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DERMATITIS HERPETIFORMIS: EFFECT OF GLUTEN-RESTRICTED AND GLUTEN-FREE DIET ON DAPSONE REQUIREMENT AND ON IgA AND C_3 DEPOSITS IN UNINVOLVED SKIN

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Abstract. Of 58 patients with classical dermatitis herpetiformis (DH), 17 were treated with a gluten-free diet (GFD) for periods varying from 6 to 47 months and 11 with a gluten-reduced diet (GRD) for 7 to 29 months. The patients were able to reduce their requirement of dapsone significantly compared with 30 patients on a normal diet, of whom only an 86-year-old man was able to discontinue his 10 mg dapsone dose. In 7 of the 17 patients on GFD, dapsone could be completely withdrawn after diet periods of 4 to 38 months. None of the patients on GRD could stop dapsone treatment. The occurrence and amount of immunoglobulin A (IgA) and of the third component of complement (C_3) in non-lesional skin were studied in the three diet groups during treatment. At the start of the study all patients had IgA deposits of the granular pattern. This pattern remained unchanged during the follow-up period. The amount of IgA in the skin did not decrease more in the patients on GFD than in those on an unrestricted diet. The occurrence of C_3 diminished in all patient groups, but the decrease was most pronounced in the group on GFD, where C_3 disappeared completely. Deposits of IgA and C_3 were not uniform throughout the skin. Slightly more IgA was found in skin from the buttocks than from the forearms. Patients taking a higher dose of dapsone had less frequent C_3 deposits in the skin than those taking a lower dose, which might indicate a suppressive effect of dapsone on C_3 deposition.

Key words: Dermatitis herpetiformis; Gluten-free diet; Skin IgA; Skin C_3; Dapsone

At least two-thirds of all patients with dermatitis herpetiformis (DH) have jejunal villous atrophy identical with that found in coeliac disease (16, 8). This bowel abnormality in DH is in most cases reported to be healed by a gluten-free diet (GFD) (5, 20). The effect of GFD treatment on the skin, however, is less clear. Thus, some authors have reported no or little effect (19, 30), whereas others have found improvement of the skin symptoms in almost all of their patients (6, 24).

The presence of IgA deposits in the clinically uninvolved skin is claimed by many to be the most reliable criterion for a diagnosis of DH (7). The significance of this IgA is still unknown, but it is possible that these deposits are related to the small-bowel abnormality (15), in that case one would expect them to be influenced in patients observing a strict GFD. C_3 has been found in the skin in a high frequency of patients with DH (27, 22, 14), indicating an active disease process. It may thus be reasoned that C_3, along with the IgA deposits, might decrease and finally disappear parallel with clinical improvement on a strict GFD.

This paper reports a prospective study of the effects of a GFD on the clinical status, assessed according to the dose of dapsone required, and on the IgA and C_3 deposits in the skin of 17 patients. The patients were followed for 6 to 47 months and were compared with 11 patients on a gluten-reduced diet (GRD) and 30 patients on an unrestricted diet.

MATERIAL AND METHODS

Patients

During the years 1976 to 1980, 58 patients (18 women and 40 men) with a mean age of 51 years (range 21–82 years) and with clinically typical DH were studied for a period of 6 to 47 months. Forty-eight of them were followed for more than 2 years. They had all had typical papulo-vesicular pruritic lesions, predominantly affecting extensor surfaces of the extremities and the buttocks, shoulders and scalp, which had reacted promptly to dapsone treatment. The histo-pathological findings were consistent with the diagnosis of DH in all cases. Four patients were excluded because they had an atypical clinical picture. All 4 were found to have homogeneous linear deposits of IgA at the epidermal basement membrane zone at direct immunofluorescence (IF) examinations.

At the last visits before the start of our study, all 58 patients were asked to reduce their dapsone consumption to the minimum dose required. If the patients did not take dapsone each day, the average daily consumption was calculated. Subsequently, 6 patients found that they needed less than 25 mg of dapsone daily. In addition, all patients were asked to withdraw dapsone for 3 or more days before the first examination. Only 3 of them could

not manage without the drug for this length of time and had taken dapsone on the day of examination or the day before.

At the first examination one skin biopsy from uninvolved gluteal skin was taken and examined by direct IF for the presence of IgA and C_3.

The patients were reminded about the dose-related side effects of dapsone and were again asked to attempt gradual reduction of the dose to the minimum acceptable. All were told about the possible benefits of a GFD. After this information, 8 women and 26 men were willing to try the diet and were given thorough information by a dietitian in a personal interview. As a compensation for wheat, rye, barley and oats, they were recommended a gluten-free commercial flour (Juvel). However, only 5 women and 12 men managed to observe a strict diet. The strictness was evaluated by direct interviews, and errors were corrected with the help of dietitian. Two women and 9 men adopted a GRD of varying gluten content. These 11 patients used the gluten-free flour in their own cooking but did not keep strictly to gluten-free food when having meals in other places than their own home. The ages of the patients and the duration of their DH are given in Table I.

All patients were seen about three to four times a year. The daily minimum dose of dapsone required for control of the rash and pruritus was recorded at every visit. At least once a year, when the patients were having their dapsone medication as usual, further gluteal skin biopsies were taken for examination of IgA and C_3. On one occasion biopsies were taken simultaneously from both a buttock and a forearm of 34 patients, of whom 20 were on an unrestricted diet, in order to compare the amounts of IgA and C_3 in two different areas of the skin.

At the end of the study all patients were again recommended to withdraw dapsone for at least 3 days, which was possible in all but 2. Further biopsies from non-lesional skin were taken, this time one from each buttock. One and the same physician saw all the 58 patients at every visit.

Direct immunofluorescence (IF)

The principles recommended by Beutner et al. (1) were followed.

Skin biopsies were taken with a 3 mm diameter punch, quick-frozen in isopentane at −70°C and stored at the same temperature. The specimens were cut into 6 μm sections on a cryostat microtome, washed in phosphate-buffered saline (PBS), air-dried and incubated for 30 min with fluorescein-isothiocyanate-conjugated goat-antihuman IgA and C_3 purchased from Hyland Laboratories. The conjugates were diluted to 1/10 with PBS containing 4% bovine serum albumin. After extensive washing in PBS, the slides were mounted in glycerol containing 10% PBS and read blind, all by one and the same investigator. The Leitz microscope used had a Xenon XBO 75 lamp and incident light with blue narrow-band activation.

A semi-quantitative evaluation was used to estimate the surface area of material with specific brilliant fluorescence in the dermis, which was recorded as: 0 = negative; +1, +2 and +3 representing small, intermediate and large fluorescent areas respectively (see Fig. 1*a*, *b*). At least 20 sections were investigated from each biopsy and the different sections most often showed the same degree of deposits. If there was a difference between sections, the heaviest deposits in each biopsy were recorded. Biopsies recorded as negative were serially sectioned and investigated *in toto*.

To check the subjective grading of the deposits, gluteal biopsies taken initially were also re-examined blind in 12 patients at the end of the study for the presence of IgA after storage for 4 years.

RESULTS

Dapsone requirement

Prior to the start of dietary treatment, the daily requirement of dapsone varied between 10 and 350 mg, with a mean value for all the patients of 78±60 (SD) mg. The daily requirement of dapsone was significantly lower with increasing age ($r = -0.39$; $p < 0.01$). There was no significant correlation, however, between dapsone requirement and duration of the disease. Patients who started on a GFD were younger than those who chose to continue with their habitual diet and also had a higher mean initial dapsone consumption, a difference not statistically significant, however (Tables I and II). All patients in the GFD group started on a dapsone dose of 25 mg or more daily.

At the end of the study the mean daily need for dapsone was significantly lower than at the beginning in both men and women on GFD, whereas this requirement was unchanged in those on a normal diet (Table II). The mean dapsone requirement was also reduced in the GRD group (Table II). Thus all 17 patients on GFD and 10 of the 11 on GRD had reduced their consumption of dapsone, while no such consistent change was noted among the patients on an unrestricted diet.

Seven patients on GFD were able to discontinue dapsone completely, one within 4, 3 within 12 and 2 within 18 months of the start of the diet and one after 3 years. The mean daily pre-diet requirement of dapsone was lower in these 7 patients than in those on a GFD who still had to take dapsone. The values were 79±27 mg (SD) and 106±60 mg (SD) respectively and the difference not statistically significant.

Three of the 11 patients in the GRD group, all on a rather low dapsone dose at the start, 10–50 mg daily, were able to manage without dapsone. However, they did not achieve remission while on the GRD, but had to wait until they had been on a GFD

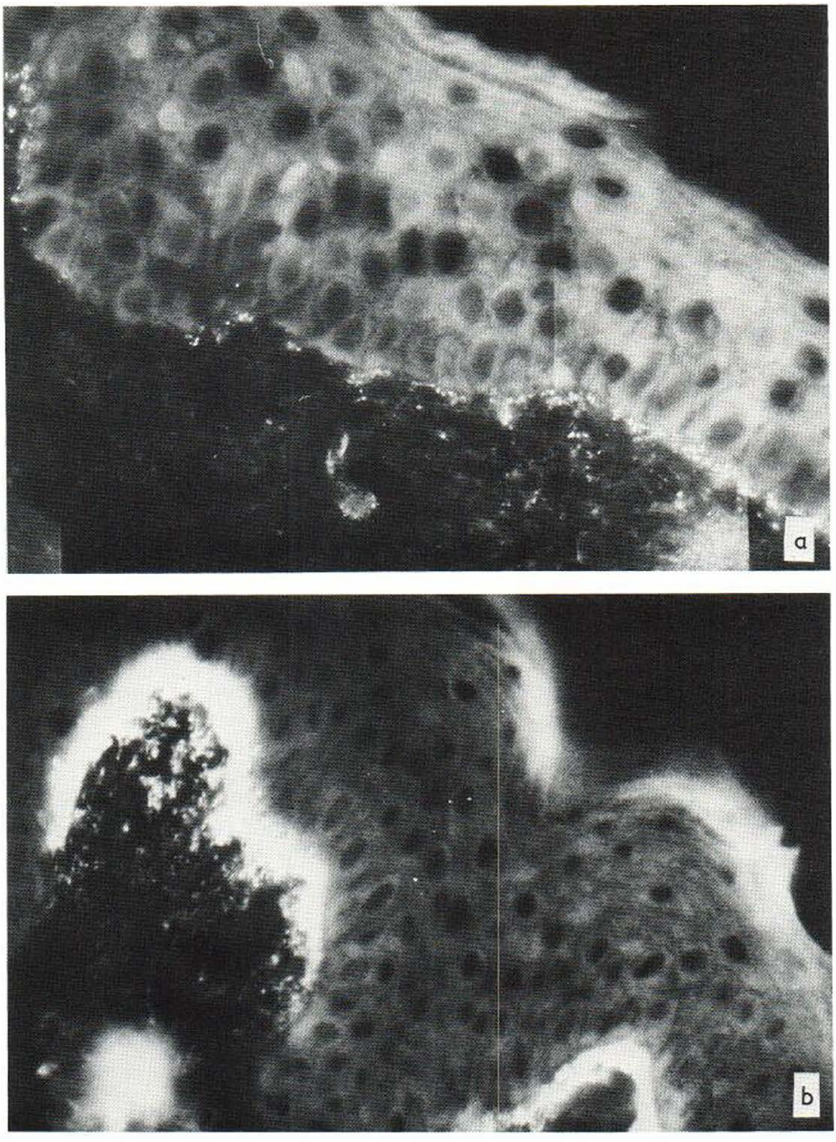

Fig. 1. Direct immunofluorescence of thin sections of non-lesional skin from dermatitis herpetiformis patients showing granular deposits of IgA. (*a*) Deposits graded +1. (*b*) Deposits graded +3.

for a short period. After some months they again commenced on a GRD without their symptoms returning.

One patient on an unrestricted diet was able to stop medication. He was 86 years old and had had the disease for 43 years. Some years ago he had needed 100 mg dapsone daily but at the start of the study his requirement was down to 10 mg. All the 11 patients in remission who were able to stop dapsone medication remained free from recurrent symptoms during a follow-up period of 2 to 35 months, with a median of 24 months for those on GFD.

IgA deposits

Before dietary treatment, granular dermal IgA deposits were observed in all 58 patients. Only one patient had to be biopsied twice for demonstration of IgA.

The anti-IgA fluorescence was seen in a granular–fibrillar pattern. The deposits were located mainly in the dermal papillae, sometimes along the basal membrane zone and sometimes with an empty space between this zone and the deposits. This picture is usually referred to as the papillary pattern. In some patients granular–linear deposits along

Table I. *Age of the patients and duration of their dermatitis herpetiformis (DH) (mean ± SD) at the start of the study*

Ranges given in parentheses

Patients	Age in years	Years with DH
Gluten-free diet ($n=17$)	44±14** (21–68)	13±9 (0.5–33)
Gluten-reduced diet ($n=11$)	45±14 (27–70)	9±5 (2–17)
Normal diet ($n=30$)	58±14 (32–82)	16±13 (0.5–53)

**$p<0.01$ compared with those on a normal diet; t-test.

the whole basal membrane zone were seen in all sections of a biopsy. However, consecutive biopsies from these patients showed the papillary pattern or even a mixture of the two patterns in different parts of the same biopsy. No patient changed from a granular to a homogeneous linear IgA pattern during follow-up. This indicates that the granular–linear IgA pattern is not a specific one, and in contrast to the homogenous linear pattern, is not distinct from the papillary pattern.

The comparison between IgA deposits in biopsies taken from 34 patients simultaneously from a forearm and a buttock showed in 15 of 19 diverging results more pronounced deposits in gluteal skin ($p<0.05$; sign test). Only in one case, however, did the difference amount to more than one grade. Comparisons between simultaneous biopsies from both buttocks taken at the end of the study showed a close relationship regarding the amount of IgA deposits.

Table II. *Daily mg dose of dapsone (mean ± SD) required for control of dermatitis herpetiformis skin lesions and duration of dietary treatment in the three diet groups*

Range values shown in parentheses

Patients	Beginning of study	End of study	Months of diet
Gluten-free diet ($n=17$)	94±51 (25–200)	25±41*** (0–150)	32±11 (6–47)
Gluten-reduced diet ($n=11$)	88±63 (10–200	44±43** (0–110)	19±8 (7–29)
Normal diet ($n=30$)	66±63 (10–350)	62±44 (0–200)	37±7 (17–47)

** $p<0.01$ compared with pre-treatment value; paired t-test.
*** $p<0.001$ compared with pre-treatment value: paired t-test.

Table III. *The individual changes in the amount of IgA deposits (graded +1 to +3) during the study of 56[a] patients with dermatitis herpetiformis on gluten-free ($n=17$), gluten reduced ($n=11$) and normal ($n=28$)[a] diets*

		IgA deposits at the end			
		0	+1	+2	+3
Number of patients with IgA graded +3 at the start					
Gluten-free	7	–	2	4	1
Gluten-reduced	0	–	–	–	–
Normal	6	–	3	1	2
Number of patients with IgA graded +2 at the start					
Gluten-free	6	–	5	1	–
Gluten-reduced	7	–	3	4	–
Normal	12	1	10	1	–
Number of patients with IgA graded +1 at the start					
Gluten-free	4	2	–	2	–
Gluten-reduced	4	–	3	1	–
Normal	10	–	6	3	1

[a] Grading data missing for 2 IgA-positive patients.

In the following the gluteal biopsy with the largest IgA deposit of the two taken is used in the presentation of the results. There was no consistent correlation between the amount of IgA demonstrated by direct IF and the patient's age, duration of the disease or requirement of dapsone.

During the study the IgA deposits decreased in 13 of 17 patients on a GFD, in 3 of 11 on a gluten-reduced and in 15 of 28 on an unrestricted diet (Table III). Two patients in the GFD group had a decrease of more than one grade, while 4 patients in the normal diet group had a two-grade decrease. However, in altogether 7 patients there was an increase in the IgA deposits. When these changes were also considered there was no difference between the diet groups regarding the effect of diet on IgA deposits. At the termination of the study, IgA was still observed in all but 3 patients; 2 of them were on a GFD and one on a normal diet.

Twelve gluteal biopsies were examined for IgA deposits at the start of the study and again at the

end after 4 years' storage. No systematic difference was noted.

A total of 297 gluteal punch biopsies were performed during the study and of these, 6.7% were negative.

C_3 deposits

At the initial examination, when only one biopsy was taken from non-lesional skin, C_3 deposits were observed in 29/55 (53%) of the patients. However, in the follow-up period when two biopsies were taken simultaneously from a forearm and buttock, 15 of 20 patients on a normal diet were found to have C_3 deposits, when both sites were taken into consideration.

The proportion of C_3-positive biopsies was the same in the forearm and buttock. Nor was there any difference in the occurence of C_3 deposits in gluteal biopsies from both sides taken simultaneously at the end of the study. In the following, unless otherwise stated, the results presented refer to the one of these gluteal biopsies with deposits, if both were not positive.

There was no pre-treatment difference in the occurrence of C_3-positive biopsies between the three diet groups. At the end of the study C_3 had decreased in all three groups. It had disappeared completely in all the patients on a GFD and was only found in 9 (30%) of the 30 patients on a normal diet ($p<0.05$ compared with the patients on GFD; Fischer's exact test for two-by-two tables) and in 3 (27%) of the 11 patients on GRD.

C_3 deposits were more common in patients with pronounced IgA deposits than in those with less IgA in the skin.

In order to study the relation between dapsone medication and C_3 deposits in the skin, one gluteal biopsy was examined from each patient on a normal diet while the dapsone was being taken as usual in the middle of the follow-up period (not withdrawn as at the start and the end of the study). It was found that of 9 patients taking a dapsone dose of 75 mg or more daily, only one had C_3 deposits, while among 14 patients on a daily dose of 50 mg or less there were 8 in whom C_3 deposits were demonstrated in the skin ($p<0.05$; χ^2-test).

DISCUSSION

Clinical response to gluten-free diet

This study confirms the view that a strict GFD will allow most patients to reduce their dose of dapsone and many of them to stop this medication completely. It also shows that a GRD is better in this respect than a wholly unrestricted diet, as has also been reported by Frödin et al. (4).

All the 17 patients on GFD were able to reduce their dose of dapsone. Reunala et al. (24) found that the ability to diminish the dose is not related to better absorption of the dapsone when the bowel mucosa heals. Thus, in their study the concentration of dapsone in the serum was significantly lower in patients treated with GFD than in those on a normal diet. Also speaking against the theory that a beneficial effect results merely from better absorption is the fact that many patients on GFD become completely free from symptoms without dapsone medication.

In many dietary studies, in which GFD has otherwise had beneficial results, there are some patients with a poor response to this dietary treatment (24, 15). Among our patients, 2 women were unable to reduce their dapsone dose more than by 33 and 25% respectively. They had been on a GFD for more than 3 years and were believed to observe their diet strictly, as found by repeated interviews by dietitians. At the start both had intestinal problems, with diarrhoea, which disappeared completely after some months on the diet. On one of them a small intestinal biopsy was performed before the diet, showing subtotal villous atrophy of the jejunal mucosa. At the end of the study this was restored to normal. On the other woman no intestinal biopsy was performed until the end of the study, at which time it showed intestinal villous atrophy probably indicating a continuing intake of gluten.

Complete remission in many patients on GFD has been reported earlier, as compared with none or only a few in control groups on a normal diet (6, 24, 4). We found that 41% of the patients on a GFD and taking 25 mg or more of dapsone at the start were able to stop this medication, whereas none of the patients on an unrestricted diet who started at such a dapsone dose could stop the treatment. Heading et al. (13) reported a reduction of dapsone doses on GFD but found that complete remission did not occur significantly more often than with a 'normal' diet.

The length of time until complete remission is attained on GFD varies in different patients. Our finding that most hitherto appearing remissions occurred within 18 months of starting on the diet is

in agreement with reports by Fry et al. (6) and Reunala et al. (24). With time, one will probably see even longer times before remission is attained.

None of our patients on a GRD were able to discontinue their dapsone medication completely on this diet alone, but the length of dietary treatment was shorter for these patients than for those on gluten-free and unrestricted diets. In one patient on GRD for 20 months, a change to GFD allowed discontinuation of dapsone after a further 3 months. However, patients who cannot keep to a strict diet may nevertheless obtain some benefit from a reduced gluten intake, as compared with no dietary restriction at all, although they will probably not achieve remission.

The differences in results observed between the extreme diet groups (gluten-free and unrestricted diet) might have been even larger if the patients could have been randomly assigned to their type of diet. All our patients were informed about the GFD at the start of this study, and it is therefore probable that the patients on a 'normal' diet also became more restrictive regarding gluten than previously.

IgA and C_3

This study confirms the suggestion first made by Seah & Fry (28) and later supported by Chlorzelski & Jablonska (2) and Katz et al. (15) that the best diagnostic criterion of DH is the finding of granular IgA deposits in the skin. This has been questioned by Marks (17, 18), Cooper & Cooke (3) and Ross et al. (25), but further strengthened by Fry et al. (10).

We found the granular IgA pattern in all the 58 patients with a clinical picture typical of classical DH. We consider this pattern to be very specific for DH, as we never observed the same pattern either in healthy persons or in patients with skin diseases other than DH in about 1 200 skin biopsies investigated for immunoglobulins by direct IF. Ross et al. (25) found IgA of the granular pattern in biopsies from 4 of 15 patients with coeliac disease, but it might be suspected that these patients had a latent DH.

At the start of the study we excluded 4 patients in whom the DH was suspected because of their pruritic vesicular and bullous lesions. They were all atypical in respect to the distribution of lesions or the largeness of the bullae and 3 of them responded less promptly to treatment with dapsone than did those with the typical clinical picture. All 4 were found in repeated biopsies to have IgA of the homogeneous linear pattern in the basement membrane zone of the skin. Among our patients with clinically unquestionable classical DH we did not find one with that IgA pattern. Thus, we could not confirm the finding of a homogeneous linear pattern of IgA deposits in 5–15% of classical DH patients reported by others (28, 15). Nor did any patient change from the granular to the linear pattern or vice versa, as was found by Harrington & Read (12) and Fry et al. (9). Furthermore, in contrast to the report by Haffenden et al. (11), both patterns together were never found in any biopsies from the same patient or in the same biopsy. The granular pattern, however, could change between a linear and a papillary distribution. In all but one of our 58 patients we found the IgA in the first biopsy taken, so in most patients it will evidently be sufficient to take one biopsy for diagnosis. If the first one is negative, with a clinical picture suggestive of DH, further biopsies are recommended. We would also recommend that these biopsies be taken from the buttock, as we found more pronounced deposits of IgA in this area than in skin from the forearm.

The patients with the largest dapsone requirement did not have more IgA deposits in the skin than those with a smaller requirement of the drug. Nor had those on a large dose of dapsone smaller IgA deposits, which would have indicated some influence of dapsone on IgA deposition.

Regarding the influence of GFD on the IgA deposits in the skin, we cannot draw any firm conclusions from this study, as the IgA deposits did not decrease more in the gluten-free than in the other diet groups. Other authors have reported a tendency to decreasing IgA deposits on a GFD (11, 23, 4). Harrington & Read (12) even found that IgA disappeared from the skin after 6 months of GFD. They did not mention, however, how many sections from the biopsies were investigated or whether more than one biopsy was taken from each patient. Salo & Reunala (26) observed that IgA disappeared from the skin in some patients on a GFD after about 3 years. Fry and his colleagues, however, followed up patients on a GFD for about 10 years without finding complete disappearance of IgA deposits, not even in those in remission (9). Three of our patients had no detectable IgA deposits in the skin at the end of the study, even though two biopsies taken simultaneously from each of them were serially sectioned *in toto*. All 3 still needed dapsone. It is possible that

IgA might have been revealed if still more biopsies had been examined.

Regarding C_3, this study shows that the site of biopsy (forearm or buttock) is irrelevant, but that it is important to take several biopsies. During the follow-up period, when the occurrence of C_3 deposits in the forearm was compared with that in the buttock, 18% of the C_3-positive patients would have been missed if only one biopsy had been taken. Like other authors (11), we found a positive correlation between the occurrence of C_3 and the amount of IgA deposits in the skin. The results also indicate that the presence of C_3 in non-lesional skin is related to gluten consumption, which is in agreement with previous reports (23, 11).

An interesting finding was that more patients on a normal diet and taking low doses of dapsone had C_3-positive biopsies than those taking a higher dose. One might expect the high-dose consumer to have the most active disease and thus more C_3 in the skin than the low-dose consumer. The present results indicate that dapsone may alter the deposition of C_3 in the skin. Provost et al. (22) and Millikan et al. (21) reported similar findings, while other authors did not observe such an effect of dapsone treatment on C_3 deposition (14, 29).

Besides the reduction in IgA deposits and the disappearance of C_3 in the GFD group, both the amount of IgA and the frequency of C_3 deposits decreased in all diet groups, even in patients on a normal diet. The reason for this finding is not known. It does not seem to be explained by technical or human factors, since blind re-examination of the 4-year-old biopsies concerning IgA deposits confirmed earlier results. Could the explanation be that all patient groups might have reduced their gluten intake in consequence of information about the diet, given to all the patients?

Removal of gluten from the diet is the most satisfactory treatment for patients with DH. For many patients a strict diet seems very difficult, but those who manage to follow it report that after acclimatization the diet does not cause much social or other trouble. It gives most of them a new feeling of well-being and, not least important, it is a harmless form of therapy compared with many others.

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