References

[1] Hoogstraten, B, *et al*, *Blood*, 1969, **33**, 370.
[2] Luce, J K, *et al*, *Cancer*, 1971, **28**, 306.
[3] Bagley, C M, Jun, *et al*, *Annals of Internal Medicine*, 1972, **76**, 227.
[4] Rappaport, H, *Publication of the Armed Forces Institute of Pathology*, 1966, 91.
[5] Gerard-Marchant, R, *et al*, *Lancet*, 1974, **2**, 406.
[6] Armitage, P, *Statistical Methods in Medical Research*, London, Halstead Press, 1971.
[7] Gehan, E A, *Biometrika*, 1965, **52**, 203.
[8] Young, R C, *et al*, *Cancer Treatment Reports*, 1977, **61**, 1153.
[9] Chaffey, J T, *et al*, *International Journal of Radiation Biology and Related Studies in Physics, Chemistry and Medicine*, 1976, **1**, 399.
[10] Schein, P S, *et al*, *Blood*, 1974, **43**, No 2, 181.
[11] Skarin, A T, *et al*, *Cancer*, 1974, **34**, 1023.
[12] Gorin, N C, *et al*, *Medical and Paediatric Oncology*, 1977, **3**, 41.
[13] Portlock, C S, *et al*, *Blood*, 1976, **47**, 747.
[14] Young, R C, *et al*, *ASCO Abstracts*, 1977, 356.
[15] Jones, S E, *et al*, *Cancer*, 1973, **31**, 806.
[16] Oazi, R, Aisenberg, A C, and Long, J C, *Cancer*, 1976, **36**, 1923.
[17] Bloomfield, C D, *et al*, *Cancer*, 1974, **33**, 870.
[18] Bloomfield, C D, McKenna, R W, and Brunning, R D, *Briitsh Journal of Haematology*, 1976, **32**, 41.
[19] Fisher, R I, *et al*, *American Journal of Medicine*, 1977, **63**, 177.
[20] McKenna, R W, Bloomfield, C D, and Brunning, R D, *Cancer*, 1975, **36**, 428.
[21] Spiro, S, *et al*, *British Journal of Cancer*, 1975, **31**, suppl No II, p 60.
[22] Rodriguez, V, *et al*, *Blood*, 1977, **49**, 325.
[23] Skarin, A T, *et al*, *Blood*, 1977, **49**, 759.

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Coeliac disease and immunological disorders

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Summary and conclusions

Out of 314 patients with coeliac disease, 63 had associated disorders of known or suspected immunological cause (excluding aphthous stomatitis and dermatitis herpetiformis). Autoimmune diseases appeared to occur more often in patients with coeliac disease than in the normal population, 52 such diseases being found in 45 patients. Of individual disorders, diabetes mellitus, thyroid diseases, and ulcerative colitis seemed to be more common than expected. Atopy (asthma and eczema) occurred in 7% of the patients.

Most of these immunological disorders developed when the patients were on normal diet. A gluten-free diet and virtually normal jejunum did not prevent their development, and the diet had little ameliorating effect on their course apart from an occasional dramatic improvement in atopic patients.

Introduction

There have been many reports of patients with coeliac disease and a coexistent disorder of known or suspected immunological aetiology.[1-7] It has been suggested that such disorders are common as a result of either circulating immune complexes originating in the damaged small intestine[1] or the passage of antigens across the damaged intestine.[7] Furthermore, Scott and Losowsky[1] thought that some immunological disorders in patients with coeliac disease might improve with a gluten-free diet. No supporting evidence for the suggestion was obtained from either individual patients or relatively small series of patients with coeliac disease,[8] however, and the effect of a gluten-free diet on the progress of these associated conditions has not been reported.

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We describe the various immunological disorders found in a large series of patients with coeliac disease and examine the relation of a gluten-free diet to the time of presentation and course of the disorders.

Patients and methods

During 1958-77, 314 adults with coeliac disease confirmed by jejunal biopsy[11] were followed up in this unit under the care of one of us (WTC). Fifty-four patients with coeliac disease seen before 1958 were excluded because either jejunal biopsy had not been carried out or their notes were inadequate for analysis. Of the 314 patients, 177 were women and 137 men; 28 of the women and 35 of the men died during the study.

Information about diseases of possible autoimmune or atopic aetiology was verified with the patients when possible and by review of notes on patients who had died or were seen only yearly. Aphthous ulceration and dermatitis herpetiformis—disorders with possible immunological aetiology related to gluten—were not included because of their known association with coeliac disease.[9 10]

Results

IMMUNOLOGICAL DISEASE

We found 75 immunological disorders in 63 (20%) of the 314 patients (see table). Of the 177 women, 34 (19%) had 41 immunological diseases, and of the 137 men, 29 (21%) had 34 diseases. Four women and five men had two immunological disorders each, and one woman had four coexistent disorders. In patients with autoimmune disorders the mean age at diagnosis of coeliac disease was 46 years, and in those with atopy it was 39 years. The mean age at onset of the autoimmune disorders was 38 years, but that of the atopic disorders could not be established.

Autoimmune disorders

Altogether, 52 autoimmune disorders were seen in 45 patients (14%); 28 were seen in 23 of the women (13%), and 24 in 22 of the men (16%). The most common disorder was diabetes mellitus. Ten patients had insulin-dependent diabetes, and four (three women and one man) had maturity-onset diabetes controlled by diet and oral hypoglycaemic agents. Eleven patients had thyroid disorders: four had thyrotoxicosis, of whom three (two women, one man) had Graves's disease and one man had a toxic adenoma; and seven (four women, three men) had myxoedema, of whom two had histologically proved Hashimoto's thyroiditis, one with a coexistent reticulum cell sarcoma of the thyroid.

Incidences of autoimmune disease and atopy in 314 patients with coeliac disease, and mean ages at diagnosis of coeliac disease and onset of autoimmune disease. Mean age at onset of atopy could not be established

Disorder	Patients in whom disorder seen*				Mean age in years at onset of immunological disease (range)	Mean age in years at diagnosis of coeliac disease (range)
	Men	Women	Total	%		
Autoimmune disease						
Diabetes mellitus	6	8	14	4·5	34 (4-62)	48 (28-66)
Thyroid disorders	5	6	11	3·5	46 (33-66)	47 (32-66)
Inflammatory bowel disease	3	1	4	1·3	31 (17-41)	34 (17-53)
Connective tissue disorders	8	11	19	6·1	34 (5-64)	48 (21-73)
Rheumatic fever	3	5	8		15 (5-42)	51 (33-73)
Rheumatoid arthritis	0	2	2		49 (48, 50)	54 (43, 64)
Seronegative polyarthritis	1	2	3		55 (55, 55, 56)	48 (55, 39, 50)
Ankylosing spondylitis	1	0	1		35	37
Chronic discoid lupus erythematosus	1	0	1		64	60
Periarteritis nodosa	0	1	1		58	49
Scleroderma	1	1	2		38 (21, 54)	42 (21, 63)
Cutaneous vasculitis	1	0	1		39	25
Chronic liver disease	1	2	3	1·0	55 (37, 64, 65)	46 (25, 64, 50)
Diffuse lung disease	1	0	1	0·3	57	60
Total	24	28	52	16·6	38	46
Atopy						
Asthma	3	3	6	1·9		36 (10-59)
Eczema	7	10	17	5·4		42 (17-66)
Total	10	13	23	7·3		39

*Some patients had more than one autoimmune or atopic disease.

Scleroderma was present in two patients: a man had sclerodactyly, and a woman had severe diffuse scleroderma of the bowel, which led to her death. Eight patients with joint swellings had histories suggestive of rheumatic fever in childhood but only one progressed to chronic rheumatic carditis. Inflammatory bowel disease occurred in four patients. Three (two men, one woman) had ulcerative colitis, but although the woman developed rectal carcinoma and died, the men survived without bowel complications or surgery; the other man had Crohn's disease, confirmed by rectal biopsy. He had recurring iridocyclitis but no other extrabowel manifestation and did not need surgery. Liver biopsy confirmed chronic active hepatitis in two patients (a man and a woman) and cryptogenic cirrhosis in one woman. One man had diffuse pulmonary fibrosis, although he had no rheumatoid factor, avian precipitins, or precipitins to thermophilic actinomycetes in his serum.

Two men had more than one autoimmune disease—namely, diabetes with diffuse lung disease, and chronic active hepatitis with seronegative polyarthritis. Three women had two autoimmune diseases—namely, rheumatic fever with diabetes, cryptogenic cirrhosis with diabetes, and thyrotoxicosis with diabetes. One woman had three autoimmune disorders—thyrotoxicosis, rheumatoid arthritis, and rheumatic fever—as well as eczema. Three men with one autoimmune disease each also had one atopic disorder each.

Atopic disorders

Twenty-three atopic disorders were found in 22 patients (7%); 13 were seen in 12 of the women (7%), and 10 in 10 of the men (7%). One woman had asthma and eczema.

RELATION OF TIME OF ONSET TO GLUTEN-FREE DIET

Autoimmune disorders—Of the 45 patients with autoimmune disorders, 36 had received a gluten-free diet; five were taking the diet when the disorder developed. One man developed thyrotoxicosis within a few months of starting the diet, and in one woman the diagnosis was made only after failure of the diet to relieve diarrhoea. One woman developed myxoedema while on the diet; a repeat biopsy specimen showed continued severe abnormalities of the jejunum. One woman developed seronegative polyarthritis after two years of inadequate dietary control. Chronic active hepatitis developed in another woman taking the diet, although the jejunal mucosa continued to be flat despite symptomatic improvement. One man developed ulcerative colitis while on diet, although repeat biopsy showed a near-normal jejunum. Cutaneous vasculitis appeared in one patient after 12 years on diet, and periarteritis nodosa in another after two years of strict dieting; in neither case was the state of the mucosa known.

Atopic disorders—Of the 22 patients with atopic disorders, 15 had received a diet. Two (one man, one woman) developed eczema while on the diet, though in neither was the state of the jejunal mucosa known.

RESPONSE TO GLUTEN-FREE DIET

Autoimmune disorders—There was no evidence that any autoimmune disorder improved with the gluten-free diet, although insulin-dependent diabetes became easier to control.

Atopic disorders—Two men with eczema had dramatic and persisting relief from their rash when on diet, but there was no change in the other 20 patients.

TIME ON NORMAL DIET COMPARED WITH THAT ON GLUTEN-FREE DIET

Most of the patients with immunological disorders presented while on a normal diet or while the jejunal mucosa was still abnormal; for the 51 patients who had some dietary control, however, the mean time on a normal diet was 44 years as compared with only 7·5 years on a gluten-free diet.

Discussion

Hodgson *et al*[7] found atopic asthma and eczema in 6 (17%) out of 35 patients with coeliac disease compared with 3% of a control series of patients with peptic ulcer. If hay fever had been included the incidence would have increased to 29%. Hay fever was excluded from the present series owing to the difficulty of confirming it in patients who had died or could not be interviewed. Comparison between the figures of Hodgson *et al* and the 7% incidence of atopic disorders found in the present series suggests that atopic asthma and eczema are more common in patients with coeliac disease than in the normal population. Lancaster-Smith *et al*[8] found autoimmune disorders in 11 (19%) out of 57 patients with coeliac disease. If we exclude from the present series rheumatic fever because of lack of diagnostic confirmation and maturity-onset diabetes because of lack of evidence of islet-cell antibodies,[12] the number of patients with autoimmune disease falls from 45 to 34, or from 14% to 11%. No firm conclusion can be drawn about the significance of these figures, however, since the incidence of coeliac disease in the community is not known, and that of immune disorders is even less certain. Nevertheless, even if affecting only 11% of the patients, autoimmune disorders appear to be more common in people with coeliac disease than in the population as a whole.

Individually, only diabetes mellitus, thyroid disease, and inflammatory bowel disease seem to be more common in patients with coeliac disease. The incidence of diabetes in Birmingham[13] leads to the tentative conclusion that while coeliac disease may be no more common in patients with diabetes than in the normal population, diabetes is more

common in patients with coeliac disease.[14] Even without reliable figures on the incidence of thyroid disorders, these also appear to be more common in patients with coeliac disease. Similarly, the number of patients with ulcerative colitis was greater than expected. The other individual associations may well have been fortuitous. No patients were seen with vitiligo,[8] Addison's disease,[15 16] Sjögren's syndrome,[17-19] or amyloid[20] or idiopathic pulmonary haemosiderosis,[21] apart from one patient with Addison's disease who died before the introduction of jejunal biopsy and was therefore excluded from the study. Also among the excluded patients were six with chronic rheumatic heart disease.[22] The association between coeliac disease and scleroderma has not been reported, that with Crohn's disease has been reported twice,[23 24] and that with diabetes and thyrotoxicosis only once.[2]

These associations may possibly be explained by a genetic link through HLA genes, since coeliac disease is associated with HLA-B8[25 26] as also are diabetes mellitus,[27 28] thyroid disease,[29] and allergic alveolitis,[30] although other disorders such as inflammatory bowel disease are not.[31] Various autoantibodies are common in the serum of patients with coeliac disease[7 8 32 33] and may be related to the jejunal mucosal damage. Scott and Losowsky,[1] using as an analogy the lesions of dermatitis herpetiformis, suggested that circulating immune complexes originating in the small intestine might cause other disorders by deposition in the appropriate organ, the antigen being either a product of gluten or derived from the abnormal jejunal mucosa. In the present series the time spent on a normal diet was much greater than that spent on a gluten-free diet; thus not surprisingly most of the autoimmune disorders developed while the patients were on a normal diet and when the small bowel was damaged. Some did develop, however, when the jejunal mucosa was macroscopically normal. There was no evidence that the autoimmune disorders other than insulin-dependent diabetes[14] improved with a gluten-free diet, as has been suggested.[1]

Hodgson *et al*[7] suggested that atopy in coeliac disease is due to either the passage of antigens across the damaged mucosa or predisposition as a result of abnormal mucosal IgA responses, for it has been claimed that selective IgA deficiency predisposes to atopy.[34 35] Although in our series atopy was not common, the dramatic and persistent relief of eczema with a gluten-free diet[36] seen in two patients suggests that jejunal mucosal abnormalities do predispose to atopy in some cases.

Our experience suggests that jejunal biopsy should not be performed routinely in cases of autoimmune disorders, as has been recommended,[1] but should be performed in any patient who also has folate-deficiency refractory anaemia or diarrhoea.

References

1 Scott, B B, and Losowsky, M S, *Lancet*, 1975, **2**, 956.
2 Chambers, T L, *Archives of Disease in Childhood*, 1975, **50**, 162.
3 Toivonen, S, Pitkanen, E, and Siurala, M, *Acta Medica Scandinavica*, 1964, **175**, 91.
4 Green, P A, and Wollaeger, E E, *Gastroenterology*, 1960, **38**, 399.
5 Berrill, W T, *et al*, *Lancet*, 1975, **2**, 1004.
6 Robinson, T J, *British Medical Journal*, 1976, **1**, 745.
7 Hodgson, H J F, *et al*, *Lancet*, 1976, **1**, 115.
8 Lancaster-Smith, M J, *et al*, *Postgraduate Medical Journal*, 1974, **50**, 45.
9 Fry, L, *et al*, *Lancet*, 1968, **1**, 557.
10 Ferguson, R, *et al*, *Gut*, 1975, **16**, 393.
11 Cooke, W T, and Asquith, P, *Clinics in Gastroenterology*, 1974, **3**, 3.
12 Irvine, W J, *et al*, *Lancet*, 1970, **2**, 763.
13 College of General Practitioners, *British Medical Journal*, 1962, **1**, 1497.
14 Walsh, C H, *et al*. Submitted for publication.
15 Goodie, R B, *et al*, *Lancet*, 1969, **1**, 186.
16 Clinicopathological Conference, *British Medical Journal*, 1970, **2**, 711.
17 McLaurin, B P, Matthews, N, and Kilpatrick, J A, *Australian and New Zealand Journal of Medicine*, 1972, **4**, 405.
18 Lancaster-Smith, M J, and Strickland, I D, *Lancet*, 1971, **1**, 1244.
19 Pittman, F E, and Holub, D A, *Gastroenterology*, 1965, **48**, 869.
20 Presbury, D G C, *British Journal of Dermatology*, 1975, **92**, 109.
21 Lane, D J, and Hamilton, W S, *British Medical Journal*, 1971, **2**, 89.
22 Cooke, W T, Feeney, A L P, and Hawkins, C F, *Quarterly Journal of Medicine*, 1953, **22**, 59.
23 Clinicopathological Conference, *British Medical Journal*, 1967, **2**, 222.
24 Euler, A R, and Ament, R E, *Gastroenterology*, 1977, **72**, 729.
25 Falchuk, Z M, Rogentine, G N, and Strober, W J, *Journal of Clinical Investigation*, 1972, **51**, 1602.
26 Stokes, P L, *et al*, *Lancet*, 1972, **2**, 162.
27 Curdworth, A G, and Woodrow, J C, *Diabetes*, 1975, **24**, 345.
28 Nerup, J, *et al*, *Lancet*, 1974, **2**, 864.
29 Grumet, F C, *et al*, *New England Journal of Medicine*, 1971, **285**, 193.
30 Flaherty, D L, *et al*, *Lancet*, 1975, **2**, 507.
31 Mallas, E G, *et al*, *Gut*, 1976, **17**, 906.
32 Seah, P P, *et al*, *Gut*, 1973, **14**, 311.
33 Williamson, N, *et al*, *Journal of Clinical Pathology*, 1976, **29**, 484.
34 Schwartz, D P, and Buckley, R H, *New England Journal of Medicine*, 1971, **284**, 513.
35 Collin-Williams, C, Chia, A W, and Varga, E A, *Clinical Allergy*, 1971, **1**, 381.
36 Friedman, M, and Hare, P J, *Lancet*, 1965, **1**, 521.

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Diet and retarded growth

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Summary and conclusions

The diets of 36 children below the third centile for height but with no organic disease were compared with the diets of a control group. In most cases retarded growth was associated with a long-continued deficiency in calorie intake. When the diets were reassessed about a year later the shortfall in calorie intake was significantly reduced. This improvement, which tended to be followed by an increase in the rate of growth in height, might have been due to alteration in the child's circumstances or improvement in the family attitudes and feeding habits or both. Advice given at the clinic is thought to have played a part in bringing these changes about.

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Introduction

We previously discussed our hypothesis[1] that short stature in otherwise healthy children is associated with a long-continued deficiency in calorie intake. We now report on a new series of children under the third centile for height and compare their diets with those of a control sample representative of Bristol children. Most of the children were followed up over several years.

There are two reasons why short children might eat too little.