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The role of gluten, milk, and other dietary proteins in chronic or intermittent dyspepsia

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Summary

In twenty-seven patients with chronic or intermittent dyspepsia raised levels of the gamma-M-globulin and of the α_1- and of the α_2-globulin were encountered. Malabsorption, present in about three-quarters of the cases, was usually mild. Various degrees of villous abnormalities were seen but no flat mucosa. Eight patients also had dermatitis.

During dietary treatment with the elimination of gluten, milk, or other food elements the dyspepsia and the malabsorption subsided in all but two, and the dermatitis in all but one. In nearly all the investigated cases the raised levels of the gamma-M-globulin and of the α_1- and of the α_2-globulin decreased.

During challenge feeding with the offending food the dyspepsia and the dermatitis reappeared. Also the faecal fat excretion increased again, and a rise was noticed in the α_1- and in the α_2-globulins and in the gamma-M-globulins.

The findings suggest that gluten, milk and other dietary proteins may play a role in some chronic dyspepsias by exerting an antigenic stimulus on the small intestinal mucosa, and thus inducing a state of hypersensitivity towards these foods.

The clinical and laboratory findings favour the view that the condition is different from coeliac disease

Introduction

Intolerance to milk, mimicking coeliac disease has amongst others been described by Kunstadter & Schulz (1953), who attributed the symptoms to cow's milk allergy. Widespread intolerance to milk and milk products in various gastrointestinal disorders has been reported by Sewell *et al.* (1963). Kuitunen (1966) and Visakorpi, Immonen & Kuitunen (1967) noticed sensitivity to gluten and to milk in malabsorption syndromes. Some of their patients had a flat intestinal mucosa but in others the villous abnormalities were less pronounced.

In coeliac disease a flat or low convoluted small intestinal mucosa (subtotal villous atrophy) is mandatory (Roy-Choudhury *et al.*, 1966). Malabsorption is usually severe,

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indicated by a significant rise in the faecal fat excretion and by a decrease in the D-xylose absorption (Benson, Kowlessar & Sleisenger, 1964; Fone *et al.*, 1960). The rise in the blood glucose levels during oral glucose loads in the majority of the cases is less than 40 mg/100 ml (Stewart *et al.*, 1967), and a decreased lactase activity is common (Sheldon & Tempany, 1966; Prader, Shmerling & Hadorn, 1966).

The beneficial effect of a gluten-free diet in this disease is well known, but has been questioned in dyspepsias, where only minor villous abnormalities were found. However, Fone *et al.* (1960) could report on a beneficial effect of a gluten free diet also in malabsorption syndromes, where only minor villous changes were encountered. Thus several reports suggest that gluten and milk may play a role in various gastrointestinal disorders.

Twenty-seven patients with certain chronic or intermittent dyspepsias were investigated for malabsorption. The immunoglobulins were determined to elucidate possible immunological mechanisms. The patients then were treated with a gluten free, a gluten and milk free or an elimination diet to investigate the role of dietary proteins in the dyspepsia. After at least 1 month on the diet challenge with one or more food elements was done. Various laboratory investigations were carried out before and during the diets and during the challenge feeding.

Patients and methods

Twenty-seven patients, age range 6–74 years, with an average age of 34 years, were selected on account of an uncharacteristic dyspepsia, dominated by abdominal colic and usually frequent loose stools. All but one suffered from meteorism and complained of a prominent abdomen, increasing during the day. In the majority of the patients the dyspepsia had begun during childhood, but a period without or with minor complaints only had occurred during adolescence. Four patients had localized, dry, scaly eczema on the hands or on the face. Two others were cases of Besnier prurigo with generalized eczema. Two patients had dermatitis herpetiformis, and their cases have been described before (Pock-Steen & Niordson, 1970; Engquist & Pock-Steen, 1971). Asthma, vasomotor rhinitis and urticaria each, occurred in one patient and a fourth had urticaria during childhood. Dyspepsia was known to occur in near relatives of fourteen patients, and dermatitis or allergic symptoms occurred in near relatives of fifteen patients. Four patients had more than one near relative with dyspepsia, and eight patients had more than one near relative with allergic symptoms.

The following investigations were carried out. Biopsy of the small intestinal mucosa was done with a Crosby capsule under fluoroscopic control. The faecal fat excretion was determined according to a modified method of van de Kamer, Ten Bokkel Huinink & Weijers (1949). An oral lactose and an oral glucose plus galactose load was carried out with 1 g or with 0·5 plus 0·5 g/kg bodyweight respectively and the blood glucose levels were determined by reduction method in an autoanalyzer. The D-xylose test was performed with 25 g D-xylose according to the method of Roe & Rice (1948) and the urine was collected during 24 hr. The titres of the α_1- and of the α_2-globulin were determined by serum-electrophoresis, and the immunoglobulins by immunoelectrophoresis and by radial immunodiffusion (Clausen, 1969). Besides routine haematological investigations the Schillings test was carried out, and the serum folate and the serum B_{12} were determined. The eosinophil cells were counted before and during challenge with food elements.

In all patients but one, a gluten free diet was first instituted for 1 month. In one

patient only a milk free diet was tried, to which she responded well. With failure of improvement, a gluten and milk free or an elimination diet beginning with rice was tried. With favourable responses the elimination diet was slowly built up by adding a new food every day until a relapse was noted. This food was then omitted from the diet and other food elements were added to the diet until a new relapse was noted—in which case this food also was omitted—or until a normal diet without the suspected food or foods was built up. Then all patients were challenged with the suspected food. Control of the fat excretion and of the other investigations were carried out on a diet, from which the offending food or foods had been eliminated for 2–4 weeks, and also during the challenge with these foods.

In the statistical analysis of the laboratory findings the Students *t*-test was used in the α_1- and in the α_2-globulins, and the Wilcoxon test or the sign test in the other parameters.

Pretreatment findings

The results of the various investigations are listed in Table 1. A quarter of the patients had no malabsorption, and in only three cases the faecal fat excretion exceeded 10 g

Table 1. Laboratory findings in patients with chronic or intermittent dyspepsia

	No. of patients	Means ±s.d.	Normal range
Faecal fat excretion (g/day)	18	7·2±4·6	<6
D-Xylose excretion (g/24 hr)	13	5·3±2·0	>5·0
Oral glucose plus galactose load: rise in blood glucose (mg/100 ml)	15	50±21	>40
Oral lactose load: rise in blood glucose (mg/100 ml)	16	45±17	>25
α_1-Globulin (g/100 ml)	26	0·60±0·15	0·2–0·6
α_2-Globulin (g/100 ml)	26	0·85±0·22	0·4–0·9
Gamma-G-globulin (g/100 ml)	27	0·953±0·200	0·930–1·400
Gamma-A-globulin (g/100 ml)	27	0·206±0·127	0·067–0·253
Gamma-M-globulin) (g/100 ml)	27	0·188±0·115	0·048–0·123

per day. The remaining had an excretion between 6 and 10 g per day. Impaired absorption of D-xylose was found in three patients. The rise in blood glucose levels during oral carbohydrate loads was less then 40 mg/100 ml in one-third of the cases. In one case a lactose malabsorption was suspected as an oral lactose load yielded an entirely flat curve, whereas a glucose plus galactose load resulted in a normal rise in the blood glucose level. The α_1- and the α_2-globulins usually showed slightly elevated titres. The gamma-M-globulins were raised, whereas no consistent changes were noticed in the levels of the gamma-A- and of the gamma-G-globulins. The serum folate and the serum B_{12} levels were normal in all the cases. The Schilling test was within low normal range in one case and normal in the others.

Biopsy of the small intestinal mucosa was done in ten cases. In one the villi were slender without cellular infiltration. Seven patients had oedematous and often shortened villi with various degrees of cellular infiltration, consisting predominantly of plasma cells and of lymphocytes. In two cases a more severe partial villous atrophy was seen with heavy cellular infiltration, but no flat mucosa.

Results of dietary treatment

In twenty-five patients the dyspeptic complaints disappeared during the diets. Twelve patients benefited from a gluten free diet only. Six improved when gluten as well as milk was excluded from the diet. One patient improved on a milk free diet only. In the remainder other food elements, besides gluten, seemed to cause relapse. During the diet the dyspepsia usually subsided in a few days. Two patients were on a gluten free diet for 1 month and 2 weeks respectively, without improvement, and they did not wish to try further elimination diets.

During the elimination diets the dermatological complaints responded favourably in about a week. This was the case during the elimination of gluten in two patients,

Table 2. Laboratory findings (means ± s.d.) in patients with chronic or intermittent dyspepsia before and during the elimination of gluten

	No. of patients	Normal range	Diet with gluten	Gluten free diet	*P*
Faecal fat excretion (g/day)	10	< 6	9·1 ± 5·1	5·3 ± 1·6	< 0·01
D-Xylose excretion (g/24 hr)	4	> 5·0	4·0 ± 1·5	5·1 ± 1·0	n.s.
Oral glucose plus galactose load: rise in blood glucose (mg/100 ml)	6	> 40	35·3 ± 16·0	60·3 ± 13·7	< 0·05
Oral lactose load: rise in blood glucose (mg/100 ml)	4	> 25	32·2 ± 11·8	52·3 ± 10·0	n.s.

n.s. = not significant.

Table 3. Serum proteins (g/100 ml: means ± s.d.) in patients with chronic or intermittent dyspepsia before and during the elimination of gluten

	No. of patients	Normal range	Diet with gluten	Gluten free diet	*P*
α_1-Globulin	12	0·2–0·6	0·59 ± 0·13	0·45 ± 0·11	< 0·01
α_1-Globulin	12	0·4–0·9	0·90 ± 0·23	0·74 ± 0·11	< 0·01
Gamma-G-globulin	6	0·930–1·400	1·073 ± 0·241	1·193 ± 0·224	n.s.
Gamma-A-globulin	6	0·067–0·253	0·230 ± 0·156	0·298 ± 0·127	n.s.
Gamma-M-globulin	6	0·048–0·123	0·221 ± 0·137	0·142 ± 0·082	< 0·05

n.s. = not significant.

and during the elimination of gluten and milk in one patient. One patient repeatedly got severe outbreaks of generalized eczema and another patient got urticaria after the consumption of gluten, milk, pork, and of several fruits. In one patient who tried a gluten free diet only, the eczema was unchanged.

Gluten free diet

The dietary results during a gluten free diet are listed in Tables 2 and 3. The faecal fat excretion, repeated in nine patients, decreased in all but one. The difference is signifi-

cant ($P<0{\cdot}01$). The blood glucose levels during oral glucose plus galactose loads, repeated in six patients rose significantly in all ($P<0{\cdot}05$). During oral lactose loads in four patients the maximal blood glucose levels increased in all. The D-xylose test showed a rise in three out of four investigated cases, the fourth being normal before and during the diet. These differences are not significant. The α_1- globulin decreased in nine and remained unchanged in three ($P<0{\cdot}01$). The α_2-globulin decreased in ten and rose in two patients ($P<0{\cdot}01$). The gamma-M globulin decreased significantly in all, from a mean of $0{\cdot}221\pm0{\cdot}137$ to $0{\cdot}142\pm0{\cdot}082$ g/100 ml ($P<0{\cdot}05$), whereas no consistent changes were noticed in the levels of the gamma G and of the gamma-A-globulin (Table 5).

Milk free diet

During the elimination of milk in one patient the faecal fat excretion decreased from 15·4 to 8·8 g per day. In the same patient an oral lactose load showed an increase in the maximal rise in the blood glucose level from 25 to 55 mg/100 ml. Four patients were on a gluten free diet, when milk was eliminated and one was on a normal diet. The α_1-globulin showed a slight but not significant decrease, whereas the α_2-globulin, repeated in five patients, decreased significantly in all ($P<0{\cdot}025$). In four cases the gamma-M-globulin decreased during the diet from a mean of $0{\cdot}270\pm0{\cdot}209$ to a mean of $0{\cdot}107\pm0{\cdot}055$ g/100 ml ($P\simeq0{\cdot}1$). The results are listed in Tables 4 and 5.

Table 4. Serum proteins (g/100 ml: means ± s.d.) in patients with chronic or intermittent dyspepsia before and during the elimination of milk

	No. of patients	Normal range	Diet with milk	Milk free diet	*P*
α_1-Globulin	5	0·2–0·6	$0{\cdot}46\pm0{\cdot}05$	$0{\cdot}40\pm0{\cdot}07$	n.s.
α_2-Globulin	5	0·4–0·9	$0{\cdot}96\pm0{\cdot}21$	$0{\cdot}74\pm0{\cdot}15$	$<0{\cdot}025$
Gamma-G-globulin	4	0·930–1·400	$1{\cdot}124\pm0{\cdot}285$	$0{\cdot}983\pm0{\cdot}095$	n.s.
Gamma-A-globulin	4	0·067–0·253	$0{\cdot}270\pm0{\cdot}169$	$0{\cdot}283\pm0{\cdot}171$	n.s.
Gamma-M-globulin	4	0·048–0·123	$0{\cdot}270\pm0{\cdot}209$	$0{\cdot}107\pm0{\cdot}055$	$\simeq0{\cdot}1$

n.s. = not significant.

Other elimination diets

During the elimination of other offending food elements such as rice, pork, cheese and coffee there was usually a definite decrease in the level of the gamma-M-globulin (Table 5).

Elimination diets in controls

In eleven controls (one healthy volunteer, one patient with asthma but without dyspepsia, and in nine patients with various dyspeptic complaints) a gluten free or a milk free diet was instituted. None of the controls benefited from the diets, and no change was seen in the levels of the serum proteins. In five controls the mean of the gamma-M-globulin was $0{\cdot}131\pm0{\cdot}032$ before and $0{\cdot}137\pm0{\cdot}036$ g/100 ml during a gluten free diet. Also on this diet in six controls the α_1-globulin was $0{\cdot}41\pm0{\cdot}25$ before and $0{\cdot}40\pm0{\cdot}21$ g/100 ml during the diet, and the α_2-globulin $0{\cdot}60\pm0{\cdot}06$ before and $0{\cdot}63\pm0{\cdot}09$ g/100 ml during the diet. During a milk free diet in five other controls the mean of the

Table 5. The gamma-M-globulins in patients with chronic or intermittent dyspepsia during elimination diets

g/100 ml

Case no.	Pre-elimination diet	Level during elimination diets					
		Gluten	Milk	Cheese	Pork	Rice	Coffee
1	0·176*	0·150					
	0·150		0·143				
	0·135			0·108			
2	0·428*	0·304					
	0·304		0·165				
3	0·099*	0·076					
	0·076		0·055				
4	0·360*	0·106					
	0·106					0·081	
5	0·150*	0·118					
6	0·115*	0·100					
7	0·550*		0·065				
8	0·190					0·156	
9	0·158				0·156		
10	0·191				0·156		
	0·156						0·138

* Levels on normal diet

gamma-M-globulin was found to be $0{\cdot}083 \pm 0{\cdot}040$ before and $0{\cdot}088 \pm 0{\cdot}037$ g/100 ml during the diet. On a milk free diet in three controls the α_1-globulin was determined as $0{\cdot}37 \pm 0{\cdot}05$ before and as $0{\cdot}43 \pm 0{\cdot}05$ g/100 ml during the diet. The α_2-globulin level remained unchanged $0{\cdot}73 \pm 0{\cdot}06$ g/100 ml.

Challenge feedings

All patients were challenged several times with the suspected foods. Only when a food invariably caused dyspepsia or dermatitis, and the renewed elimination was followed by a remission of the symptoms, it was accepted as an offending food. Control of the laboratory investigations was usually performed after 1–2 weeks of challenge feeding with the suspected food.

Challenge feeding with gluten

In four patients the faecal fat excretion increased during the challenge in all from a mean of $5{\cdot}0 \pm 1{\cdot}8$ to a mean of $8{\cdot}9 \pm 4{\cdot}8$ g/day ($P \simeq -0{\cdot}1$). Also in four patients the α_1-globulin increased in all from a mean of $0{\cdot}40 \pm 0{\cdot}09$ to $0{\cdot}53 \pm 0{\cdot}13$ g/100 ml ($P < 0{\cdot}1$) and the α_2-globulin level rose in all from a mean of $0{\cdot}63 \pm 0{\cdot}05$ to a mean of $0{\cdot}85 \pm 0{\cdot}13$ g/100 ml ($P < 0{\cdot}05$). Two patients showed a rise in the gamma-M-globulin during the challenge with gluten (Table 6).

The eosinophil cell count was performed before and during the challenge with gluten in five patients and in nine controls. In the controls a decrease was seen with minimum levels at 2 and 4 hr, and the initial level was reached again after 6 hr. In all the patients an increase was observed, which continued for 6 hr or more before the

Table 6. The gamma-M-globulins (g/100 ml) in patients with chronic or intermittent dyspepsia during dietary treatment and during challenge feeding

Case no.	Pre-challenge level	Level during challenge feeding				
		Gluten	Milk	Cheese	Pork	Coffee
1	0·143	0·158				
	0·110				0·128	
	0·124			0·135		
	0·108		0·111			
3	0·055		0·091			
5	0·144	0·150				
10	0·138					0·154

cell count became normal again. After 2 hr the difference is significant at the 0·005 level and after 4 hr at the 0·01 level (Table 7 and Fig. 1).

Challenge feeding with milk

In one patient during the challenge the faecal fat excretion increased from 3·3 to 6·4 g/day. In four patients the α_1-globulin level rose from a mean of $0{\cdot}40 \pm 0{\cdot}09$ to a mean of $0{\cdot}50 \pm 0{\cdot}09$ g/100 ml ($P < 0{\cdot}1$), and the α_2-globulin levels from $0{\cdot}73 \pm 0{\cdot}13$ to $0{\cdot}98 \pm 0{\cdot}17$ g/100 ml ($P < 0{\cdot}05$). In one patient the gamma-M-globulin increased from 0·55 to 0·078 during 2 weeks of challenge with milk and to 0·091 g/100 ml during the following 2 weeks, in which he continued to consume milk. In a second patient, only challenged for 1 week because of the reappearance of severe colicky pain, the gamma-M-globulin only rose slightly. In a third patient the gamma-M-globulin was determined as 0·220 and as 0·304 g/100 ml during two periods of challenge feeding and as 0·165 g/100 ml during the following milk free period. In the same patient the gamma-M line in immunoelectrophoresis was estimated during four periods without milk, where it was found normal in three periods and slightly accentuated in the fourth. During the consumption of milk the gamma-M line was slightly accentuated in one and definitely increased in the other period.

Table 7. Increase and decrease in the number of the eosinophil cells per μl during challenge feeding (means $\pm$ s.d.)

		2 hr		4 hr	
Challenge with gluten	5 patients	+ 51 ± 12	$P < 0{\cdot}005$	+ 71 ± 84	$P < 0{\cdot}01$
	9 controls	− 39 ± 46		− 64 ± 72	
Challenge with milk	4 patients	+ 38 ± 31	$P < 0{\cdot}01$	+138 ± 117	$P < 0{\cdot}05$
	6 controls	− 82 ± 18		− 74 ± 86	
Challenge with cheese	1 patient	+ 56		+100	
	1 control	−206		−261	
Challenge with coffee	1 patient	+131		+125	
Challenge with rice	1 control	− 19		− 19	

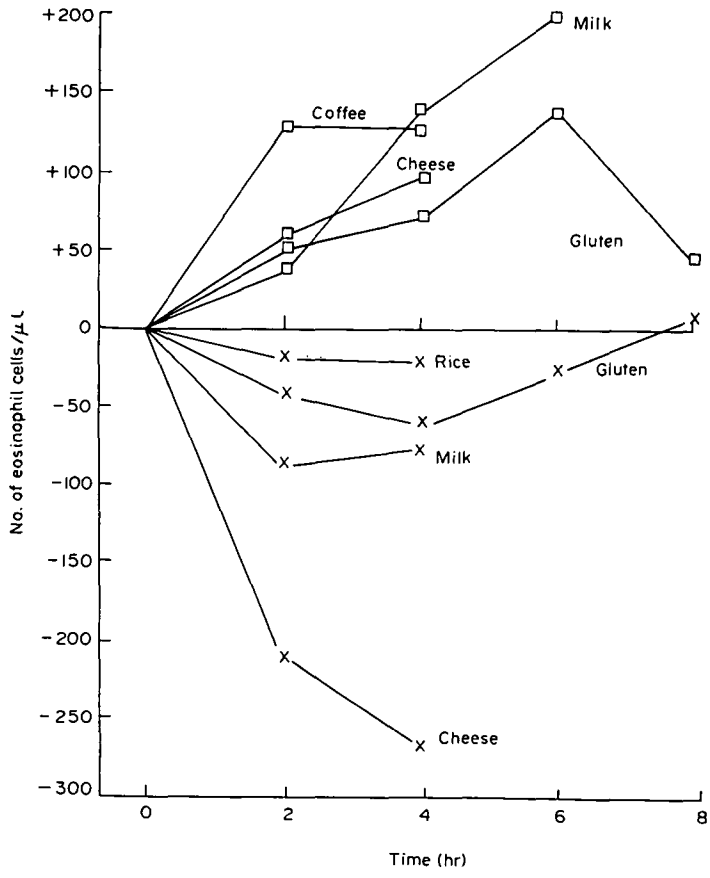

Fig. 1. Mean increase and decrease in the number of the eosinophil cells per μl during challenge feeding. □, Patients; ×, controls.

The eosinophil cells were counted before, and 2 and 4 hr after the intake of milk in four patients and in six controls. In the patients a definite rise was seen, whereas the number of the eosinophil cells decreased in all the controls but one. In this control a decrease was seen after 2 hr but a rise after 4 hr. The difference is significant at the 0·01 and at the 0·05 level respectively (Table 7 and Fig. 1).

Other challenge feedings

Three patients were challenged with pork, cheese and coffee respectively, and also in these patients a rise in the gamma-M-globulin was noticed (Table 6). In two of these patients a rise in the number of the eosinophil cells was obtained by the challenge feeding with cheese and coffee (Table 7 and Fig. 1). In two controls, challenged with cheese and rice respectively, a decrease in the number of the eosinophil cells was seen.

Discussion

Repeated attacks of asthma, skin eruptions or severe systemic reactions following the ingestion of certain foods are highly suggestive of a hypersensitivity reaction towards

these foods, whereas evidence of immunological mechanism is difficult to provide, when the intake of some food results in gastrointestinal complaints. Skin tests are not always positive and the levels of circulating antibodies may not be raised in the individual patient.

Diarrhoea and abdominal complaints after the consumption of milk is seen in lactose malabsorption. Of the twenty-seven patients eleven benefited from the elimination of milk from the diet. However, amongst these eleven only one patient was suspected of a lactose malabsorption. In eight patients lactose malabsorption could be excluded by an oral lactose load as the rise in the blood glucose was more than 25 mg/100 ml (Gudmand-Høyer & Jarnum, 1968). In the remaining two patients no oral lactose load was performed. However, both patients relapsed during the challenge feeding with milk and with milk products such as cheese as well, and in one the eczema flared up again. Thus, their symptoms hardly could be explained by a lactose malabsorption only.

In this study the malabsorption in a certain type of dyspepsia could be controlled by the elimination of food elements from the diet, of which gluten and milk were the most common. These results are in accordance with the findings of Visakorpi *et al.* (1967) and of Pock-Steen & Lorenzen (1968). In seven out of eight patients the dermatitis improved during the elimination diets. Besides, a decrease in the gamma-M-globulin and in the α_1- and in the α_2-globulins was noticed. Raised levels of the α_1- and of the α_2-globulins have been reported by Friedman & Hare (1965) in patients in whom severe eczema could be provoked by gluten.

During repeated challenge feedings followed by renewed elimination of certain foods the dyspepsia and the dermatitis reappeared and disappeared again. During the challenge feeding the faecal fat excretion increased and the levels of the serum proteins rose towards pre-treatment values.

The question arises, whether the disorder described in the present study is identical or in some way related to coeliac disease. There are some points of similarity between the disorder and coeliac disease: the dominating role of gluten, the malabsorption, and the clinical course with a history of dyspepsia in early life; the differences might be of quantitative rather than of qualitative nature.

According to Asquith, Thompson & Cooke (1969) coeliac disease might be elicited by the antigenic stimulus of gluten to the small intestinal mucosa, as these authors found significantly raised gamma-A-globulins in untreated coeliac disease, and a decrease during a gluten free diet. The rise in the gamma-A-globulins might be explained by an antigenic stimulus of the gluten molecule. However, as the decrease in the gamma-A-levels during the diet usually was modest and took place over several months, it might have been a secondary phenomenon also.

Untreated coeliac disease without a sub-total villous atrophy apparently is never seen (Roy-Choudhury *et al.*, 1966). Thus, it is unlikely that the patients in the present study were cases of coeliac disease, in spite of their sensitivity to gluten. Moreover, normal levels of serum folate and of serum B_{12} and normal Schilling tests are rare in patients with coeliac disease. Dermatitis and other allergic symptoms were common amongst the patients and their relatives. Apart from a scaly, dry skin, these features are unusual in coeliac disease (Alvey, Anderson & Freeman, 1957; Badenoch, 1960).

Immediate and severe anaphylactic reactions towards certain food elements are well known. Such anaphylactic reactions have also been described in infants after the intake of gluten and milk (Fällström, Winberg & Andersen, 1965; Visakorpi &

Immonen, 1967). In none of the patients described in this study were immediate reactions towards food elements noticed. However, the elevated levels of the gamma-M-globulins and the decrease during the elimination diets and the increase of these serum proteins during challenge feeding as well within a few weeks indicates a close relation between the raised levels of the gamma-M-globulins and the intake of certain food elements. These findings and the rise of the eosinophil cells during the intake of the offending food element suggest that the disorder might be the result of a hypersensitivity reaction elicited by these foods.

This hypersensitivity reaction probably is based on different immunological mechanisms than in patients with immediate and anaphylactic reactions after the intake of some foods, and might be of the delayed type as the remission during the elimination diets and the relapse during challenge feedings takes place in the course of some days.

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