Response of the skin in dermatitis herpetiformis to a gluten free diet, with reference to jejunal morphology

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SUMMARY Twenty-one patients with dermatitis herpetiformis have been on a gluten free diet and regularly followed up for at least one year (mean four years). Eighteen patients had a 'flat' mucosal appearance (grade III), one patient had moderately severe mucosal abnormality (grade II), one patient had mild mucosal abnormality (grade I), and one patient had a normal mucosal appearance (grade 0). On the diet, 10 patients had no skin rash and took no dapsone, seven patients controlled the skin rash on a lower dose of dapsone, and four noticed no improvement. There was no correlation between pre-diet jejunal morphology and response of the skin. A repeat jejunal biopsy, on the gluten free diet, was possible in 15 patients. While all those with skin improvement showed some improvement in jejunal morphology, there was no association between the degree of skin improvement and the degree of recovery of the jejunal mucosa.

Following the work of Marks *et al.* (1966), dermatitis herpetiformis (DH) is recognised as being associated with a high incidence of abnormality in the jejunal mucosa which is identified with that of coeliac disease (Brow *et al.*, 1971) and which improves morphologically with gluten withdrawal from the diet (Fry *et al.*, 1968, 1969; Shuster *et al.*, 1968; Marks and Whittle, 1969; Weinstein *et al.*, 1971; Fry *et al.*, 1972). The skin rash also is claimed by Fry *et al.* (1973) and by Heading *et al.* (1976) to show improvement but this is doubted by Marks and Shuster (1970), Weinstein *et al.* (1971), and by Marks (1974). A point considered in detail only by Fry *et al.* (1969) is the state of the jejunal mucosa in relation to the response of the skin lesion while on a gluten free diet. The purpose of this paper therefore is to repeat such studies.

Methods

PATIENTS

Twenty-one patients, 12 female and nine males, varied in age from 16 to 58 years (mean 37 years) at the time of diagnosis of dermatitis herpetiformis. The length of history of the disorder to its diagnosis

ranged from two months to 21 years (mean 5½ years) and the time of follow-up from diagnosis to the start of a gluten free diet ranged from one month to 17 years (mean 4 years). None of the patients in this series was related, but two patients (one male, one female) had first-degree relatives with biopsy proven coeliac disease, but no dermatitis herpetiformis. All patients were alleged to have been on a strict diet for at least 12 months and in one case 10 years (mean four years). The patients in this series were unselected except by their willingness to adhere to a strict gluten free diet. Each patient has been regularly followed-up in the Nutritional and Intestinal Unit while on the gluten free diet.

DIAGNOSIS OF DERMATITIS HERPETIFORMIS

The diagnosis was based on the characteristic intensely irritating vesicular eruption sited symmetrically on elbows, exterior surfaces of arms, scapular area, scalp, buttocks, and the front of the knees, together with rapid clearance of the skin lesions with dapsone. Any patient with an atypically distributed rash or a rash which did not rapidly resolve with dapsone was excluded even if they had coeliac disease. Eleven patients had biopsies taken of the vesicles, the histology of which was compatible with dermatitis herpetiformis. Twenty of the 21 patients had uninvolved skin biopsied from the

thigh and stained for IgA deposits using direct immunofluorescence (Seah *et al.*, 1972).

JEJUNAL BIOPSIES

Peroral jejunal biopsy, using a multiple biopsy capsule (Roy-Choudhury *et al.*, 1964), was performed on each patient before starting on a gluten free diet, obtaining between two and five specimens at a time and each invariably much larger than the single specimens obtained by a Crosby capsule. The resulting specimens were examined by dissecting microscopy; 5 μ sections of each piece of jejunum were cut and stained with haematoxylin and eosin for histological examination and for cell counting. Each biopsy obtained was graded from 0 to III using the classification of Roy-Choudhury *et al.* (1966) and the lamina propria and epithelial cellular infiltrate were counted using the technique of Holmes *et al.* (1974) and Ferguson *et al.* (1975). Jejunal biopsies were repeated in 15 patients after at least one year on a gluten-free diet. Five patients refused further jejunal biopsies and one patient was pregnant at the time of this study.

ANTIRETICULIN ANTIBODIES

The sera of 16 of the 21 patients were tested, while on the gluten free diet for the presence of IgG and IgA class antireticulin antibodies using the standard immunofluorescent technique (Seah *et al.*, 1971).

Results

JEJUNAL HISTOLOGY

The classification of the jejunal histology and the mucosal and epithelial cell counts before and after a gluten free diet are detailed in Table 1 and the relationship of the improvement of the skin rash and the mucosal change in Table 2. There was no corre-

lation between the skin response and the initial jejunal cell counts.

Of the six patients not rebiopsied, five had grade III and one grade II biopsies initially. One of the grade III patients was pregnant but the other five refused a repeat biopsy. Four of these patients (three grade III and one grade II) were entirely without skin or bowel symptoms and did not feel that a repeat biopsy was necessary. The remaining patient (grade III) had no bowel symptoms but still required a small dose of dapsone to control his rash and he too would not agree to a repeat biopsy.

SKIN RESPONSE TO GLUTEN FREE DIET (Table 2)

Currently, 10 patients have no skin rash and take no dapsone and, in seven patients, the rash has greatly improved on the diet, requiring a much lower dose of dapsone. The mean daily dose of dapsone for these patients before the diet was 143 mg/day whereas after at least one year on the diet it was 66 mg/day (mean difference, 77 mg/day $\pm$ 22 mg/day; $N = 7$; $t = 3.38$; $P < 0.02$). Four of the 21 patients have noticed no benefit to their skin whatsoever on the diet, including the patient with normal histology of jejunal mucosa.

TIME ON GLUTEN FREE DIET RELATED TO SKIN RESPONSE

Patients with no rash, who took no dapsone, had been on the diet for 1½ to 9½ years (mean 4½ years). Those with reduced dapsone requirements had been on the diet for 1½ to 7½ years (mean 4½ years). The non-responders have been on the diet for one to 2½ years (mean 2¼ years).

IGA SKIN DEPOSITS AND SKIN RESPONSE (Table 2)

Ten of the 20 patients who were examined for the

Table 1 Jejunal biopsy morphology and cell counts on normal and gluten free diets

	No.	Lamina propria				Epithelium	
		Plasma cells per mm ²		Lymphocytes per mm ²		Lymphocytes per mm length	
		Mean	SE	Mean	SE	Mean	SE
Normal subjects	17	1544	98	2962	159	50	4
Patients grade III on ND	18	8849	654	1460	150	147	9
Same patients on GFD							
Grade III	1	8280	—	1640	—	112	—
Grade II	8	4917	327	1617	97	130	6
Grade I	4	2760	257	1600	165	77	8
Patient grade II on ND	1	3600	—	2040	—	126	—
Patient grade I on ND	1	1820	—	3020	—	104	—
Same patient grade I on GFD	1	2200	—	2560	—	29	—
Patient grade 0 on ND	1	640	—	1160	—	48	—
Same patient grade 0 on GFD	1	760	—	1080	—	36	—

ND: normal diet. GFD: gluten free diet.

Table 2. Improvement of skin rash and mucosal dosage

Case no.	Sex	Jejunal biopsy grade		Skin response	Skin IgA	Serum ARA	
		Initial	GFD			IgG	IgA
21	M	III	ND	1	NEG	NEG	NEG
5	F	III	ND	1	NEG	POS	NEG
6	F	III	ND	1	POS	POS	NEG
11	M	III	ND	1	ND	ND	ND
15	M	II	ND	1	POS	NEG	NEG
7	F	III	I	1	POS	ND	ND
11	F	III	I	1	NEG	POS	NEG
18	F	III	I	1	NEG	NEG	NEG
4	F	III	II	1	POS	NEG	NEG
10	F	I	I	1	NEG	ND	ND
12	M	III	ND	2	NEG	NEG	NEG
3	M	III	I	2	POS	NEG	NEG
9	M	III	I	2	POS	NEG	NEG
2	F	III	II	2	NEG	NEG	NEG
6	M	III	II	2	POS	NEG	NEG
8	F	III	II	2	NEG	ND	ND
13	M	III	II	2	POS	NEG	NEG
14	M	III	II	3	NEG	ND	ND
19	F	III	II	3	POS	POS	NEG
20	F	III	III	3	NEG	POS	NEG
17	F	0	0	3	POS	NEG	NEG

ND: not done.

1: no rash, no dapsone. 2: rash controlled, less dapsone. 3: no change.

ARA: antireticulin antibodies. GFD: gluten free diet.

presence of IgA in areas of uninvolved skin, had a positive result ranging from an almost continuous line of deposit to an isolated patch on a single papilla. All 10 patients in whom IgA deposits were not found had the characteristic rash clearing rapidly with dapsone; four had vesicle biopsies consistent with dermatitis herpetiformis, and nine had a 'flat' jejunal mucosa. The patient with normal jejunal histology not responding to a gluten free diet but with a rapid response to dapsone had both a positive histological skin biopsy and IgA deposits in her uninvolved skin. The presence or absence of IgA skin deposits bore no relationship to the response of the skin rash or that of the jejunal mucosa to a gluten free diet.

ANTIRETICULIN ANTIBODIES ON GLUTEN FREE DIET (Table 2)

IgG class antireticulin antibodies were found in the serum of five patients but IgA class antireticulin antibodies were not found in any patients. The skin of three of the patients with a positive result showed an excellent response to a gluten free diet and two showed none, one showing improvement to grade II histology and the other improvement in cell count of the jejunal mucosa.

Discussion

Misdiagnosis is thought by Fry and Seah (1974) to be the explanation for the reported differences of

response of the skin in dermatitis herpetiformis to a gluten free diet, for they consider that the presence of IgA deposits is essential for the diagnosis and also that the papillary pattern of IgA deposits in the skin occurs only in dermatitis herpetiformis (Seah and Fry, 1975). The specificity of these findings has been doubted by Marks (1974), Alexander (1975) and Scott *et al.* (1976) while Ross *et al.* (1977) found IgA deposits in the dermo-epidermal junction and/or dermal papillae in eight of 16 coeliac patients and in seven of 54 control subjects. The incidence of IgA deposits in this series (50%) is considerably less than that reported by others which varies from 83 to 100% (Fry and Seah, 1974; Seah and Fry, 1975). However, Jablonska (1976) has stressed the difficulties of the technique, for a second biopsy may be necessary to produce a positive result even after 30 sections have been examined. The fact that only one biopsy from each patient was examined with a maximum of 10 sections may explain the low incidence in our patients. They did, however, have the clinical characteristics, histological features, and response to dapsone which, in the presence of coeliac disease, justifies the diagnosis of dermatitis herpetiformis (Alexander, 1975). Furthermore the lack of correlation in the present series between the presence of IgA deposits in the uninvolved skin and the response of the rash to a gluten free diet supports the doubts expressed about this finding being a prerequisite of the diagnosis.

Seventeen (81%) of our 21 patients had a significant improvement in their skin rash after at least

one year on a gluten free diet. Such improvements have, however, been attributed to factors such as the natural remittance of the rash, the variability of dapsone requirements (Marks and Shuster, 1970), improvement in dapsone absorption associated with the improvement of jejunal morphology, and the placebo effect of regular follow-up (Marks and Whittle, 1969). However, none of these factors appeared to play a part in this series. Thus spontaneous remission had not been noted before the diet and two noticed recurrence of rash after lapses with diet. All seven patients with reduced dapsone dosage noticed that the rash was easier to control and with less variation in dose while on a gluten free diet. Regular follow-up and surveillance had done no good to the patients before diet or to those four who did not respond to diet. Finally, Alexander *et al.* (1970) found no difference in dapsone absorption between patients on a gluten containing or a gluten free diet.

The improvement in the skin rash was unrelated to the state of the jejunal mucosa before the start of the diet. The one patient with the grade I biopsy before the diet lost the rash completely on the diet and, when biopsied during the diet, while there was no change in morphological grading, did show a dramatic fall in epithelial lymphocytes as has been described by Fry *et al.* (1972).

All those whose skin responded to the diet showed some morphological improvement in their jejunal mucosa but there was no correlation between the degree of improvement of the skin and the degree of recovery of the jejunal mucosa. Some excellent skin responders had a grade II biopsy while some partial skin responders had a grade I biopsy. Fry *et al.* (1973) stressed the importance of the length of time on diet for an optimal response. In our series the responders had been on the diet longer than the four non-responders, but there was no difference in time on the diet between the excellent and partial responders.

Marks and Whittle (1969) noted 10 of 21 patients showed morphological improvement in the jejunal mucosa but they did not link skin response and the state of the jejunal mucosa in the individual patients. This was done by Fry *et al.* (1969) who studied seven patients of whom three had abnormal biopsies and improved on a gluten-free diet. Taking the whole group, there was an increase in the mean height of the villi and of the surface epithelium together with a decrease of crypt height and a reversal of this improvement when gluten was reintroduced. All the patients except one showed a marked improvement, either losing their skin rash or showing a significant reduction of dapsone requirements. Weinstein *et al.* (1971) reported morphological improvement of the jejunal mucosa after 2½ to six months on a gluten

free diet in six patients with dermatitis herpetiformis with an initial flat biopsy but in only one patient was there any benefit to the skin from the diet. Fry *et al.* (1973) and Heading *et al.* (1976) made no reference to the jejunal morphology of their subjects while on a gluten free diet.

Of particular interest are the four patients who have not benefited from the diet. The patient with an initial grade 0 biopsy had no change in jejunal morphology or cellularity on the diet, and therefore had no evidence of an enteropathy despite an HL-A8 phenotype, suggesting that gluten is not a factor in the aetiology of the skin rash in every case. This is at variance with the view of Seah *et al.* (1976) that there is a conclusive association between the skin lesion in dermatitis herpetiformis and gluten intake. The three other non-responders had grade III biopsies before the diet and repeat biopsies on the diet showed no change in one and improvement to grade II in the other two. The lack of response in these patients may indicate some failure in dietetic control. Nevertheless, the grade II biopsies in these patients show no difference whatsoever from the grade II biopsies of the responders and these patients had been on the diet for as long as some of the responders.

An antireticulin antibody of IgG class has been reported in the serum of 17% of patients with dermatitis herpetiformis (Seah *et al.*, 1971; Lancaster-Smith *et al.*, 1975), which tended to disappear on a gluten free diet (Lancaster-Smith *et al.*, 1975). In the present series, IgG class antireticulin antibodies were found in the serum of five of the 16 patients tested, all of whom were on a gluten free diet and all but one of whom had an initial grade III biopsy. There was no correlation between skin response to the gluten free diet and the presence of these antibodies in the serum. Seah *et al.* (1972) have suggested that antireticulin antibody cross-reacts with a component of gluten so that the antireticulin antibody can trap gluten complexes in the skin, thus initiating the skin lesion of dermatitis herpetiformis. The occurrence of antireticulin antibody in the serum of three patients on a gluten free diet who have no skin rash and take no dapsone makes this theory less likely.

In conclusion, the majority of patients with dermatitis herpetiformis can expect their skin rash to improve on a gluten free diet, regardless of pre-diet jejunal histology, but the variable response of the skin in the patients with jejunal improvement on the diet suggests either that gluten is only one factor involved in the aetiology of the rash or that the degree of sensitivity of the rash to gluten varies from individual to individual.

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