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Is bird fancier's lung associated with coeliac disease?

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Is bird fancier's lung associated with coeliac disease? Precipitin responses to different avian serum antigens occur in bird fancier's lung (BFL) and coeliac disease. Failure to distinguish between them could encourage an erroneous diagnosis of BFL in patients with coeliac disease, and the recent suggestion that these two disorders are strongly associated may be questioned, partly for this reason. In the present study small bowel biopsy specimens were obtained from 12 of a series of 14 patients proved to have BFL by inhalation provocation tests. None was suggestive of coeliac disease. Of a further 61 patients with biopsy-proved coeliac disease, seven were found to be exposed currently and 33 formerly to birds. As a result of clinical evaluation, BFL was considered a possible cause of undue breathlessness reported by three of the current bird fanciers only, and all underwent inhalation provocation tests. One alone gave positive results. We conclude that if a real association does exist between these two disorders, its clinical importance has been greatly exaggerated.

Interest in a possible association between coeliac disease and diffuse pulmonary disease was first kindled by the report by Hood and Mason (1970) of two patients with both these disorders. One was thought to have specifically budgerigar fancier's lung, but in the other intrinsic "autoallergic mechanisms" were postulated. The following year Lancaster-Smith *et al* (1971) reported diffuse lung disease occurring in three of 24 patients with coeliac disease, the proportion later being amended to three of 57 (Lancaster-Smith *et al*, 1974). Like Hood and Mason, they considered that both disorders might depend on common disturbances of immunity, and that the lung and intestinal disease might be autoimmune in nature.

The possible association of extrinsic allergic alveolitis with coeliac disease has subsequently attracted rather more attention (Robinson, 1976; Editorial, 1976). In particular, Berrill *et al* (1975) have suggested a strong association involving BFL. Of 16 patients thought to have BFL, nine were selected for jejunal biopsy, which showed villous atrophy in five. The assumption that the diffuse lung disease was BFL depended partly on the finding in all cases of precipitins to bird serum. No inhalation provocation tests were performed, and only one of the five subsequently achieved an adequate and persisting pulmonary response from bird avoidance alone.

It is now known that coeliac disease is independently associated with a precipitin response to bird serum (Faux *et al*, 1978). The antigen concerned differs from the antigens associated with BFL. It is not found in the bird droppings but it does occur in chicken egg yolk, surviving light cooking immunologically intact. It consequently seemed possible that this antibody response, which is unrelated to bird exposure, was provoked by dietary egg.

This study examines the alleged association between BFL and coeliac disease by determining the prevalence of coeliac disease in a group of patients proved to have BFL by inhalation provocation tests, and conversely of BFL in a group of patients with biopsy-proved coeliac disease. It also examines the relationship between precipitins to the bird serum antigen associated with coeliac disease and the activity of the accompanying small bowel disease as measured by the morphological changes observed in roughly concurrent mucosal biopsy specimens.

Methods

PATIENTS WITH BFL

During 1973–6, 14 patients were proved to have BFL by inhalation provocation tests using bird antigens. Thirteen were invited to undergo small

bowel biopsy using a Crosby capsule or a fibreoptic duodenoscope and 12 consented. Ten were exposed to budgerigars and two to pigeons.

PATIENTS WITH COELIAC DISEASE

Attempts were made to question (by postal circular, telephone, or personal interview) all 73 patients registered at the Oxford coeliac disease clinic in 1976. Small bowel biopsy specimens consistent with coeliac disease had been obtained from them all. Answers to questions about undue breathlessness on exertion and its relation to episodes of bird exposure were obtained from 61. Whenever BFL seemed possible, the patient was interviewed and assessed clinically. This included chest radiography and measurement of pulmonary function. If the breathlessness remained unsatisfactorily explained, and the patient was suitably fit, he was invited to undergo inhalation provocation tests with avian antigens designed to confirm or exclude BFL.

SMALL BOWEL BIOPSY SCORES

A 0–9 point scoring system was devised to quantify the degree of mucosal derangement. The villi, crypts, and lamina propria were scored independently as follows

Villi—length, shape, epithelial cells, lymphocytes 0–3
Crypts—depth, mitoses 0–3
Lamina propria—oedema, inflammatory cells 0–3

All biopsy specimens were examined by one of us without prior knowledge of their source.

SEROLOGICAL TESTS

Precipitin tests were carried out using extracts of the following avian antigens—budgerigar, pigeon and chicken sera, budgerigar and pigeon droppings, chicken egg yolk, and chicken egg white. The results have been reported elsewhere together with a description of the features distinguishing the different responses to "BFL associated" and "coeliac disease associated" antigens (Faux *et al*, 1978).

INHALATION PROVOCATION TESTS

Before a diagnosis of BFL was excluded a minimum of three active and one control inhalation tests were carried out using increasing doses of nebulised avian serum suspended in carbol-saline (dilutions of 1/20 for 5 minutes, 1/10 for 12·5 minutes, and 1/5 for 30 minutes; control—carbol-saline alone). Responses were monitored by symptoms, and by changes in body temperature, circulating leucocyte counts, and minute volumes during a five-minute exercise test on a treadmill. A detailed account of the procedure and the significance of the responses is given elsewhere (Hendrick *et al*, 1978).

Results

PREVALENCE OF COELIAC DISEASE IN PATIENTS WITH BFL

None of the biopsy specimens from the 12 patients with BFL was suggestive of coeliac disease. The mean biopsy score was 0·5, the range being 0–2 (Villi alone: mean 0·1, range 0–1).

PREVALENCE OF BFL IN PATIENTS WITH COELIAC DISEASE

Seven of the 61 coeliac disease patients were currently exposed to birds (three to budgerigars, two to canaries, one to both, and one to turkeys). Two of the budgerigar fanciers together with the budgerigar/canary fancier reported the onset of undue breathlessness during the period of bird exposure. The cause in each case was not evident from clinical evaluation alone. All three were considered to be suitable for inhalation provocation tests. The one showing several clinical features suggestive of BFL (moderate but variable exercise limitation, basal crackles, reduced carbon monoxide gas transfer (DLCO) to 57% of the normal predicted) but normal chest radiograph and ventilatory function, gave reproducible typical positive responses to the provocation tests with both budgerigar and canary sera, and to an "occupational" exposure to budgerigars. She subsequently improved with bird avoidance. The other two showed no crackles, normal ventilation and DLCO, normal chest radiographs, and negative provocation test results.

The 33 former bird fanciers had been exposed chiefly to chickens (22) and to budgerigars (20). Only two claimed to have developed undue breathlessness at the relevant time, and subsequent clinical evaluation was considered adequate to exclude the possibility of BFL.

RELATION BETWEEN SMALL BOWEL MUCOSA AND PRECIPITINS TO THE "COELIAC DISEASE ASSOCIATED" ANTIGEN

Precipitin tests were carried out on the sera of 25 patients with coeliac disease who had undergone initial or follow-up small bowel biopsies during 1974–6. Each biopsy was paired with the temporally most closely related precipitin test. The intervals between precipitin tests and biopsies ranged from 0–31 months, being less than 12 months in 21 patients and less than 3 months in

11 patients. In a few patients more than one biopsy could be paired with a separate precipitin test, but with one exception the precipitin test results and the biopsy scores did not differ, and only one pair per patient was included in the overall analysis. The excepted patient had a very different post-treatment biopsy score (0 compared with 6) but both precipitin tests, which were carried out near the middle of the intervening 11 months, gave positive results. Both pairs are consequently included in the analysis.

The relationship between the precipitins to the antigen associated with coeliac disease and the degree of mucosal derangement of the small bowel, as measured by the biopsy scores, is illustrated in the figure. The mean biopsy scores of the precipitin-positive compared with the precipitin-negative patients are given in the table. The difference between them was not much greater in the group with the shortest precipitin test/biopsy interval than in the other groups, and the same degree of statistical significance was found in all three. This reflects the fact that the biopsies associated with the longer intervals were generally follow-up procedures in patients whose mucosal appearances were known to have changed little over long periods.

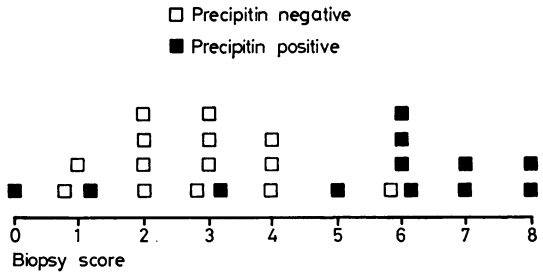

Figure *Distribution of biopsy scores in patients with and without precipitins to "coeliac disease associated" antigen.*

Table *Comparison of mean biopsy scores between patients with and without precipitins to the "coeliac disease associated" antigen*

	Mean scores—small bowel mucosa biopsies		
	Precipitin test/biopsy intervals		
Coeliac disease associated precipitins	*< 36 months (mean 6·0 months) 26 paired results*	*< 12 months (mean 3·1 months) 22 paired results*	*< 3 months (mean 1·1 months) 11 paired results*
Positive	5·3	5·1	6·2
Negative	2·9	2·9	3·0
P<	0·05	0·05	0·05

Statistical significance established by Mann Whitney test.

Discussion

It has been shown that the precipitin response to the antigen of bird serum and egg yolk associated with coeliac disease is not related to BFL or even to bird exposure (Faux *et al*, 1978). The present study shows there is a close relation to the degree of derangement of the small bowel mucosa, and it seems reasonable to assume that it is dietary egg that is the provoking factor. Such an immune response to dietary antigens is well recognised in coeliac disease, though it is not diagnostic of it.

Patients with active coeliac disease are consequently likely to show positive precipitin test results to bird serum irrespective of bird exposure or lung disease, and special care should be taken in interpreting the results when BFL is suspected in such patients. The precipitin response associated with coeliac disease entails a single reaction and hence presumably a single antigen. A common reaction is obtained with sera from other avian species and with chicken egg yolk but not with droppings nor with chicken egg white. By contrast precipitins to "BFL associated" antigens are confirmed by the demonstration of common reactions to both the serum and the droppings of the avian species concerned. More than one reaction may be seen depending on the degree of exposure. Reactions may also be obtained with sera from other avian species, but these are typically less numerous and less intense. Precipitins to the antigen associated with coeliac disease may consequently be distinguished from those to "BFL associated" antigens, but the latter are not pathognomonic of BFL nor does their absence exclude it. Similar limitations apply to the diagnostic specificity of chest radiographs and pulmonary function tests. For these reasons we have confined our investigations in this study to patients in whom the diagnosis of BFL had been established beyond reasonable doubt—all those in whom we had obtained typical positive responses to inhalation provocation tests.

Our dependence on diagnostic provocation tests does introduce a potential bias to the selection of our patients, since any with advanced pulmonary disease and limited pulmonary reserve would be excluded. So, too, would patients with serious illness from any cause, including coeliac disease, though this did not in fact occur in the present study. This bias is of some relevance since Berrill *et al* (1975) suggest intestinal absorption of avian antigens might be a factor in the pathogenesis or persistence of BFL. If this is so patients with coeliac disease might be expected to develop BFL more severely and hence be unsuitable for provo-

cation tests. There is no obvious reason why initial presentation should be delayed until such advanced stages are reached, however, and so this minor bias is unlikely to influence our results significantly.

Our failure to show villous atrophy among our patients with BFL provides compelling evidence against an association between these two disorders of the strength suggested by Berrill *et al* (1975). That one of our seven coeliac disease patients currently exposed to birds was shown to have BFL is, however, an intriguing finding. She was one of four currently exposed to budgerigars. This proportion may be compared to a prevalence of BFL of 0·5–7·5% predicted among current budgerigar fanciers in general (Hendrick *et al*, 1978). Little significance can be attached to this single case in a statistical sense, and larger surveys will be required to investigate the possibility that a weak association may exist between these two interesting diseases.

The discrepancy between our findings and those of Berrill *et al* (1975) may depend on several factors. Each series of patients with presumed BFL was selected using different criteria, so that in our patients the pulmonary disease was less likely to be of long duration or great severity, while in theirs it may not have been specifically BFL in all cases. That villous atrophy should have been found so commonly in their patients with diffuse pulmonary disease of whatever cause is, however, surprising in view of the known low prevalence of diffuse pulmonary disease in patients with coeliac disease. This implies that a bias in favour of villous atrophy may have operated in the selection of their patients. Indeed one of the five with both pulmonary and jejunal disease presented with symptoms referable to coeliac disease alone. The pulmonary disease was found only after routine chest radiography. A further two of the five were already known to have villous atrophy. They were the two reported by Hood and Mason (1970) at which time the suggestion was first made that diffuse pulmonary disease and coeliac disease might be associated. It is therefore questionable whether these two should be included in a subsequent epidemiological study designed to test the validity of that initial hypothesis.

We are sympathetic to the hypothesis that intestinally absorbed avian antigens could influence BFL because a surprising proportion of our patients with BFL dislike and/or avoid eating eggs. Some are unable to provide an explanation for this, while others believe eggs provoke gastrointestinal discomfort, general malaise, or even increased breathlessness on exertion. Coincident coeliac disease could consequently be of great relevance to BFL because of defective mucosal handling of ingested avian antigens, even if no true association between the two disorders exists. It is of some interest that our only patient with both disorders first developed her pulmonary symptoms at the time of her only coeliac disease relapse. She had successfully followed a strict gluten-free diet for 18 years throughout which she had been exposed to budgerigars or canaries. Domestic stress and a short-lived depression had led to a transitory lapse from her diet, and a prompt full recovery (apart from slowly progressive exertional dyspnoea) followed its reintroduction. She did not like boiled eggs, but was unaware of any specific ill effect after eating them.

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