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Invited Review

The nature and implication of intestinal endocrine cell changes in coeliac disease

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Summary. Coeliac disease is associated with intestinal lesion. This lesion causes architectural derangement of the mucosa in the form of villus atrophy, increased crypt length and increased volume of the lamina propria. Several changes in the intestinal endocrine cells have been reported over the years, e.g. the number of secretin cells and increased numbers of GIP, CCK/gastrin, motilin, and serotonin cells. There is no consensus about the nature of the changes in somatostatin-cells. It has been postulated that the changes in the endocrine cells are a selective process to meet the new demands exerted by the dramatic decrease in intestinal absorptive area. It has been speculated further that the changes in the endocrine cells would cause an incomplete digestion of the ingested food and its rapid elimination from the intestine. These changes may be responsible for the diarrhoea and steatorrhoea that occur in patients with coeliac disease.

Key words: Absorption, Coeliac disease, Endocrine cells, Intestine, Motility

Introduction

The first description of coeliac disease is attributed to Aretaeus, who lived in the first or second century AD (Major, 1945). In 1888, Samuel Gee described the features of the condition with remarkable accuracy and even suggested that a cure might be found in the diet (Gee, 1888). It was not until 1954, however, that the characteristic intestinal lesion was described by Paulley (1954). The prevalence of this disease in adults, based on detected symptomatic cases, has been reported to be 1:950 in Sweden (Hallert et al., 1983) and 1:1700 in Scotland (Logan et al., 1986). The true prevalence of coeliac disease is believed to be much greater, viz. close to a rate of 1 in 300 in the general population (Auricchio et al., 1990). In Swedish children its prevalence was estimated by Berg and Lindberg (1979) to be 1:982. The sex frequency is almost evenly balanced in childhood (Corazza and Gasbarrini, 1995), whereas in adults the female:male ratio is 2:1 (Howdle and Losowsky, 1992).

Coeliac disease has an extraordinary breadth of manifestations and many cases are unrecognised or latent (Duggan, 1997). Coeliac disease is accompanied by malabsorption of minerals, vitamins, carbohydrates and fat (Sjölund, 1982). The clinical manifestations of the disease are alike in juvenile and adult form. Diarrhoea, weight loss, abdominal destination and pain, cramp or tetany and oedema are common symptoms in patients with coeliac disease (Corazza and Gasbarrini, 1995; Littlewood, 1995). In juvenile form, slow development also occurs (Littlewood, 1995).

The small-intestinal lesion of coeliac disease results in architectural derangement of the mucosa and changes in several endocrine cells. These cells play an important role in the regulation of several functions of the gut, such as motility and secretion (Harvey, 1975; Allescher and Ahmed, 1991; Ekblad et al., 1991; Dockray and Walsh, 1994). It is conceivable, therefore, that these changes may be involved in the pathogenesis of the disease and its clinical manifestation. The nature and types of endocrine cell affected are debatable, however. In the present review, a survey of the changes in the intestinal endocrine cells of patients with coeliac disease is presented. The nature of these changes is discussed, and their pathophysiological role and clinical implications are speculated upon.

Mucosal architecture changes

The mucosa of small intestine in untreated coeliac disease shows an architectural derangement in the form of villus atrophy and increased crypt length (Wright et al., 1973a,b; Watson et al., 1980). These abnormalities are a result of damage to villus enterocytes (Booth, 1970; Perera et al., 1975; Wastson et al., 1980) and a compensatory increase in crypt cell proliferation and production rate (Booth, 1970; Wright et al., 1973a,b; Perera et al., 1975; Watson et al., 1980). The mean

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volume of surface enterocytes in a severe, flat-destructive (type 3) lesion is reduced by 25% (Crowe and Marsh, 1993). The lamina propria is also involved, and in the flat-destructive lesion, the volume is doubled (Dhesi et al., 1984). This increase in volume is caused by an efflux of plasma proteins as a result of microvascular hyper-permeability and to an increase in the size of lamina propria cell populations, including lymphocytes, plasma cells, mast cells, basophils, eosinophils and neutrophils (Dhesi et al., 1984; Marsh and Hinde, 1985).

The infiltrative lesion of gluten sensitivity was first identified by Fry and colleagues (1972, 1974). Since then, several studies over the years have amply demonstrated that gluten sensitivity can be associated with any type of mucosal abnormality, ranging from a superficially normal appearance to the severe classical flat lesion (Marsh and Crowe, 1992). Scanning electron microscopy analyses of intestinal mucosa have been reported to reveal early stages of fine villous alterations that can not be detected by light microscopy (Magliocca et al., 1992). Thus, the intestinal lesion in coeliac disease has been classified by Marsh (1992) into five types, namely pre-infiltrative (type 0), infiltrative (type 2), infiltrative-hyperplastic (type 3), flat-destructive (type 3) and atrophic-hypoplastic (type 4). Recently, a new morphological classification by scanning electron microscopy has been proposed (Magliocca et al., 1996). In this classification, the healing process of the small intestinal mucosa in correlation with the time of start of dietary therapy has been taken in consideration.

Changes in intestinal endocrine cells

Over the years, the intestinal endocrine cells in adults and children with coeliac disease have been the subject of several studies (Challacombe and Robertson, 1977; Polak et al., 1978; Sjölund et al., 1979, 1982a,b, 1983; Jones and Elemes, 1982; Enerbäck et al., 1983; Buchan et al., 1984; Wheeler and Challacombe, 1984; Pietroletti et al., 1986; Johnston et al., 1988; Bel'mer et al., 1991; Moyana and Shukoor, 1991). These studies have revealed abnormalities in certain endocrine cell types, though Their nature and the endocrine cell types affected, have varied in different studies. Thus, the number of secretin cells has been reported to decrease in adults with coeliac disease (Sjölund et al., 1979; Buchan et al., 1984). In our laboratory (unpublished data), we too found a decrease in the number of secretin cells (Fig. 1) in untreated juvenile coeliac patients. It has been stated, however, that the number of these cells increases in juvenile coeliac disease (Polak et al., 1973). Gastric inhibitory peptide (GIP) cells have been found to increase in number in adult coeliac disease (Sjölund, 1982). We have observed similar changes in children with coeliac disease (unpublished data). These findings contrast to those reported by Bel´mer et al. (1982), who found a reduced number in juvenile coeliac disease.

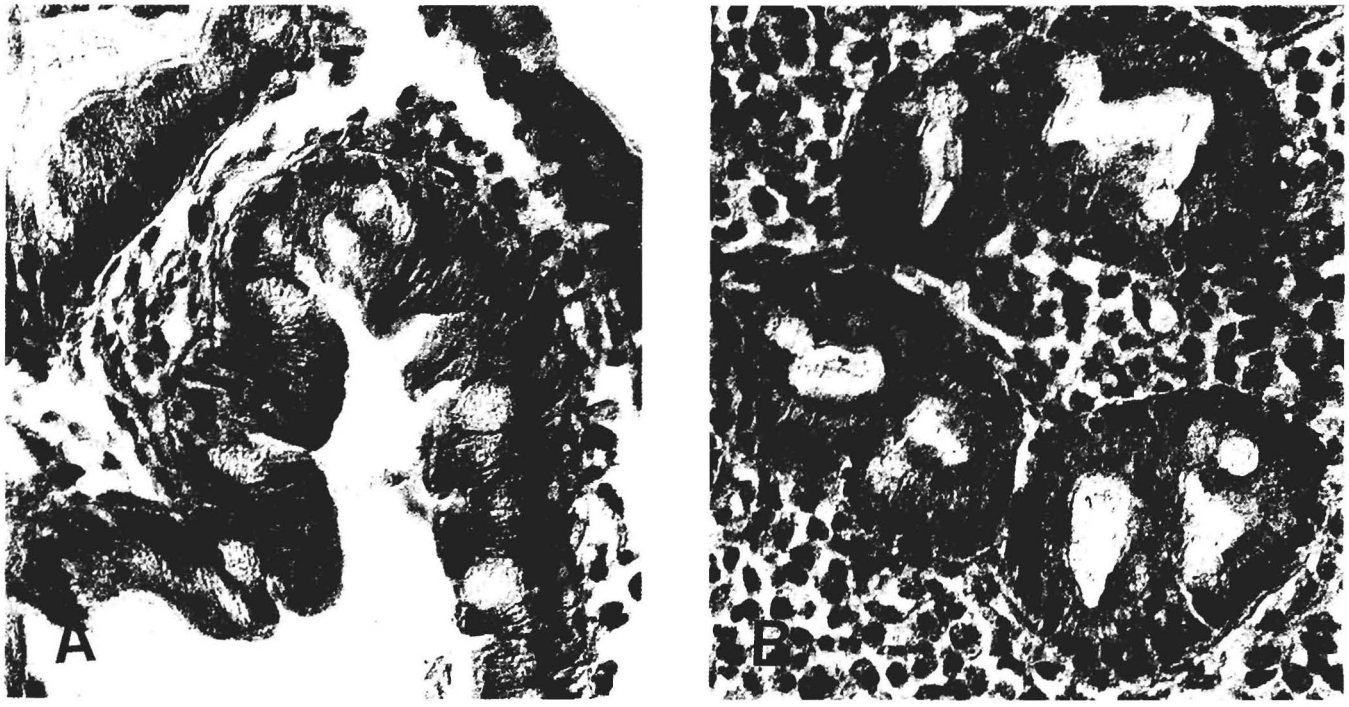

Fig. 1. Secretin-immunoreactive cells in the crypts of the duodenum of a one-year-old boy with a short stature non-specific diarrhoea **(A)**, and of a boy with clinical symptoms and laboratory data of active coeliac disease **(B)**. These cells decrease in number in the coeliac disease. Avidin-biotin complex method with haematoxylin counterstaining. x 400

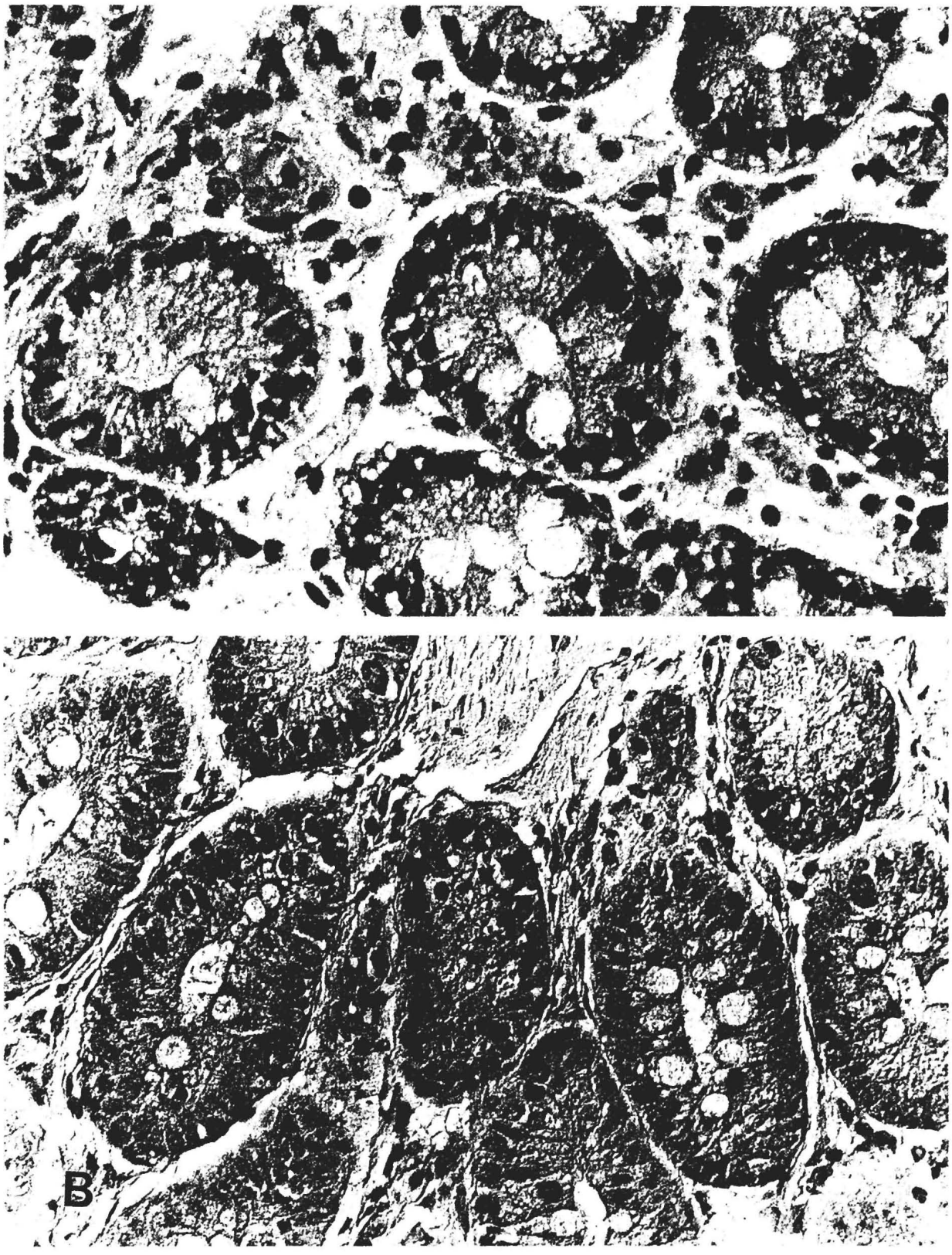

Fig. 2. Gastrin/CCK-immunoreactive cells in the duodenum of a 2-year -old girl with chronic non-specific diarrhoea **(A)** and of a patient with active coeliac disease **(B)**. These cells increase in number in the coeliac disease patient. Avidin-biotin complex method with haematoxylin counterstaining. x 600

There is a consensus in all the studies reported that the cholecystokinin (CCK)/gastrin cells (Fig. 2) increased in number both in adult and juvenile coeliac disease (Polak et al., 1978; Sjölund et al., 1979; Bel´mer et al., 1991, unpublished data). There are, however, contradictory results with regard to the somatostatin cells in patients with coeliac disease. Motilin cells have also been found to increase in number in both adult and

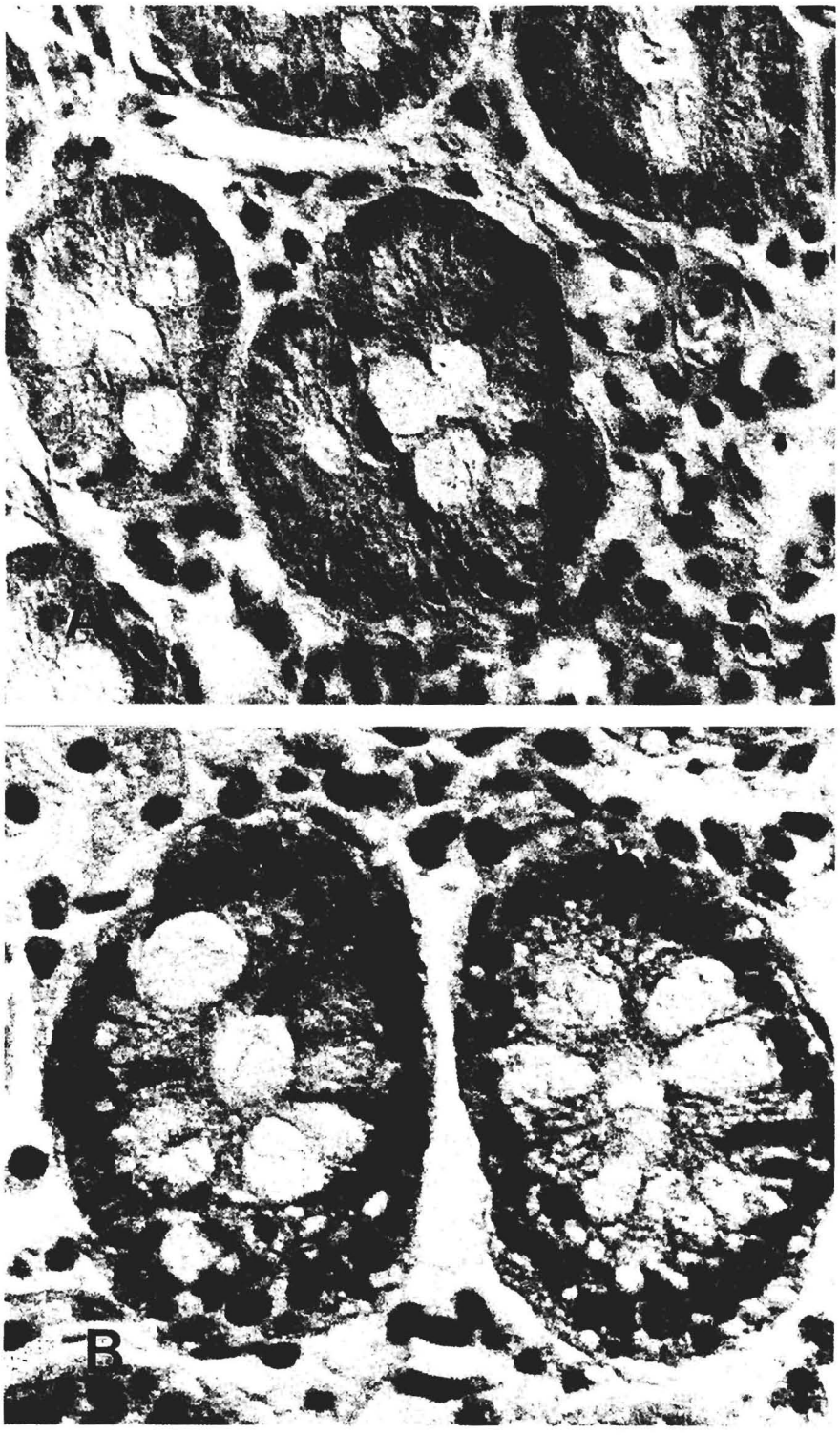

Fig. 3. Serotonin-immunoreactive cells in a 1-year-old boy with a short term diarrhoea **(A)** and in a 1.5-year-old boy with active coeliac disease **(B)**. Observe that the number of cells is increased in the patient. x 500

juvenile coeliac disease (Sjölund et al., 1982; unpublished data). There is general agreement that a serotonin-cell hyperplasia occurs in the small intestine of patients with coeliac disease (Challacombe and Robertson, 1977; Sjölund et al., 1982; Buchan et al., 1984; Moyana and Shukoor, 1991; unpublished data).

Considering the evidence presented in the above-mentioned studies, one can summarise the changes in the intestinal endocrine cells in coeliac disease as follows: there is hyperplasia of CCK/gastrin, GIP, motilin and serotonin cells. The secretin cells decrease in number and the changes in somatostatin cells are uncertain.

The nature of changes in intestinal endocrine cells

It has been claimed that there is no abnormality in the intestinal endocrine cells of patients with coeliac disease, and that the previously reported findings were artefactual, resulting from using inappropriate quantification methods (Johnston et al., 1988). In endocrine cell quantification, mucosal architectural abnormalities in coeliac disease should be taken into consideration and measurements should be made in such a way as to eliminate the effect of the mucosal changes in coeliac disease. As a matter of fact, earlier studies (Challacombe and Robertson, 1977; Sjölund et el., 1979; Sjölund, 1982; Enerbäck et al., 1983; Buchan et al., 1984; Wheeler and Challacombe, 1984; Moyana and Shukoor, 1991) have done that elegantly by counting the number of endocrine cells per visual field, per mm mucosal length, per mm^2 mucosa, per crypt, or per mm basement membrane length. Quantification of endocrine cells per mm crypt length, as has been suggested (Johnston et al., 1988), would give misleading results, as any changes observed could be caused by the mucosal architectural abnormalities and not by actual deviations in endocrine cell number. Furthermore, the endocrine cells in the small intestine show a topographical distribution (Sjölund et al., 1983; El-Salhy et al., 1994). Thus, CCK/gastrin and secretin cells occurred mostly in the villi, somatostatin and GIP cells in the crypts, while motilin and serotonin cells are evenly distributed in both crypts and villi. If the endocrine cells do not change, the architectural changes in the mucosa will result in increased numbers of secretin and CCK/gastrin cells (villus atrophy), fewer GIP and somatostatin cells (increased crypt length), and unchanged numbers of motilin and serotonin cells. As mentioned earlier in this paper, this is not consistent with the reported changes in the endocrine cells in coeliac disease.

It seems that change in the intestinal endocrine cells in coeliac disease is not a haphazard process, but a selective phenomenon affecting certain endocrine cell types. It is unlikely that these changes are primary or that the coeliac disease is a hormonal disorder (Buchanan and O'Connor, 1978). The changes are most probably a response to new physiological demands imposed by the architectural derangement of the mucosa in this disease

Implication of intestinal endocrine cell changes

CCK stimulates intestinal motor activity and shortens intestinal transit time (Liddle, 1994). Motilin induces gastroduodenal contraction (Poitras, 1994). Serotonin stimulates pyloric contraction, and small intestinal and colonic motility as well as accelerating small and large intestinal transit (Lidberg, 1985; Tally, 1992; Osterbosch et al., 1993; Goarard et al., 1994; von der Ohe et al., 1994). CCK, motilin, and serotonin cells are more numerous in coeliac disease. This increase ought to accelerate intestinal motility and shorten transit time.

Secretin stimulates pancreatic exocrine secretion of water and bicarbonate and increases the bicarbonate secretion of the bile (Leiter et al., 1994). CCK stimulates pancreatic enzyme secretion (Liddle, 1994). Consequently one would expect an increase in pancreatic enzyme secretion in patients with coeliac disease, as CCK cells are more numerous. These enzymes would not be effective however, as they would be active in an unfavourable pH caused by the reduced number of secretin cells and secretin release (Bloom et al., 1976).

CCK is the major hormonal regulator of gallbladder contraction (Liddle, 1994). Motilin, on the other hand, induces contraction of the sphincter of Oddi (Poitras, 1994). Both CCK and motilin cells are increased in numbers in coeliac disease, which ought to cause contraction of the gallbladder and the sphincter of Oddi, resulting in defective emptying of the gallbladder. This assumption is supported by observations that in patients with coeliac disease, there is a defective emptying of the gallbladder in response to fat in the duodenum (Low-Beer et al., 1971; Di Magno et al., 1972).

Against this background, one may speculate that the changes in the intestinal endocrine cells result in an incomplete digestion of the ingested food and its rapid elimination from the intestine in order to adapt to the reduced intestinal absorption area by 80% in patients with coeliac disease (Marsh and Crowe, 1992). These changes may be responsible for the diarrhoea and steatorrhoea occurring in patients with coeliac disease.

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