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Present trends in coeliac disease

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Introduction

Much has been achieved and learned since the first full clinical description of coeliac disease nearly a century ago (Gee, 1888), the demonstration of the harmful fraction in wheat and rye responsible for the clinical symptoms (Dicke, 1950), the role of gluten in these cereals (Anderson *et al.,* 1952), and the effect of gluten on the pathogenesis of the small bowel mucosa (Shiner and Doniach, 1960). Yet the mechanism whereby gluten causes its harmful effect or indeed the precise fraction in gluten responsible for the mucosal pathology has still not been elucidated. To fill these pages with well worn repetitions of past achievements in this subject would indeed be an injustice to Sir Francis Avery Jones who is well known for his forward-looking attitude in all fields of gastroenterology and who could justly be regarded as one of the founding fathers of British gastroenterology. Rather I propose, after a short summary of the salient landmarks in coeliac disease, to delineate certain recently investigated aspects which I regard as important trends towards a better understanding of the underlying mechanisms operating in coeliac disease.

Clinicopathological definition of coeliac disease

Coeliac disease is a condition caused by gluten intolerance which clinically leads to malabsorption and pathologically to villous atrophy and associated mucosal changes within the upper small intestine. So important was it to accurately define coeliac disease because of its protean nature that the European Society for Paediatric Gastroenterology (Meeuwisse, 1970) put forward the criteria for the diagnosis based exclusively on the effect of gluten on the upper small bowel mucosa obtained by peroral biopsy (Shiner, 1956). This definition—1. a structurally abnormal duodenal and jejunal mucosa on a gluten containing diet, 2. clinical and histological improvement on a gluten free diet and 3. clinical and histological relapse after re-introduction of dietary gluten—is today generally accepted. These criteria however require three peroral biopsies, do not take into account the condition of transient gluten intolerance and exclude asymptomatic relatives of coeliac patients with abnormal jejunal biopsies. Nevertheless it is the best working definition to date.

Landmarks in coeliac disease

The chemistry and absorption of dietary gluten

An inherent defect of absorption by the villous epithelium (enterocytes) of dietary gluten, its alcoholic extract or its peptic-tryptic digest, all of which are 'toxic', has never been demonstrated. The further purification and fractionation of gluten has been attempted by many laboratories and the progress that has been made is worthy of more detailed description. Wheat, rye, barley and perhaps oats are toxic to the coeliac mucosa and though they share common antigens believed to reside in their prolamine fraction no significant antigenic similarity between the various proteins contained in these cereals has been demonstrated. Wheat prolamines or gliadins have been mostly studied and of the four gliadin fractions separated by gel electrophoresis alpha gliadin was the first shown to be toxic to the small intestinal mucosa (Hekkens, Haex and Willighagen, 1970). Some investigators believe that it is the only toxic fraction in wheat (Kasarda *et al.,* 1978). However, different wheats differ in their alpha gliadin content, some containing very little yet are still toxic to coeliac patients (Ciclitira, Hunter and Lennox, 1980). Other workers have shown that the beta gliadins are also toxic to the coeliac mucosa (Dissanayake *et al.,* 1974; Jos *et al.,* 1982). Further purification of alpha and beta gliadins has produced a large variety of peptides of molecular weight as small as 5000D and these await testing on the small bowel mucosa by *in vivo* and *in vitro* techniques.

The complexity of the subject does not end here. Kieffer *et al.* (1982) found raised serum antibodies (IgG) to wheat peptides other than gliadins in coeliac patients, although they and other workers (O'Farrelly

et al., 1983) confirmed previous reports that the highest antibody titres in coeliacs were against alpha gliadin. Kieffer *et al.* (1982) further concluded that raised gliadin antibodies in coeliacs need not necessarily be directed against specific antigens but may merely signify reactions against overall increased antigen absorption. In terms of mucosal events this would correlate well with the concept of a 'leaky' gut in coeliac disease as demonstrated by altered intestinal permeability to sugars (Menzies *et al.*, 1979) and other probe molecules (Cobden *et al.*, 1978; Chadwick, Phillips and Hoffman, 1977) and by electron microscopic evidence of widening of the intercellular junctions of the enterocytes (Madara and Trier, 1980). Recently it was shown (Bjarnason, Peters and Veall, 1983) that this permeability defect persists after treatment with a gluten-free diet. It is possible that this defect is of primary importance in coeliac disease. The observed local and systemic immune response may follow the increased absorption of numerous antigens of large molecular size, but principally those contained in gluten, as a result of an inborn anatomical defect within the enterocytes.

Local immune responses

The importance of immunological responses in the pathogenesis within the upper small intestinal mucosa following a gluten challenge is well acknowledged yet their nature is complex and poorly understood. Amongst other immune reactions there is a sustained increase in local antibody production, mainly of IgA and IgM type (Maffei *et al.*, 1979; Savilahti, 1972) and in only exceptional circumstances is there evidence of immune deficiency (selective IgA). It has been shown experimentally that not only will an excess of specific (ingested) antigen produce an antibody response but it will also lead to a state of immune tolerance (Challacombe and Tomasi, 1980) when the same antigen is given parenterally. Such a state of tolerance would be expected to limit any ongoing local reaction and thus prevent mucosal damage. Why does this not happen in coeliac disease? In explaining prolonged responsiveness in coeliac disease it was suggested (Nicklin and Miller, 1983) that immune tolerance required an intact mucosa for its induction whereas in coeliac or any other disease with a damaged mucosa antigen presentation associated with mucosal damage (or leak) may modify the normal tolerogenic response and change the balance between tolerance and hypersensitivity to a specific antigen.

How is this damage produced in the first place? The antibody response in the human small intestinal mucosa by antibody-processing lamina propria lymphocytes (B cells) is controlled by T lymphocytes and by macrophages. The T lymphocytes have recently been characterized by the use of heterologous and monoclonal antibodies and have been shown to consist of at least two subpopulations—the intraepithelial (or thelio-) lymphocytes with mainly suppressor-cytotoxic phenotype and the lamina propria lymphocytes which are mainly helper cells (Selby, Janossy and Jewell, 1981). The intraepithelial lymphocytes play an important role following a gluten challenge in treated coeliacs as demonstrated by their dose-dependent rise in numbers, increase in rate of mitotic proliferation, increase in the number of immunoblasts and increased transit across the basement membranes of enterocytes (Marsh, 1980). Comparing the proportion of type-specific intraepithelial lymphocytes in normals and in coeliacs, Selby *et al.* (1983) found in coeliacs an increase in those bearing not only cytotoxic expression (OKT8+) but also another antigen (OKT1+) on the precursor cytotoxic T cells. This antigen is normally absent. Thus the immunoblasts of Marsh may indicate specific recruitment of OKT1+ bearing cytotoxic intraepithelial T-lymphocytes into an area which is also known to express strong major histocompatibility antigens.

The histocompatibility antigens

Coeliac disease has a hereditary disposition of polygenic origin and this may at least in part be associated with the major histocompatibility antigens and specific DR antigens which control the immune responses (Ir genes). Strong association has been confirmed between coeliac disease and HLA-B8 (Stokes *et al.*, 1972; Falchuck, Rogentine and Strober, 1972), HLA-Dw3 (Keuning *et al.*, 1976), HLA-DRw3 and HLA-DRw7 (Betual *et al.*, 1980). HLA-DR like antigens have been demonstrated on the surface membrane of intraepithelial lymphocytes (Selby *et al.*, 1981) as well as on the surface of enterocytes (Scott *et al.*, 1980) and in their supranuclear cytoplasm (Avigad *et al.*, in press). Cytotoxic T cells in man can recognize foreign antigens (?gluten) in the context of HLA-antigens within or on the surface of enterocytes altered by the foreign antigen (Scott *et al.*, 1980). Once stimulated the cytotoxic intraepithelial T cells could be active in various ways: they could elaborate lymphokines which could be directed against neighbouring cells, leading to the disruption, damage and extrusion of the enterocytes following small doses of antigen, such as the peptic-tryptic digest of gluten, as demonstrated by Marsh (1983). Or they could re-enter the lamina propria and stimulate antibody production by B lymphocytes possibly via macrophages and/or helper T cells as suggested by the observed increase in traffic of intraepithelial lymphocytes to and from the enterocyte layer to the lamina propria (Marsh, 1980). Alternatively a fraction of gluten could directly bind

to lamina propria B lymphocytes (Verkasalo, 1982) or macrophages which carry DR antigens and activate the production of autoantibodies recognized as foreign by gut wall lymphocytes or entering the circulation and contributing to immune complex disease (Scott and Losowsky, 1975, Neild, 1981). HLA-linked specific immune response genes may be important genetic factors predisposing to susceptibility to a variety of autoimmune diseases which have been frequently reported in coeliac disease (Maclaurin, Matthews and Kilpatrick, 1972; Lancaster-Smith *et al.,* 1974; Cooper, Holmes and Cooke, 1978).

Autoimmune diseases associated with coeliac disease

One or more autoimmune diseases have been described in 14–19% of coeliac patients (Lancaster-Smith *et al.,* 1974; Cooper *et al.,* 1978). They include rheumatoid arthritis, Sjögren's disease, scleroderma, interstitial lung disease, cirrhosis, ulcerative colitis and Addison's disease. Autoantibodies including antireticulin antibodies, were demonstrated in 1/3 of coeliacs tested. In untreated coeliac children antireticulin antibodies in high titres are almost the rule (Alp and Wright, 1971) and have been used as a screening test (Unsworth, Walker-Smith and Holborow, 1983). Recently autoantibodies against gut epithelium have been demonstrated in children with a subtotal villous atrophy and protracted diarrhoea though non-responsive to a gluten-free diet (Walker-Smith *et al.,* 1982; Savage *et al.,* 1982). The association of coeliac disease and dermatitis herpetiformis is particularly strong and is further emphasized by the recent demonstration of dimeric IgA deposition in the skin which is thought to have been derived from the gut (Unsworth *et al.,* 1982) and by relapse of the rash after gluten challenge (Leonard *et al.,* 1983).

What is the mechanism underlying the development of antibodies against self components which are normally not expressed? Certain antibodies against self, like rheumatoid factors, are produced when antigenic stimulation is prolonged and immune complexes are formed. This situation may arise also in coeliac disease as a result of chronic stimulation with dietary gluten (Doe, Henry and Booth, 1974). This may lead to dominance of suppressor T cells, as shown above, perhaps due to an alteration in the balance of the idiotype/anti-idiotype network whereby these cells, triggered by antigen, react with idiotypes on T-helper cells or on B cells of self (Humphrey, 1982). An intermittently circulating lymphocytotoxic autoantibody might also explain the tendency to hyposplenism and splenic atrophy in coeliacs in later life (Marsh and Stewart, 1970; Bullen and Losowsky, 1978). Splenic atrophy is in turn related to impaired function of lymphocyte subpopulations in coeliac disease (Bullen and Losowsky, 1978; Maclaurin, Cooke and Ling, 1971). The frequent finding of splenic atrophy is also compatible with the view that coeliac disease is caused by a chronic graft versus host reaction as postulated by Neild (1981) and might therefore be related to the reported increased incidence of malignant lymphomas and other tumours (Gough, Read and Nash, 1962; Harris *et al.,* 1967; Asquith and Haeney, 1979).

Coeliac disease and malignancy

Much has been written on this subject and it is now clear that the association between coeliac disease and malignancy is multifocal in that the latter is not confined to that site of the small intestine in which the histopathological changes of coeliac disease occur. In a recent National Collaborative Study (Swinson *et al.,* 1983) only half the malignancies in 235 coeliac patients studied arose from the gastrointestinal tract. The types of malignancies fell broadly into 2 categories: malignant lymphomas (51%) and others, mainly carcinomas (48%), including small bowel adenocarcinoma (16%). Of 109 malignant lymphomas well over one half were found in the small intestine and 89% of these were classified as malignant histiocytic tumours. A third type of small intestinal infiltration associated with coeliac disease and a poor prognosis has been described in which multiple ulcerations (ulcerative jejuno-ileitis) was the predominant clinico-pathological presentation (Baer, Bayless and Yardley, 1980). This may be a heterogeneous entity since in at least a proportion of patients the cellular infiltration at the base of the ulcers proved to be malignant histiocytes (Isaacson and Wright, 1978; Robertson *et al.,* 1983).

The aetiopathology of malignancies in coeliac disease, though speculative, is intriguing and suggestive that the disease itself is not confined to the small intestinal mucosa and that adverse immune mechanisms, affecting T or B lymphocytes and/or macrophages, though they may originate within the mucosa have a widespread effect on other organs. The best example of multi-organ involvement with tumour cells in coeliac disease is seen in malignant histiocytosis of the intestine where small intestinal infiltration with such 'histiocytes' may be difficult to identify until multiple sections of the bowel are examined or the malignant cells are present in the mesenteric nodes, liver, spleen or bone marrow (Isaacson and Wright, 1980). What is the morphological origin of this histiocyte? Some would argue that it is a precursor of the macrophage (Lukes, 1979) whilst others consider it a transformed lymphocyte (Levine and Dorfman, 1975). As Isaacson and Wright (1980) point out and our own study confirms (Horowitz and Shiner, 1981) there is difficulty in identifying the

origin of the malignantly transformed cell even with ultrastructural, histochemical or immunochemical techniques and the malignant 'histiocyte' could in fact, as we believe, be a transformed plasma cell. It is interesting to note that both macrophages and plasma cells (B lymphocytes) express DR or Ia-like antigen on their cell surface and are under the influence of T-helper and -suppressor cells; it may also be recalled that lymphocyte dysfunction in coeliac disease has been widely reported.

Another potential malignancy of the small intestinal mucosa involving immunologically active cells and associated with villous atrophy is seen in alpha chain disease (mediterranean-type lymphoma or immunoproliferative small intestinal disease). The abnormal cell type is the B lymphocyte (plasma cell) which in the early stage of the disease is a mature, morphologically normal cell but secreting abnormal immunoglobulin and in the late stage turns into a morphologically malignant cell (Seligman, 1977) with abnormal ultrastructural features (Shiner, 1979). Although alpha chain disease is not thought to arise in the coeliac mucosa it is an interesting example of how immunologically active cells (B cells) within the small intestinal mucosa could escape normal immunological surveillance by T cells and/or macrophages. We do not understand the triggering mechanisms involved though villous atrophy may be one of the factors responsible. Dutz and his colleagues (1971) considered that a sprue-like villous atrophy, seen in 90% of their necropsies in Iran, and possibly due to repeated gut infections, is a triggering factor in the development of small intestinal malignancy. This author has observed a subtotal villous atrophy in the jejunal mucosa in a 15-year-old Libyan girl, associated with a dense inflammatory infiltrate of the lamina propria 90% of which consisted of IgA producing plasma cells. On ultrastructural examination these cells showed abnormalities identical to those seen in alpha chain disease (Shiner, unpublished observations). IgA light chains were however present and the patient responded to a gluten-free diet clinically and histologically. This example highlights the relationship between villous atrophy, local immune cell activity and malignancy.

The exact role of splenic atrophy in the development of malignancy is not known. Hyposplenism was reported in a similar proportion of coeliac patients with and without malignancy (Robertson *et al.*, 1982). This does not necessarily imply that those coeliac patients with splenic atrophy will not be more prone to eventual development of tumours in the future. Mention should also be made of reports that many coeliac patients who developed lymphomas in later life did so despite treatment with a gluten-free diet and histological improvement (Stokes and Holmes, 1974).

Conclusion

During the 30 odd years since the discovery of the importance of gluten in the aetiopathology of coeliac disease the emphasis has shifted from a genetically determined enzyme defect within the enterocytes of the small bowel mucosa to a genetically determined specific tissue reactivity triggering off a variety of immunological reactions both locally and systemically. The difficulty lies in bringing all the factors discussed under one roof. The hypothesis tentatively proposed leads to the following conclusions: coeliac disease is caused by a specific dietary protein or proteins which may be regarded as antigens. Genetically determined receptors for these antigens are present on small intestinal mucosal epithelial cells, lymphocytes, macrophages and many other cells in the affected individual and the upper small intestine, being the site of maximal dietary protein absorption, is also the site of maximal reaction and damage. Apart from interaction between antigen and receptor sites a leak in the epithelial cell junctions could cause direct contact between antigen and immune reactive cells lying either in the intraepithelial spaces or in the lamina propria of the mucosa below the epithelial cell layer. The increase in suppressor (cytotoxic) T lymphocyte activity may be a reaction to antigens on other cells (e.g. enterocytes) and lead to villous atrophy through epithelial cell damage. Or it may alter the balance between lamina propria helper and suppressor T lymphocytes and their influence on local macrophages and B lymphocytes. Alternatively, direct stimulation of lamina propria B lymphocytes may cause continuous activity in production of immunoglobulins which may become unresponsive to T lymphocyte or macrophage influence. Chronic stimulation of T or B lymphocytes and/or macrophages may eventually lead to lymphocyte dysfunction with consequent appearance of autoimmune disease, splenic atrophy and malignancy.

The inadequacy of our present understanding of immune mechanisms adds to our incomplete evaluation of coeliac disease but its importance in the aetiopathology of the disease is clear. The present rapid advances in immunology and genetics will surely lead to a more unified concept in aetiology.

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