Studies of intestinal lymphoid tissue. IV—The predictive value of raised mitotic indices among jejunal epithelial lymphocytes in the diagnosis of gluten-sensitive enteropathy

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SUMMARY It has been established that considerable blast-transformation and mitotic activity occurs among epithelial lymphocytes of untreated coeliac mucosa. This paper is concerned solely with the proliferative activity of epithelial lymphocytes (expressed as percentage "mitotic index") in the prospective diagnosis of coeliac disease, in comparison with other conditions such as lymphoma, Crohn's disease and immunodeficiency which are often associated with malabsorption and flattening of jejunal mucosa. The results demonstrate that a high mitotic index (>0.2%) clearly distinguishes, and hence predicts, gluten-associated enteropathies (including dermatitis herpetiformis and malignant histiocytosis) from others in which gluten plays no aetiological role and where the mitotic index differs insignificantly from normal control mucosae (<0.2%). Furthermore, it has been demonstrated that the mitotic index is raised in so-called "non-responsive coeliacs," thus suggesting that such patients may also be gluten-sensitive despite their subsequent failure to respond morphologically to dietary gluten restriction.

Despite considerable investigation over many years, the pathogenesis of gluten-sensitive enteropathy (GSE) still remains unsolved. For clinical purposes, diagnosis requires demonstration of a severe lesion of the upper jejunum that responds to a gluten-free diet (GFD) with restoration of villus architecture, such criteria permit recognition of most symptomatic individuals.

However, in recent years there has been increasing use of gluten challenge as a further means of confirming the diagnosis once an initial response to dietary treatment has occurred. This additional procedure demands at least three biopsies from the jejunum and the question arises as to whether such practice is reasonable or justifiable for that purpose alone.

Other difficulties arise in practice regarding confirmation of diagnosis of gluten-sensitive enteropathy. Firstly, it is apparent that "flattening" of the upper intestinal villi cannot be regarded as a specific feature of GSE since similar mucosal changes are now known to occur in approximately 30 other clinical and experimental circumstances. Secondly, there are certain patients who despite reasonably strict adherence to a gluten-free diet fail to regenerate small intestinal villi. To label such patients as having "unresponsive coeliac disease" contradicts accepted diagnostic criteria, while if they are indeed gluten-sensitive, the definition should be appropriately modified and other reasons for lack of mucosal regeneration sought.

Thirdly, the difficulty in distinguishing between "lymphomas" complicating pre-existing coeliac disease and the coeliac-like syndrome resulting from primary lymphomas of intestine highlights another controversial aspect of diagnosis to which there is currently no rational solution, or hence certainty in determining whether GFD should be given, or not. Similar problems are encountered in patients with malabsorption and a "flat" mucosa due to immunodeficiency. Thus, if after gluten restriction further biopsy of the intestine fails to show evidence of villus regeneration, it is then difficult to be sure whether the diet should be continued or withdrawn, especially in the face of continuing ill-health, or diarrhoea.
In these circumstances, it is surprising that no further refinements in diagnostic accuracy, or more discriminatory criteria have been proposed since the earliest definitive descriptions of the “coeliac lesion” were given. It therefore seemed timely to re-evaluate critically the cytological features of the small intestine in GSE and in view of its likely immunological basis to monitor changes in the behaviour of lymphoid cells within the epithelium and lamina propria.

In such an evaluation considerable blast-transformation (8%) and mitotic activity of interepithelial space lymphocytes was documented: after gluten withdrawal, the proportion of epithelial immunoblasts decreased to control levels (2%), although their mitotic activity sometimes tended to persist above control levels. These observations suggested that certain epithelial lymphocytes might be sensitised to gluten, their blastogenesis and mitotic activity representing a specific, and likely immunological, marker of gluten-sensitivity in the mucosa of affected individuals and those alone.

The purpose of the present study was to widen the scope of previous investigations and to test such conclusions more rigorously by determining mitotic indices of interepithelial space (IEL) lymphocytes in a large and unselected series of disease controls, in addition to patients with coeliac disease and dermatitis herpetiformis. The results presented here confirm that a high mitotic index among IEL is characteristic of coeliac biopsies alone thereby distinguishing them prospectively from all other “flat” lesions of upper jejunum including primary lymphomas, Crohn’s disease and certain forms of immunodeficiency. Furthermore, it was found that the proliferative activity of IEL was high in all patients with coeliac-like syndrome but who failed to respond morphologically after gluten withdrawal. These results suggest that so-called “non-responsive” patients also may be sensitised to gluten, at least in terms of this particular histological marker of mucosal lymphocyte activation.

**Material and methods**

**Patients**

Sixty control patients came to intestinal biopsy (Table 1) for various complaints related to the gastrointestinal tract, but gluten-sensitivity was neither suspected, nor ultimately considered to account for their illness. In this group there were three people with “flat” lesions, two being due to jejunal Crohn’s inflammation and one possibly to eosinophilic infiltration of the small intestine. No

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<tr>
<th>Males (age range 12-78 yr)</th>
<th>Females (age range 16-76 yr)</th>
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<tr>
<td>Age (yr) Diagnosis</td>
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<tr>
<td>12 Giardiasis</td>
<td>16 Irritable bowel syndrome</td>
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<td>17 *Jejunal Crohn’s disease</td>
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<td>21 Intestinal pseudo-obstruction</td>
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<td>23 Aphthous ulceration</td>
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<td>29 Lactose intolerance</td>
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<td>35 Alcoholism</td>
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<td>36 Pancreatic steatorrhoea</td>
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<td>36 Peutz-Jehger syndrome</td>
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<td>40 Lactose intolerance</td>
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<td>43 Traveller’s diarrhoea</td>
<td>38 Nodular prurigo</td>
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<td>46 Irritable bowel</td>
<td>38 Irritable bowel syndrome</td>
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<td>46 Zollinger-Ellison syndrome</td>
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<td>48 Giardiasis</td>
<td>40 Laxative abuse</td>
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<td>48 Post-gastrectomy anaemia</td>
<td>41 Diarrhoea ?drug</td>
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<td>50 Asucrasia</td>
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<td>54 Iron deficiency (gastrectomy)</td>
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<td>53 Malabsorption ?cause</td>
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<td>62 Pancreatic neoplasm</td>
<td>54 ? polyarteritis nodosa</td>
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<td>62 Post-gastrectomy diarrhoea</td>
<td>57 Post-gastrectomy B 12 deficiency</td>
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<td>66 Erythrodermia</td>
<td>58 Diarrhoea ?cause</td>
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<td>67 Post-gastrectomy malabsorption</td>
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<td>68 Pancreatic neoplasm</td>
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<td>72 Whipple’s disease</td>
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<td>73 Hypocalcaemia</td>
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<td>78 Dietary folate deficiency</td>
<td>70 Nodular prurigo</td>
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<tr>
<td>76 *Eosinophilic gastroenteritis</td>
<td>76 Nodular prurigo</td>
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*Denotes associated “flat” jejunal mucosa.
additional jejunal biopsies were performed in any of these individuals.

Tables 2 and 3 contain details of further groups of "proximo" disease controls who were shown to have either (a) malignant disease (lymphoma, carcinoma, or "malignant histiocytosis") or (b) various immunological conditions, especially immunodeficiency, affecting intestinal structure or function. Several of these cases have been reported elsewhere.\textsuperscript{19-24}

There were 21 coeliac patients (age range 18-75 yr). Repeat biopsies were not available in seven of these: the remainder had responded morphologically to GFD. Of 13 patients with dermatitis herpetiformis (DH), four had severe enteropathy: they were studied before and after GFD, to which all responded promptly.

All DH patients were referred for gastrointestinal investigation by physicians from the Hospital for Diseases of the Skin, Manchester. Diagnosis was based on clinical criteria, immunohistological demonstration of IgA deposits in skin, and response to dapsones. Gluten restriction was not undertaken until biopsy of the small intestine had been carried out.

Table 4 documents nine cases of presumed coeliac disease, but in whom GFD was not associated with a significant degree of mucosal regeneration. A total of 144 intestinal specimens, obtained from 131 patients, was reviewed. The majority of these patients were seen in the University Department of Medicine at Hope Hospital between 1975 and 1981.

**HISTOLOGICAL PREPARATION**
All specimens obtained within the Department were fixed in Dalton's chrome-osmium solution,\textsuperscript{25} or 2.5%
Table 4  Coeliac syndrome, with poor morphological response to GFD

| F 28: | Good clinical response to GFD: disaccharides remain low |
| F 24: | Childhood anaemia and diarrhoea. Fairly strict GFD. Well |
| M 38: | Iron deficient as child. Good clinical response to GFD. Has coeliac son |
| F 42: | Diabetes. Megaloblastic anaemia and diarrhoea. GFD religiously strict |
| F 43: | Glossitis and diarrhoea. 90% strict GFD. Weight gain 14 kg |
| F 48: | Myxedema and iron deficiency. Poor GFD control, but weight gain 6 kg |
| M 37: | Glossitis. Diarrhoea and megaloblastic anaemia. Intermittent diarrhoea persists |
| F 50: | Anaemia and loose bowels. Symptomatically well |
| F 67: | Ca jejunum resected two years after good response to GFD. Well 15 yr later. Has responsive coeliac daughter |

...cacadlyte-buffered glutaraldehyde and embedded in Epon or Emit resin, sectioned at 1 μm thickness on Sorvall MT2-B or Reichert OMU-3 ultramicrotomes and stained with toluidine blue.26 Four or five consecutive 1 μm sections were applied to each slide: a 10 μm step from the block was discarded between successive slides. Material obtained from other colleagues, or from patients referred direct to the University Department at Hope Hospital, had invariably been processed by local histopathological laboratories. These latter specimens were fixed in “formalin,” embedded in wax, sectioned at approximately 4-7 μm thickness and stained with haematoxylin and eosin.

DETERMINATION OF MITOTIC INDICES

To determine mitotic indices (MI), sections were viewed under ×100 oil-immersion objective and the number of mitotic figures within a sample of 3000 IEL per specimen was counted and expressed as percentage of total. If there was doubt about a mitotic figure it was ignored; so also were mitotic figures around the mouths and sides of crypt orifices, particularly in “flat” specimens where the possibility of confusion with epithelial cell mitoses in this region is high.27 In practice, and as discussed elsewhere17 the majority of positive scores was derived from metaphase-anaphase figures; little attempt was made to recognise and include all prophases. Underestimation was preferred, and thus the final data given are minimal values for each specimen studied. That significant results were thereby obtained justifies the cautious approach adopted.

Although many specimens were reviewed retrospectively, the diagnosis, which was not immediately known to the author, was obtained from the clinical file once the MI was determined. Thereafter, no further modification to the result by revision or recounting the specimen in the light of diagnostic information, was ever carried out. Other specimens, especially those obtained from outside the Department, were assessed “blindly”; in this way, some degree of control over the observations, and hence their validity, was achieved.

Results

MORPHOLOGICAL ASPECTS

Selected mitotic figures taken from specimens observed during this study are illustrated in Figs 1 and 2. Mitotic figures were sometimes less easy to identify in the thicker sections of paraffin-embedded material compared with 1 μm plastic sections. This difficulty was frequently encountered in routine histological preparations of untreated coeliac mucosae where there was considerable crowding, superimposition and overlapping of epithelial cell and lymphocyte nuclear profiles within the depths of each section. Furthermore, it was not always possible to check doubtful mitotic figures in these preparations, whereas with 1 μm sections, reference to adjacent sections on the same slide (see Methods) permitted “cross-checking” and hence often a more confident decision. Wherever doubt persisted about a particular configuration, it was ignored.

QUANTITATIVE DATA—MITOTIC INDICES

Controls

No mitotic activity was observed in samples of 3000 IEL from each of 45 control specimens (75%) that is, within a total sample of 135 000 epithelial lymphocytes. In 14 of the remaining specimens, less than three mitotic figures per 3000 IEL were observed. The upper limit for the entire control range was 0.15% (Fig. 3).

From Fig. 3, it can also be seen that the range of mitotic activity of IEL in the other “proximate” disease controls, but excluding malignant histiocytosis of the intestine, was similar to the control group described above. It is important to note that within the second control group were patients with malabsorption syndromes associated with “flat” mucosae—for example, proliferative lymphocytic lymphomas, carcinoma, immunodeficiency and jejunal Crohn’s disease, whose mitotic indices did not exceed 0.17%.

These observations contrast sharply with the malignant histiocytosis group, where mitotic indices...
Mitotic lymphocytes in gluten-enteropathy

Fig. 1  (A) Epithelium from “flat” mucosa in Crohn’s disease: there are no mitotic figures ×640. (B) Immunodeficiency and gluten-sensitive enteropathy. Mitotic figure (M) in epithelial lymphocyte. ×650. (C, D) Paraffin sections of jejunal mucosa from untreated coeliac patients showing mitotic lymphocytes (M). C ×650, D ×700.

Fig. 2  Mitotic figures (M) are more easily seen in 1 µm plastic sections of untreated coeliac mucosa: (A) depicts prophase (×1200) and (B) metaphase plate (×1175). G = goblet cell; isolated arrowheads locate basement membrane.
patients with severe malabsorption and "flat" mucosae, mitotic indices among IEL were high (range 0.25-0.47%), and thus identical to those obtained for coeliac patients.

Effect of GFD on mitotic indices
Data are available on four groups of patients treated with GFD: (i) classical coeliac patients, (ii) DH patients with enteropathy, (iii) patients with malignant histiocytosis of intestine, and (iv) the "non-responsive coeliac syndrome" group (Fig. 4). Here the dramatic fall in the mitotic indices of responsive coeliac and DH patients is obvious and striking, despite the preponderance of higher values after treatment compared with the majority of controls. It is also apparent from these data that the value of determining mitotic indices in patients, once gluten has been excluded from their diet, is completely lost.

Responsive coeliac patients
In this group were 21 untreated patients; the mitotic indices of IEL were markedly raised compared with controls, and ranged from 0.20-0.77%. Similar findings were seen in DH patients with enteropathy and "flat" mucosae. In DH patients without intestinal symptoms and structurally "normal" appearances, mitotic indices lay within the control range.

Non-responsive coeliac syndrome
The remaining data shown in Fig. 3 refer to nine cases of "non-responsive coeliac syndrome." In these patients, in contrast to other disease control

Fig. 3 This mitotic index (vertical axis) of mucosal specimens in each group of controls and patients is shown in this diagram. Closed symbols for each group represent "flat" mucosa. In "Neoplasia" column, △, ▲ refers to lymphomas; ✗ to carcinoma, and ▣ to "malignant histiocytosis." Horizontal dotted line marks arbitrary cut-off between all controls (<0.2) and gluten-sensitive patients. The boxed value in the immunodeficiency column represents a case of combined immunodeficiency and gluten-sensitive enteropathy.

were high, except for one patient whose specimen demonstrated marked lymphocyte depletion both within epithelium and lamina propria; it is perhaps highly significant in these circumstances, therefore, that his mitotic index was 0.17%. None of these patients was believed to have taken a GFD before these particular biopsies were obtained.

The other notable exception in this group is the case of immunodeficiency and presumed GSE, where the mitotic index among IEL in the initial biopsy on presentation with weight loss and malabsorption was markedly raised (Fig. 3).

Fig. 4 This diagram shows the effect of GFD on mitotic index of epithelial lymphocytes (vertical axis) in small intestine. Successive pre- and post-diet values are joined. Significant reductions in mitotic activity occurs in coeliac disease, dermatitis herpetiformis and one case of malignant histiocytosis; the response of the gluten-sensitive immunodeficient patient (stars) is also apparent. The closed circles in the coeliac column are mitotic indices in a group of patients studied after GFD treatment. There is a marked downward trend in indices of "unresponsive" patients, although not all had reached "control" values, when the latest biopsy for this study was obtained.

Of particular interest, however, is the consistent fall in the mitotic indices of IEL in patients with failure of villous regeneration after GFD. It is
clearly of considerable relevance to remember that the only change in these patients was removal of one dietary antigen (gluten) from their intestinal environment.

Discussion

These results confirm previous observations, providing a firm data base relevant to the mitotic activity of IEL in a wide variety of gastrointestinal conditions, and give support to the following conclusions: (i) that IEL in the majority of miscellaneous human control jejunal mucosae show little tendency to divide; (ii) that a similar range of mitotic activity occurs within IEL of disease-control mucosae, including primary intestinal lymphomas, various infections, inflammations, immunodeficiencies and epithelial malignancy; (iii) that in untreated coeliac disease, the mitotic activity of IEL is raised and greatly exceeds that found in various control and disease mucosae; (iv) that after a response to gluten restriction, the mitotic index of IEL falls within the control range, and (v) that a mitotic index of >0.2% provides a marker which prospectively distinguishes “flat” lesions due to gluten-sensitivity from other disorders, and thus identifies those patients for whom a GFD is rational therapy.

The demonstration in patients with intestinal malabsorption (“idiopathic steatorrhoea”) of severe mucosal lesions that recovered after dietary gluten restriction (as invariably occurs in childhood coeliacs28 29) led to the view that they also were suffering from (adult) coeliac disease. In view of the non-specificity of the lesion, however, the ultimate diagnosis of coeliac disease in adults rests heavily on the demonstration of a mucosal response to gluten restriction, and of mucosal deterioration after a further period of gluten ingestion. Such procedures are necessarily long, drawn-out, retrospective, and require two or often more, jejunal biopsies before the diagnosis can be affirmed. The data provided here in several responsive adult coeliac patients (Fig. 3) clearly indicate that a prospective, and confident, diagnosis can be made when the first biopsy is performed, provided no dietary manipulation takes place beforehand. Furthermore, determination of the mitotic index of epithelial lymphocytes within any mucosal specimen requires no specialised technique or methodology, and can be accomplished within 45-60 min of receipt of prepared sections of mucosa: this is an important practical issue raised by this study.

It is difficult for the histopathologist to determine clearly whether for a given flat mucosa, lymphoma is secondary to pre-existing gluten sensitive enteropathy, or whether primary lymphoma results in a secondary intestinal lesion and malabsorption syndrome. The data presented here clearly illustrate that mitotic indices of IEL are only raised in gluten-sensitive patients and not in those with lymphomas, despite the proliferative nature of the tumour itself. Such objective criteria are of considerable value in determining whether a GFD should be instituted, or not. This is of considerable advantage to the patients who, despite repeated courses of radiotherapy or chemotherapy with their attendant side-effects, can be spared the additional problem of adapting to, and maintaining, a major change in dietary habit for no good reason.

The nature of the malignancy arising in coeliac mucosae is still not entirely clear, although may be of the histiocytic cell line.20 21 30 31 In this regard, it is of considerable interest that the mitotic index of the cases studied were initially high and fell after gluten restriction, thus indicating their gluten sensitivity (similar to responsive coeliacs). Clearly, much further work is needed to categorise these tumours by appropriate immunological and cytological markers. Nevertheless, the relation of such malignancies to adult coeliac disease and hence to the mitotic activity of IEL, should be of considerable relevance in future explorations, and classifications, in this field.

Although the diagnosis of immunodeficiency can easily be established by immunoglobulin quantification, the association of villous “flattening” with malabsorption and diarrhoea often leads to the use of a GFD, albeit as an additional “non-specific” measure. Experience shows that improvement in symptoms, or regeneration of villi rarely, if ever, occurs in such circumstances.32–36 The finding that no mitotic index in the cases studied exceeded 0.2% firmly excluded the coexistence of gluten-sensitive enteropathy, and thus could have predicted from the outset that GFD would be ineffective.

The recently published case of gluten sensitivity associated with severe hypogammaglobulinaemia32 showed clear evidence of symptomatic, biochemical and histological responsiveness to gluten restriction, with subsequent deterioration within one month of recommencing a normal diet (a conventional 20 g “gluten challenge” having failed to elicit his susceptibility). The mitotic indices in the relevant specimens were high at presentation (0.43%), but low after GFD has been given (0.1%) (Fig. 4). These observations are consistent with a gluten-sensitive enteropathy, and contrast sharply with the low mitotic indices observed in the other immunodeficient patients (Fig. 3).

It likewise follows from this case that the blast-transformation and mitotic activity of IEL are not secondary to activation by antibody, or antigen-
antibody complexes, thus adding further support for the view that a state of T cell hypersensitivity exists within the intestinal epithelium of untreated coeliac patients.

Thus far, it has been shown that high mitotic indices (>0.2%) among jejunal IEL prospectively identify gluten-sensitive subjects, and secondly, that absence of a high mitotic index (<0.2%), especially in pseudocoeliac lesions secondary to immunodeficiency, lymphoma, Crohn’s disease and various other disorders associated with malabsorption or steatorrhoea, excludes gluten-sensitivity and hence the need for a GFD. Such decisions may be made prospectively after analysis of the initial small intestinal biopsy.

Finally, consideration is given to those patients who failed to regrow villi and who, by definition, cannot be regarded as coeliac patients. In these patients (Fig. 4) there was a slower fall in mitotic indices of IEL, compared with the responsive group. If, as has been argued, the blast-transformation and raised lymphocyte mitoses among epithelial lymphocytes reflects activation by luminal antigen, and since only gluten was withdrawn from the diet, what does the ultimate fall in mitotic indices represent in these patients after treatment with GFD? It is often stated, paradoxically, that failure to regenerate villi necessarily reflects poor dietary control, and it was difficult to exclude this possibility as many of these subjects were not directly under the care of the author. However, two of these “unresponsive” patients were parents of coeliac children who, by virtue of mucosal regeneration in response to gluten restriction, must be regarded as gluten-sensitive. Should these parents, one of which developed carcinoma of the jejunum, not be regarded as coelics in view of the known family prevalence and if not, to what is their disease due? Despite intensive study of intestinal malabsorption over the last 25 years, few other lifelong dietary hypersensitivities closely mimicking (adult) coeliac disease have been described.

While, in ignorance of cause, current definitions of coeliac disease should be retained the possibility that such criteria are too restrictive must always be considered. Such sentiments are embodied in previous reports of persons in whom a mucosal response initially occurred after gluten restriction, but in whom that responsiveness was ultimately lost. Thus “unresponsive” coeliac patients (excluding obvious diet defaulters) may continue to have flat mucosa for reasons (and mechanisms) other than ingestion of trace amounts of gluten. High mitotic indices in these patients, although obviously not exclusive to gluten sensitivity, are highly suggestive of the nature of the enteropathy, particularly when evaluated in parallel with the many other various disease-controls described in this study.

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References

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