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Increased numbers of IgE containing cells in gastric and duodenal biopsies. An expression of food allergy secondary to chronic inflammation?

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SUMMARY Gastric and duodenal biopsies from 2543 patients with abdominal complaints were sent to the Department of Pathology of the Stichting Samenwerking Delftse Ziekenhuizen in 1980 and 1981 and screened for plasma cells containing IgE using an indirect immunoperoxidase technique. Increased numbers of IgE containing cells were found in 2·6% of the patients. These patients all suffered from a variety of chronic non-specific inflammatory disorders of the upper gastrointestinal tract. No specific clinical, endoscopical, or histological picture could be found. The results suggest that increased numbers of plasma cells containing IgE in biopsies from the upper gastrointestinal tract are an expression of IgE mediated type I allergy presumably to food constituents as a secondary complication of chronic non-specific gastric and duodenal inflammation in these patients.

Increased numbers of plasma cells containing IgE have been described in the tonsils of atopic patients[1 2] and in the jejunal mucosa of patients with food allergy.[3] This is not surprising since both diseases are type I IgE mediated allergic disorders. Increased numbers of IgE containing cells have also been found in the rectal mucosa of patients with a distinct type of proctitis which responds to treatment with disodium cromoglycate.[4] These findings strongly suggest a relation between the presence of high numbers of IgE containing cells in mucosal biopsies and IgE mediated allergic immune responses.

In the upper gastrointestinal tract increased numbers of IgE containing cells have been found in gastric biopsies of patients with varioliform gastritis,[5] an endoscopically distinct type of gastritis. Some of these patients had raised serum IgE concentrations and those treated with disodium cromoglycate showed a favourable response; an allergic IgE mediated immune mechanism was therefore suggested. Others, however, have not confirmed this.[6] In addition, increased numbers of IgE containing cells have been found at the bases of gastric and duodenal ulcers[7] and in gastric biopsies from patients with gastritis due to duodenal reflux.[8]

We have investigated the incidence and clinical importance of plasma cells containing IgE in 2543 gastric and duodenal biopsies obtained during 1980 and 1981. In biopsies containing two or more IgE containing cells per high power field (×250) the numbers of IgE, IgA, IgM, and IgG containing cells were determined morphometrically. The clinical and endoscopical records of these patients were reviewed in order to see whether a typical clinical and endoscopical picture could be shown.

Patients and methods

For a two year period all upper gastrointestinal biopsies (a total of 2543) sent to the Department of Pathology of the Stichting Samenwerking Delftse Ziekenhuizen were stained for IgE, IgA, IgM, and IgG containing cells using an indirect immunoperoxidase technique.[9]

Biopsies containing an increased number of IgE containing cells, defined as two or more IgE containing cells per high power field (×250) in one section of a biopsy, were selected. In these biopsies the

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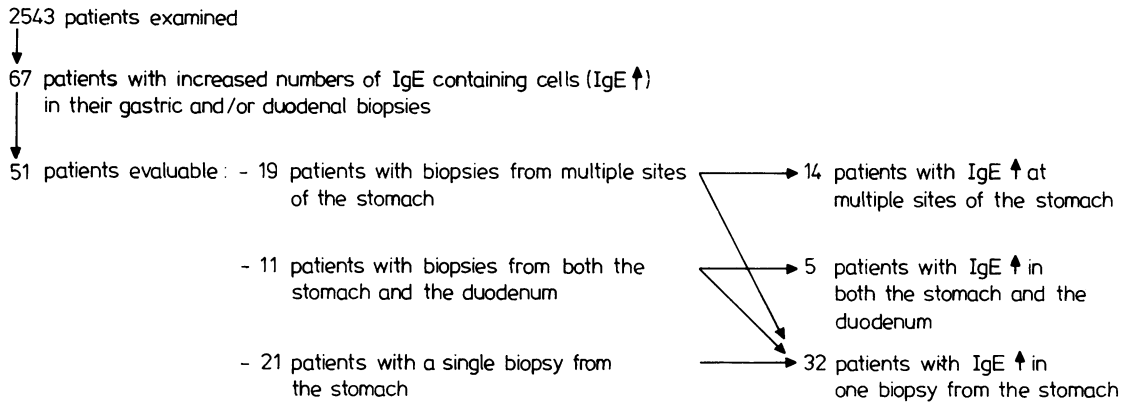

Fig. 1 *Patients and biopsies studied.*

numbers of IgE, IgA, IgM, and IgG containing cells were assessed morphometrically. The clinical and endoscopical records of these patients were reviewed retrospectively. Ten patients with chronic non-specific gastritis and duodenitis and 10 healthy volunteers described elsewhere[9] served as controls. The diagnosis was based on the histological criteria described by Whitehead[10] and Kreuning *et al.*[11] IgE containing cells were observed sporadically in these biopsies, but none of them fulfilled the criterion of two or more IgE containing cells per high power field.

All biopsies were taken during diagnostic endoscopy and fixed for 4–6 h in a sublimate-formalin mixture for optimal demonstration of immunoglobulin containing cells. Sections were stained with haematoxylin and eosin, periodic acid Schiff, and specifically for IgA, IgM, IgG, and IgE heavy chains using an indirect immunoperoxidase technique. Appropriate controls were done according to Sternberger[12] and Rosekrans *et al.*[3] Rabbit antisera against IgA, IgM, and IgG heavy chains were purchased from Dakopatts (Denmark). The rabbit antiserum against IgE heavy chains was purchased from the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam.

The specificity of the antisera was confirmed by

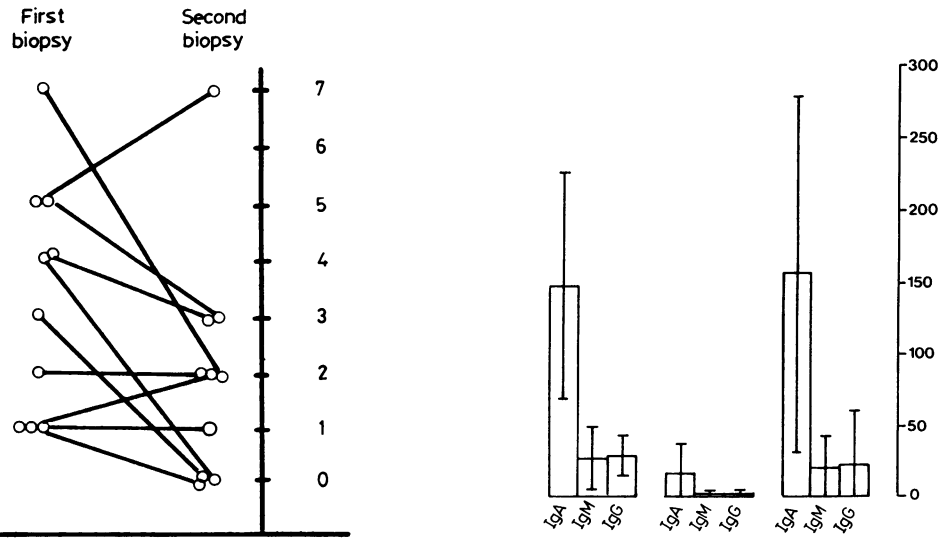

Fig. 2 *Number of IgE plasma cells per 0·5 mm muscularis mucosae in biopsies from the gastric antrum of 10 patients with follow up biopsies.*

Fig. 3 *Mean number and standard deviation of IgA, IgM, and IgG plasma cells in the gastric fundus per 0·1 mm² lamina propria area.*

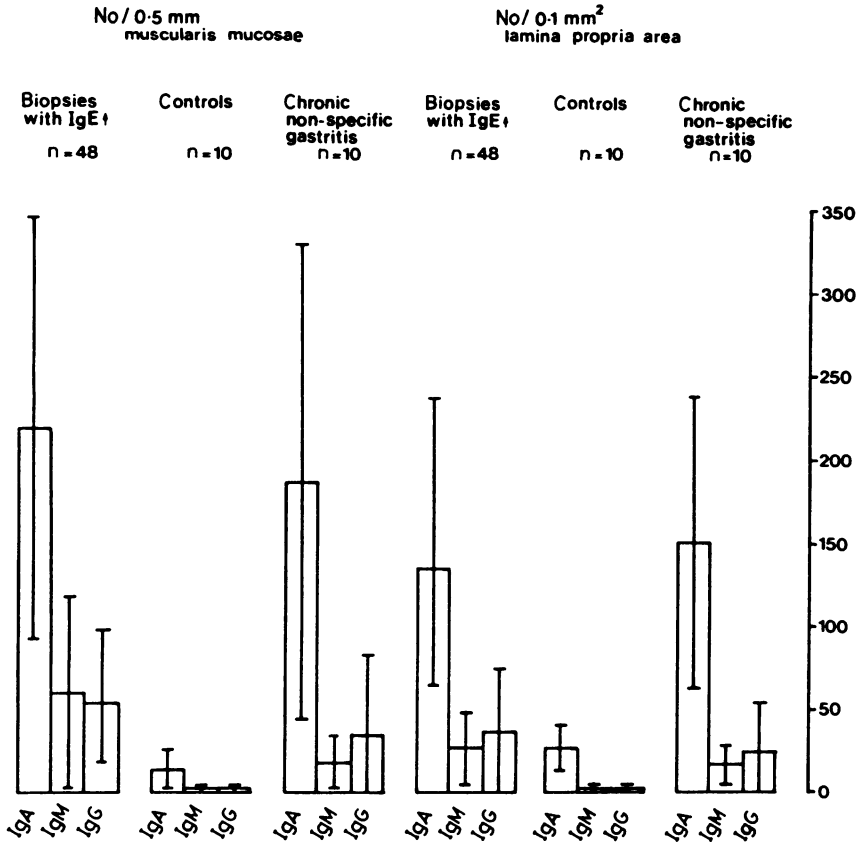

Fig. 4 *Mean number and standard deviation of IgA, IgM, and IgG plasma cells in the gastric antrum.*

immunoelectrophoresis and by immunofluorescence and immunoperoxidase staining on bone marrow preparations monoclonal for IgA, IgM, IgG, and IgE heavy chains. The IgE antiserum showed a reaction only with the IgE monoclonal bone marrow preparations and was checked for tissue performance in sections from a tonsil of an atopic patient. Such tonsils contain increased numbers of IgE containing cells.[1,2] Horseradish peroxidase-labelled goat antirabbit IgG was obtained from Miles (Yedah, Israel).

The IgA, IgM, IgG, and IgE stained sections were photographed using a standard magnification (100,8 ×) and projected on a graphic tablet interfaced to a computer (Ibas I, Kontron, Munich). The lamina propria area was limited by two lines perpendicular to the muscularis mucosae and this area was measured per mm stretched muscularis mucosae. Every photograph contained about one millimeter of muscularis mucosae. The number of immunoglobulin containing cells was counted in about the same area in two consecutive sections and expressed per 0·1 mm² lamina propria and per 0·5 mm muscularis mucosae ("mucosal tissue unit").[1,3] Some biopsies, especially those from the gastric fundus, contained no or insufficient muscularis mucosae; in these biopsies the number of Ig containing cells was only expressed per 0·1 mm² lamina propria area.

Results

In 67 of the 2543 patients (2·6%) one or more biopsies showed increased numbers of IgE containing cells. Morphologically these cells could be identified as plasma cells. Sometimes eosinophils and erythrocytes stained weakly too, but these cells could readily be distinguished on morphological grounds. Sufficient clinical data for evaluation were available from 51 of these 67 patients and all data presented refer to these 51 patients. Multiple biopsies were taken from different sites of the stomach and from both the stomach and the duodenum in several patients (Fig. 1). Follow up biopsies were obtained from 10 patients; they again showed increased numbers of IgE containing cells in seven patients (Fig. 2).

The numbers of IgA, IgM, and IgG containing

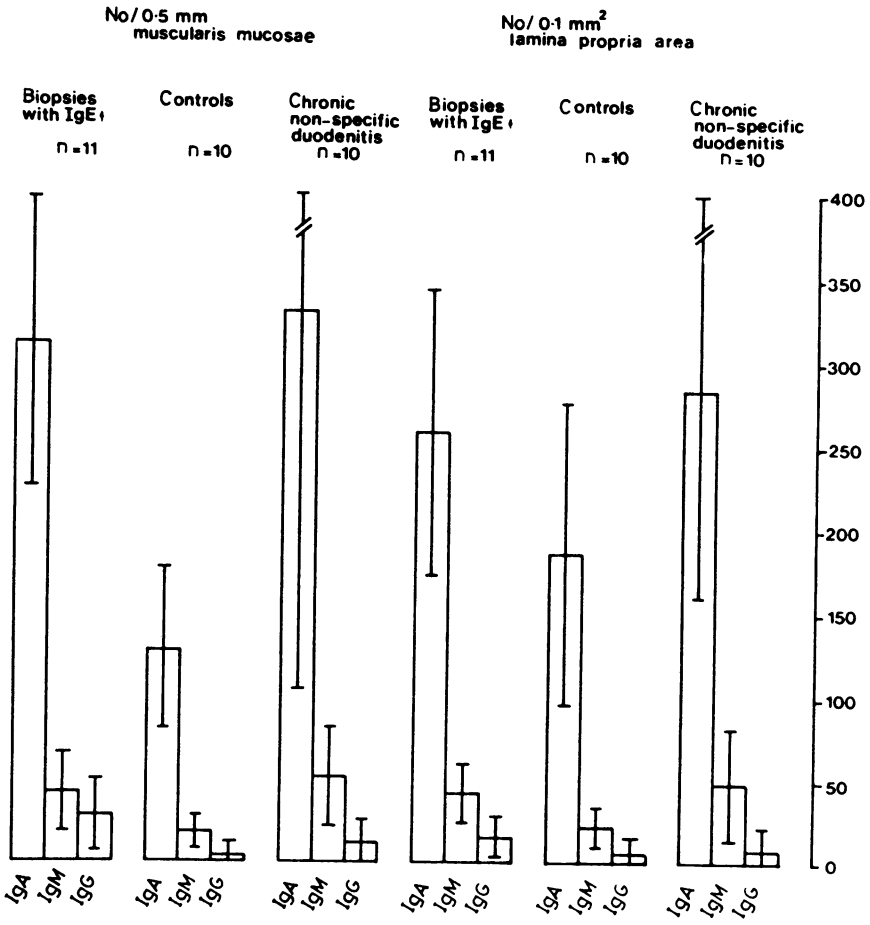

Fig. 5 *Mean number and standard deviation of IgA, IgM, and IgG plasma cells in the duodenum.*

cells, both per 0·1 mm² lamina propria area and per 0·5 mm stretched muscularis mucosae, in the gastric fundus and antrum and in the duodenal bulb are shown in Figs. 3–5. Besides an increased number of IgE containing cells patients' biopsies showed increased numbers of all major immunoglobulin classes compared with healthy volunteers, as found in patients with chronic non-specific gastritis and duodenitis.[9] The number of IgE containing cells in biopsies from patients in whom these cells were increased are shown in Table 1. IgE containing cells in these patients accounted for slightly less than 1% of the total number of immunoglobulin containing cells: 7·2‰ in the duodenum, 9·0‰ in the gastric antrum, and 7·2‰ in the gastric fundus.

The presenting symptoms of the patients with increased numbers of IgE containing cells are shown in Table 2. Heartburn, nausea, and vomiting as well as ill defined abdominal discomfort were often encountered. Intolerance of food was noted infrequently, and none of the clinical records studied mentioned a past or present history of atopy or allergy.

The findings at endoscopy (Table 3) cover the range of frequently found upper gastrointestinal abnormalities. One patient had both a gastric and duodenal ulcer and one patient had a gastric ulcer in combination with varioliform antrum gastritis. Many patients had signs of gastritis or duodenitis or both endoscopically, but in general agreement between endoscopical and histological findings was poor as far as gastritis and duodenitis was concerned. The gastric acid production was determined in 22 patients and found to be increased in 14, normal in six, and decreased or absent in two patients. Histologically all biopsies showed chronic non-specific inflammation (Table 4). Table 5 lists the clinical diagnoses. Patients with increased numbers of IgE containing cells in their upper gastrointestinal biopsies could not be distinguished from other patients

Table 1 *Mean number (+SD) of plasma cells containing IgE in gastric and duodenal biopsies*

	No of cells (+SD)
Per 0·5 mm muscularis mucosa	
Gastric fundus	—
Gastric antrum	3·0 ± 2
Duodenum	2·5 ± 2
Per 0·1 mm² lamina propria area	
Gastric fundus	2·0 ± 0·5
Gastric antrum	2·0 ± 1·0
Duodenum	2·0 ± 1·0

Table 2 *Presenting symptoms of 51 patients with increased numbers of IgE containing cells in their upper gastrointestinal biopsies*

Presenting symptom	*No of patients*
Heartburn	32
Nausea and vomiting	10
Ill defined abdominal discomfort	8
Ructus	6
Food intolerance	4
Hematemesis	4
Melaena	3
Nausea without vomiting	2
Decreased appetite	2
Tiredness	1

Table 3 *Findings at endoscopy in 51 patients with increased numbers of IgE containing cells in their upper gastrointestinal biopsies*

Findings at endoscopy	*No of patients*
Hiatus hernia oesophagéi	10
Bile stained secretion in the stomach	17
Gastric ulcers*	13
Duodenal ulcers*	9
Anastomositis in BI/BII stomach	2
Varioliform gastritis of the antrum*	3

*One patient had a gastric ulcer and a duodenal ulcer and one patient had a gastric ulcer and varioliform gastritis of the antrum.

Table 4 *Histological diagnoses in the biopsies from 51 patients with increased numbers of IgE containing cells**

Histological diagnosis	*No of patients*
Gastric fundus	
Chronic superficial gastritis	3
Active chronic superficial gastritis	2
Active chronic gastritis with atrophy	4
Gastric antrum	
Chronic superficial gastritis	9
Active chronic superficial gastritis	7
Chronic gastritis with atrophy	11
Active chronic gastritis with atrophy	18
Active chronic gastritis with atrophy and intestinal metaplasia	3
Duodenum	
Chronic duodenitis	4
Active chronic duodenitis	7

*Several patients had more than one histological diagnosis.

Table 5 *Clinical diagnoses in 51 patients with increased numbers of IgE containing cells in their gastrointestinal biopsies*

Clinical diagnosis	*No of patients*
Chronic non-specific gastritis in hiatus hernia oesophagéi	4
Chronic non-specific gastritis	15
Chronic non-specific gastritis and chronic non-specific duodenitis	10
Gastric ulcer	9
Duodenal ulcer and chronic non-specific antrum gastritis	4
Duodenal ulcer	3
Chronic non-specific gastritis in resected stomach ("anastomositis")	2
Varioliform antrum gastritis	1
Chronic non-specific duodenitis	1
Gastric and duodenal ulcer	1
Gastric ulcer and varioliform antrum gastritis	1

with chronic non-specific inflammation of the stomach and duodenum clinically, endoscopically, or histologically.

Discussion

In this study we found that 2·6% of patients in whom upper gastrointestinal endoscopy and biopsy was performed because of abdominal complaints had increased numbers of plasma cells containing IgE in their gastric and duodenal biopsies, as defined by two or more IgE bearing cells per high power field (×250).

All biopsies showed chronic non-specific inflammation of various causes. Apart from increased numbers of IgE containing cells in the upper gastrointestinal biopsies these patients were not distinct clinically, endoscopically, or histologically from other patients with inflammatory upper gastrointestinal disease. The finding of increased numbers of IgE containing cells in gastric and duodenal biopsies was usually reproduced in repeated biopsies within the same patient. However, in three patients increased numbers of IgE containing cells could not be found in repeated biopsies. This could have been due to the fact that IgE containing cells are not equally distributed along the gastrointestinal tract and tend to occur in clusters.

Previous investigators have found high numbers of IgE containing cells in biopsies from patients with diffuse varioliform gastritis,[5] gastritis due to biliary reflux in the stomach,[8] and at the bases of gastric and duodenal ulcers.[7] Others, however, have not found any differences in the numbers of IgE containing cells between patients with varioliform gastritis or chronic non-specific gastritis and healthy volunteers.[6] The latter study can be criticised on methodological grounds.[14]

We found increased numbers of IgE containing

cells in two patients with varioliform gastritis, whereas in four others they were absent. It should be stated that these patients represented antral varioliform gastritis and therefore our data do not necessarily contradict those of André *et al* on diffuse varioliform gastritis.[5 8] We found increased numbers of IgE containing cells in only a small percentage of the biopsies from all types of inflammatory lesions in the stomach. A major difference between our study and previous studies is that we used an immunoperoxidase instead of an immunofluorescence technique. This may be important since the immunoperoxidase technique, in contrast to immunofluorescence, allows study of histological details and identification of different cell types. It is known that IgE anitbodies react with activated mast cells in rats[15] and in humans with atopy.[1] Differentiation between plasma cells and mast cells is difficult if not impossible in immunofluorescence. The difference in techniques could therefore explain the higher numbers of IgE containing cells found by immunofluorescence.

What is the significance of increased numbers of IgE plasma cells in upper gastrointestinal biopsies? It is possible that IgE plasma cells are merely part of the chronic inflammatory infiltrate in some patients and that there is no aetiopathological significance. Previous studies, however, have established a relation between atopy and type I IgE mediated allergy and increased numbers of IgE containing cells in mucosal biopsies.[1-3] Since increased numbers of IgE containing cells were found in biopsies of patients with a wide variety of inflammatory disorders of the upper gastrointestinal tract, it is highly unlikely that atopy or type I allergy plays a primary aetiological role. It is, however, possible that chronic inflammation of the gastrointestinal mucosa with subsequent loss of integrity of the functional mucosal barrier leads to increased antigen exposure to the immune system. This may lead to secondary allergic reactions, presumably to food constituents, mediated by IgE in some patients. There is other evidence that allergy to food constituents may complicate gastrointestinal disease. In children, food allergy occurs more frequently than in adults and is often preceded by gastroenteritis.[16] In patients with gastrointestinal disease such as ulcerative colitis and coeliac disease high concentrations of specific IgE antibodies to food allergens have repeatedly been shown.[17] These findings support the hypothesis that allergy to food constituents may complicate damage to the gastrointestinal mucosa.

In this study the increased numbers of plasma cells containing IgE (that is, two or more plasma cells containing IgE per high power field $\times 250$) in gastric and duodenal biopsies were not correlated with a specific clinical, endoscopical, and histological picture. It is suggested that the increase of plasma cells containing IgE is a secondary reaction of the already damaged gastroduodenal mucosa to food constituents.

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References

[1] Hamashima Y. *Immunohistopathology.* Stuttgart: Georg Thieme Verlag, 1976: 24, 34, 55.

[2] Feltkamp Vroom TM, Stallman PJ, Aalbers RC, Reerink Brongers EE. Immunofluorescence studies on renal tissue, tonsils, adenoids, nasal polyp and skin of atopic and non atopic patients, with special reference to IgE. *Clin Imm Immunopathol* 1975;**4**:392–404.

[3] Rosekrans PCM, Meijer CJLM, Cornelisse CJ, Wal AM van der, Lindeman J. Use of morphometry and immunohistochemistry of small intestinal biopsies in the diagnosis of food allergy. *J Clin Pathol* 1980;**33**:125–30.

[4] Rosekrans PCM, Meijer CJLM, Wal AM van der, Lindeman J. Allergic proctitis, a clinical and immunopathological entity. *Gut* 1980;**21**:1017–23.

[5] André C, Moulinier B, Lambert R, Bugnon B. Gastritis varioliformis, allergy and disodium cromoglycate. *Lancet* 1976;i:964–5.

[6] Dekker W, Walinga H, Balk T, Tijtgat GNJ. Chronische varioliforme laesies van de maag: een onderzoek naar de aetiologie. *Ned Tijdschr v. Geneesk* 1983;**127**:240–4.

[7] Brown WR, Borthistle VK, Chen ST. Immunoglobulin E (IgE) and IgE-containing cells in human gastrointestinal fluids and tissues. *Clin Exp Immunol* 1975;**20**:227–37.

[8] André C, Valiart JL, Fargier MC. IgE-mediated reactions in inflammation of the stomach. In: Pepys J, Edwards AM, eds. *The Mast Cell, its role in health and disease*, Tunbridge Wells: Pitman Medical 1979;642–6.

[9] Spreeuwel JP van, Lindeman J, Wal AM van der, Weterman I, Kreuning J, Meijer CJLM. Morphological and immunohistochemical findings in upper gastrointestinal biopsies of patients with Crohn's disease of the ileum and colon. *J Clin Pathol* 1982;**35**:934–40.

[10] Whitehead R. *Mucosal biopsy of the gastrointestinal tract.* London: Saunders, 1973:17–32.

[11] Kreuning J, Bosma FT, Kuipers S, Wal AM van der, Lindeman J. Gastric and duodenal mucosa in healthy individuals. An endoscopic and histopathological study of 50 volunteers. *J Clin Pathol* 1978;**31**:69–77.

[12] Sternberger L. *Immunohistochemistry.* Englewood Cliffs: Prentice Hall, 1979:53.

[13] Brandtzaeg P, Baklien K, Fausa O, Hoel PS. Immunohistochemical characterisation of local immunoglobulin formation in ulcerative colitis. *Gastroenterology* 1974;**66**:1123–36.

[14] Spreeuwel JP van, Lindeman J, Meijer CJLM: Chronische varioloforme laesies van de maag. *Ned Tijdschr v Geneesk* 1983;**127**:753–4.

[15] Mayrhofer G, Bazin H, Gowans JL. Nature of cells binding anti-IgE in rats immunised with nippostrongylus brasiliensis: IgE synthesis in regional nodes and concentration in mucosal mast cells. *Eur J Immunol* 1976;**6**:537–45.

[16] Halpin T, Byrne WJ, Ament MJ. Colitis, persistent diarrhoea and soy protein intolerance. *J Pediatr* 1977;**91**:404–7.

[17] Bleumink E. Food allergy. In: Asquith P, ed. *Immunology of the gastrointestinal tract.* Edinburgh: Churchill Livingstone, 1979:195–213.

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