneficial effect of the dietary treatment on the skin disease seen in this study may be artifactual for the following reasons: (1) the course of dermatitis herpetiformis is remittent and unpredictable, (2) the absorption of dapsone may be improved after gluten withdrawal, allowing the suppressive effect to be obtained with a smaller dose, and (3) the constant surveillance and repeated investigation of these patients may itself have had a considerable placebo effect. From our data, however, it may be concluded that, so far as their skin disease is concerned, at least some patients are helped by withdrawl of gluten. The use of dietary treatment makes construction of a formal double-blind trial to test the effectiveness of gluten-free diet in dermatitis herpetiformis difficult, but the final answer to this problem lies in the results of such an investigation. In any event a gluten-free diet is indicated in those patients with the small-bowel lesion to forestall the possible sequelae of an absorptive defect such as osteomalacia and both megaloblastic and iron-deficiency types of anaemia.

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Requests for reprints to R. Marks.

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