blood of patients with M.P.G.N. (Spitzer *et al.*, 1969), it is a matter for speculation whether the disease might be transmitted to homografts (Michael *et al.*, 1969).

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The Enterocyte in Coeliac Disease*

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Conflicting Clinical Observations

Further clinical observations conflict with the theory that coeliac disease may be due to a specific enzyme defect. Firstly, though identical twin studies have usually shown concordance in children a single discordant pair of adult coeliac patients has been described. Secondly, if a patient whose mucosa has been restored to normal by a gluten-free diet is refed gluten the histological response is not always immediate. Thirdly, some individuals who have initially responded to a gluten-free diet may then relapse and sometimes die of their disease. Finally, the histological appearance of the flat mucosa is not specific and may apparently occur in conditions other than those associated with gluten sensitivity (Collins and Isselbacher, 1965; Hindle and Creamer, 1965).

Identical Twin Studies

Before biopsy techniques were available, Ebbs (1956), found concordance in five pairs of identical twins, and MacDonald *et al.* (1965), in the family study already referred to, showed concordance in a pair of male children. Jejunal biopsies were carried out in both these patients. But Hoffman *et al.* (1966) recorded a single pair of discordant adult coeliac twins. The propositus was a woman aged 54 years with steatorrhoea and a flat jejunal mucosa who responded well to a gluten-free diet. Her identical twin, however, whose dietary habits were

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apparently similar, had no symptoms or steatorrhoea, and the jejunal mucosa was normal. This observation is difficult to reconcile with the theory of a genetically determined enzyme deficiency.

Effect of Reintroducing Gluten

The direct toxic effect of gluten on the coeliac mucosa was first clearly established by Rubin *et al.* (1962). These workers instilled gluten directly into the normally appearing ileum of adult coeliac patients whose jejunal mucosa was flat, and they produced the characteristic abnormalities. Others have confirmed these findings, but these observations were made in patients suffering from the disease with an already flat jejunal mucosa. Of more interest is what happens when gluten is given to individuals who have been treated with a gluten-free diet until their mucosa has returned to normal. In such patients the response to the reintroduction of gluten, or gluten products such as gliadin, is not always immediate. Changes can occur within 6 to 24 hours, but in other patients there may be no immediate response and no changes may occur for as long as six weeks after gluten feeding (Jos *et al.*, 1969).

These observations have clinical significance, since it cannot be certain that a patient does not have coeliac disease if gluten is fed for only a week. They are also significant in that this delayed response would be unusual if the basic abnormality of the enterocyte were a persisting and genetically determined enzyme defect. Both the immediate response to gluten feeding in the ileum of the sensitive untreated patient and the delayed response sometimes found in those treated with a gluten-free diet for prolonged periods suggest that the abnormality may be immunologically determined, the delayed response being the time taken to resensitize a potentially sensitive subject.

Failure of Response to Gluten-free Diet

Studies of adult patients who fail to respond to a gluten-free diet indicate that the disorder may be associated with hypersensitivity in adult life. One such subject studied at Hammersmith Hospital had presented with malabsorption and a megaloblastic anaemia in 1953 at the age of 36 (Neale, 1968). He had been treated with a gluten-free diet over a 10-year period with a good response. In 1963 a jejunal biopsy had shown mild changes only. A year later he developed epigastric discomfort and was treated with Nulacin, which has a flour base and therefore contains gluten. There was a severe relapse and he died of his disease 18 months later. His clinical progress is shown in Fig. 15. When admitted to hospital the Nulacin was immediately stopped and he was treated with a strict gluten-free diet in hospital for six months. Despite this his condition deteriorated, his weight fell, and steatorrhoea became progressively more pronounced. At the end of this time it was thought that he might have developed intestinal lymphoma or another malignant condition such as may occur as a late complication of coeliac disease. Laparotomy, however, showed no abnormality and, despite a milk-free diet, prednisone, and then a period on a no-protein diet, the patient's condition steadily deteriorated until he died. The jejunal biopsy in this patient was severely abnormal, the enterocytes being extremely flat and thin and in some places virtually absent (Fig. 16). Beneath the enterocytes there was a thick layer of collagen material similar to that described in other coeliac patients dying of their disease (Hourihane, 1963).

It has been claimed that an absence of Paneth cells may be responsible for this severe jejunal lesion (Creamer and Pink, 1967; Pink and Creamer, 1967), and there was total absence of Paneth cells from the crypts in the jejunum of this patient. At necropsy, however, the entire gastrointestinal tract was studied histologically, and in the ileum Paneth cells were found to be present in entirely normal numbers (Neale, 1968). In this individual, therefore, who had total malabsorption of fat, the mucosal lesion had extended down the entire small intestine into the ileum, as is often the case in fatal cases of adult coeliac disease (Stewart *et al.*, 1967), but the lack of Paneth cells was restricted to the proximal small intestine.

During the last six months of his life this patient developed an erythematous rash. Discrete red areas spread progressively as the patient's condition deteriorated, covering arms, thighs, back, and trunk by the time of death. Examination of this lesion histologically showed an extensive arteritis (Fig. 17).

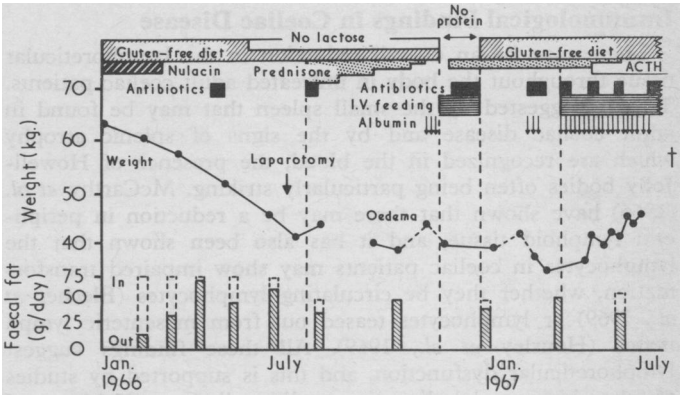

FIG. 15.—Clinical and biochemical observations in a patient with adult coeliac disease who failed to respond to treatment with a strict gluten-free diet. (From Neale, 1968.)

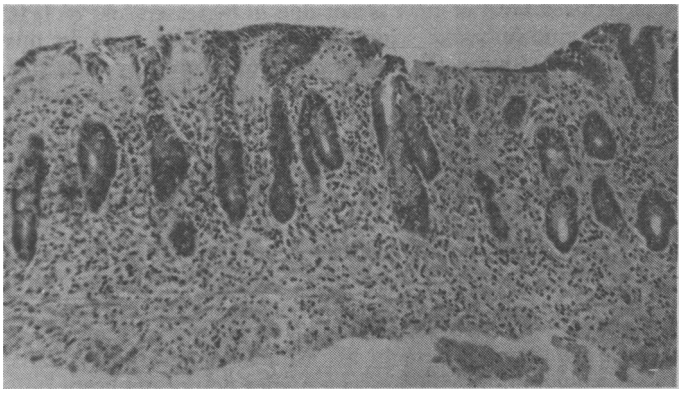

FIG. 16.—Jejunal biopsy from the patient with coeliac disease who died after failure of response to a gluten-free diet. The enterocytes are severely abnormal and there is a thick layer of collagen beneath their basement membranes. (×38.)

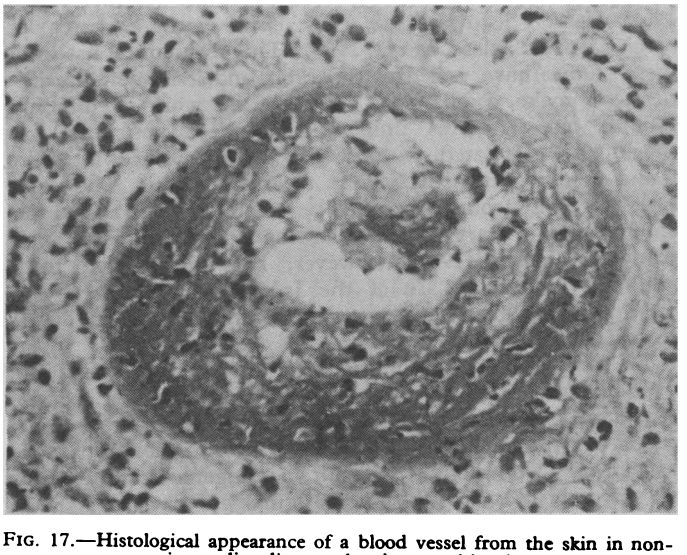

FIG. 17.—Histological appearance of a blood vessel from the skin in non-responsive coeliac disease, showing arteritis. (×140.)

We have now seen three coeliac patients who have developed an arteritis of this type, two of whom have died of their disease. These observations suggest that there may be hypersensitivity in such patients.

There is therefore no evidence at present to support the concept of an enzyme deficiency, and there are a number of clinical observations which conflict with this theory. The response to refeeding gluten, the failure of some individuals to respond to a gluten-free diet, and the occurrence of an arteritis in such patients all suggest that the disorder may be due to an immunological reaction, possibly of an allergic type.

Immunological Findings in Coeliac Disease

There may be an overall reduction in the lymphoreticular tissue throughout the body in untreated adult coeliac patients. This is suggested by the small spleen that may be found in adult coeliac disease and by the signs of splenic atrophy which are recognized in the blood, the presence of Howell-Jolly bodies often being particularly striking. McCarthy *et al.* (1966) have shown that there may be a reduction in peripheral lymphoid tissue, and it has also been shown that the lymphocytes in coeliac patients may show impaired transformation, whether they be circulating lymphocytes (Blecher *et al.*, 1969) or lymphocytes teased out from mesenteric lymph nodes (Housley *et al.*, 1969). All these findings suggest lymphoreticular dysfunction, and this is supported by studies of the immunoglobulins in coeliac disease (Hobbs and Hepner, 1968), which have shown a reduced level of IgM in about 60% of untreated patients. This is secondary, since the levels return to normal after treatment with a gluten-free diet. The reduced level of IgM is not due to increased loss of IgM into the gut, since the overall synthesis rate of IgM in this condition is reduced (Brown *et al.*, 1969), probably reflecting the general depression of lymphoreticular dysfunction in this disease. This may be an important factor in the untreated patient, as it may be associated with the greatly increased incidence of lymphoma and intestinal reticulosis in adult coeliac patients (Gough *et al.* 1962; Austad *et al.*, 1967; Harris *et al.*, 1967).

If there is an immunological response to gluten in coeliac disease it is not mediated through reaginic sensitivity, since, as Hobbs *et al.* (1969) and Asquith *et al.* (1969) have shown, serum IgE levels are normal unless coeliac patients also have atopic manifestations such as asthma or allergic rhinitis. Furthermore, immunofluorescent studies do not implicate IgE-containing cells in the gut mucosa and the concentration of IgE in the jejunal fluid is not apparently increased. Circulating antibodies to gluten fractions and other food substances, especially milk proteins, are often found in untreated coeliac patients, both in childhood and in adult life (Heiner *et al.*, 1961; Alarcón-Segovia *et al.*, 1964; Kivel *et al.*, 1964; Taylor *et al.*, 1964; Bayless *et al.*, 1967). The techniques used for these studies have varied considerably and it is therefore difficult to make comparisons between the work of different groups, but it seems unlikely that these antibodies are specifically correlated with coeliac disease, since they are found in other diseases such as ulcerative colitis. They may simply result from increased permeability of the coeliac enterocyte to dietary protein, allowing greater antigenic stimulation. Mjetens (1967), however, has shown that these antibodies to gluten are of the IgM class, an observation which may be significant in view of the infiltration of the jejunal mucosa with IgM plasma cells described below.

The normal small intestine is one of the important lymphoid tissues of the body and the lamina propria contains abundant lymphocytes and plasma cells. This infiltrate is not present in the newborn baby or in the germ-free animal, and it appears to develop as a result of antigenic stimuli in the gut in early life. Studies of the normal gut have also shown that the immunoglobulin produced by the intestinal plasma cell is predominantly IgA, and there is a marked preponderance of IgA cells in the lamina propria of the small intestine over other immunocytes (Crabbé and Heremans, 1966; Tomasi, 1968). These are likely to be the cells responsible for producing antibodies to gut-derived antigens. It has been shown, for example, that antibodies to orally ingested polio vaccine (Ogra *et al.*, 1968) or the copro antibodies that develop in cholera (Heremans, 1968) are of the IgA class. The IgA in the gut, however, is different from the IgA in the serum. There is an extra protein molecule added during its passage across the mucosa, the so-called transport piece, and the IgA in the gut is a dimer (Tomasi, 1968).

TABLE II.—*Immunoglobulins in Jejunal Juice (mg./100 ml. Mean ± S.E. of Mean)*

	Control Subjects (N = 16)	Untreated Coeliac Disease (N = 7)	Treated Coeliac Disease (N = 9)
IgG ..	5·3 ± 1·3	9·4 ± 3·2	8·9 ± 3·0
IgA ..	21·2 ± 4·1	24·2 ± 6·0	17·4 ± 4·1
IgM ..	5·3 ± 1·8	13·7 ± 3·4*	8·4 ± 3·1

*Significantly different from Control ($t = 2·44$, $P = 0·02$).
(From Crabbé, *et al.*, 1970).

Since histological studies show that there is a dense infiltrate of the lamina propria with lymphocytes and plasma cells in the flat jejunal mucosa, it is important to know the immunoglobulin classes of the intestinal plasma cells in coeliac disease. It has been suggested that the normal preponderance of IgA cells is also found in the mucosa of coeliac patients, (Rubin *et al.*, 1965). But Crabbé (1967), in a single patient, reported an excess of IgM-producing cells in the untreated coeliac mucosa, and subsequent studies on a larger number of patients have confirmed this finding (Douglas *et al.*, 1969; Søltoft, 1970). In seven untreated coeliacs there was an excess of IgM cells, and the abnormality persisted in all but 2 out of 15 patients treated with a gluten-free diet. The excess of these cells was localized to the jejunum, since examination of rectum and bone marrow showed a normal distribution of immunocytes (Douglas *et al.*, 1969).

The immunoglobulins in the jejunal secretions of control subjects and patients with coeliac disease before and after treatment were then measured and there was an excess of IgM in the jejunal fluid of most of the untreated coeliac patients (Table II). This is of particular interest, since Katz *et al.* (1968) have shown precipitating antibodies to a peptic/tryptic digest of gluten in the jejunal fluid of five out of eight untreated coeliac patients. The immunoglobulin class of these antibodies has yet to be determined, but Mietens (1967) suggested that the antibodies to gluten in the serum are of the IgM class.

Conclusions

Three observations have therefore been made. Firstly, there is an excess of immunocytes producing IgM in the gut mucosa. Secondly, there may be an increase in the IgM in the intestinal secretion. Thirdly, antibodies to gliadin of IgM class have been found in the serum. These observations may possibly provide a clue to the pathogenesis of coeliac disease. In the condition of selective IgA deficiency, IgM cells also infiltrate the intestinal mucosa. Selective IgA deficiency can be symptomless and as Hobbs (1968) has shown, occurs in 1 in 500 of hospital patients. Crabbé and Heremans (1967) were the first to describe IgA deficiency in association with coeliac disease. In our clinic at Hammersmith three patients with selective IgA deficiency and coeliac disease have been seen out of about 150, an incidence greater than in the general population. The significance of this association is not known. When selective IgA deficiency occurs, however, whether in isolation or in association with coeliac disease, the IgA cells are not for the most part replaced by IgM cells (Crabbé and Heremans, 1967). It has therefore been suggested that there may be a primary and qualitative deficiency of the IgA of the intestinal immunocytes in coeliac disease and that the infiltrate of IgM cells may be a compen-

satory response to a functional incapacity of the IgA. This hypothesis remains to be tested.

There is another observation that should be stressed. The toxic factor in gluten persists even when the many and complex original proteins in gluten have been broken down to a remarkably small size and a polypeptide with as low a molecular weight as 1000-1500 apparently retains its toxic quality (Kowlessar, 1967). This is a relatively low molecular weight to be immunogenic. If, as seems likely, a peptide of this molecular weight is inducing an immune response in coeliac gut mucosa, one may also postulate that it enters into some form of combination with substances in the brush border of the enterocyte, or with some other intracellular constituent, acting perhaps as a hapten in the same way as do some substances responsible for contact dermatitis. Whether this is so, whether there is an immunological response in coeliac disease, and whether it is mediated through humoral or cellular immunity are questions which can only be answered by future research.

Much of the work described in this lecture has been carried out at the Royal Postgraduate Medical School during the past 10 years. I am particularly grateful to my colleagues Dr. R. Holmes, Dr. J. S. Stewart, Dr. G. Neale, Dr. G. W. Hepner, Dr. A. P. Douglas, Dr. A. J. Wall. and Dr. T. J. Peters for their enthusiastic collaboration; to Dr. Ernst Riecken and Professor A. G. E. Pearse (department of pathology) for undertaking histochemical studies and for valuable discussions; to Dr. J. R. Hobbs (department of chemical pathology) and Professor J. Heremans and the late Dr. Paul Crabbé (Université de St. Pierre, Louvain) for their co-operation and advice in immunological problems; to Dr. Michael Marsh (department of medicine) and his colleagues Dr. J. A. Swift and Dr. A. C. Brown at the Unilever Research Laboratory, Isleworth, for permission to include their pictures obtained with the scanning electron microscope: and to my many colleagues both at the Royal Postgraduate Medical School and elsewhere who have kindly referred patients for investigation and treatment.

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