to this may cause less gastro-intestinal disturbance. The side-effects of chlorphentermine S.A. may not, however, be entirely local in action, and it is possible that the anorectic action of chlorphentermine may be dependent on its function as a mild central emetic at medullary level. The 10 defaulters up to three months contained five on the test preparation and five on the placebo, so that it seems unlikely that the default rate was related to the gastro-intestinal effects of chlorphentermine.

As a result of this investigation what conclusions can be drawn regarding chlorphentermine S.A ? It would appear to be of value as a supplement to the treatment of obesity, in which close medical supervision and encouragement of strict dietary measures are the mainstay of therapeutic management. By itself the drug has no definite role. It is recognized that the doctor often feels the need to prescribe an appetite suppressant for his obese patient who complains of excess appetite and requests a "slimming pill," and in such circumstances chlorphentermine S.A. may be useful, since it is an anorectic but does not act as a cerebral stimulant.

## Summary

A clinical trial on the anorectic agent chlorphentermine S.A. was performed. The drug was shown to be of value as an adjunct to dietary measures in producing loss of weight in obese patients attending a hospital clinic at regular intervals for three months. However, these patients who were subsequently prescribed the drug by their general practitioners showed no significant loss of weight over a similar period of time.

There was a strong family history of diabetes and obesity, but this bore no relation to subsequent loss of weight.

After three months' dieting the mean total 17-OHCS and 17-KS fell, the former significantly. The fall in urinary steroid excretion correlated with the loss of weight, but not statistically so.

The value of chlorphentermine S.A. and the indications for its use are discussed.

We should like to thank Dr. E. G. Oastler for advice and criticism ; Dr. J. K. Grant for the steroid assays ; and Mr. M. W. Birch, Department of Mathematics, University of Glasgow, for help with the statistics.

The long-acting chlorphentermine preparation (Lucofen SA) and identical placebo tablets were provided by Wm. R. Warner and Co. Ltd.

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# Significance of a Flat Small-intestinal Mucosa

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In 1954 Paulley described an abnormal appearance of the small-intestinal mucosa in a few patients with idiopathic steatorrhoea. With the introduction of peroral biopsy by Shiner (1956) the number of observations was greatly increased and the abnormal appearance confirmed in both idiopathic steatorrhoea and coeliac disease (Shiner and Doniach, 1960 ; Shiner, 1960). The abnormality is easy to recognize both by the dissecting microscope (Holmes *et al.*, 1961a) and on histology. It consists of loss of the normal villous pattern with a flat or convoluted appearance, and, on section, deep crypts opening on to a disorganized surface epithelium. This histological appearance has been regarded as specific for a disease entity—coeliac disease and idiopathic steatorrhoea.

We have been impressed by the number of cases in which a flat mucosa has been associated with other diseases, suggesting that the mucosal change may be a non-specific response in some patients. This report concerns a group of patients in whom a flat mucosa was found and details the associated disease present at the time of the biopsy.

## Definitions

This paper frequently refers to three concepts—a mucosal abnormality, a clinical picture, and a disease entity. The clinical picture is described in a separate communication (Hindle and Creamer, 1965) and corresponds closely to the experience of other workers. The mucosal abnormality and the disease entity, however, have been variously named, often implying slightly different definitions. In order to avoid confusion our use of terms is described.

*Mucosal abnormality.*—This is a structural alteration which is universally accepted when gross but has no absolute end-point. Shiner and Doniach (1960) introduced the terms subtotal and partial villous atrophy to describe the complete or partial loss of villi, and Holmes *et al.* (1961b) later showed that each corresponded to a dissecting-microscope appearance, a flattened surface in subtotal and a convoluted appearance in partial villous atrophy. The difficulty is that some workers appear to include rather minor abnormalities under partial villous atrophy, and also that other conditions may produce a convoluted appearance (Creamer, 1964a). In our opinion a distinction is usually easy if attention is paid not only to the structure but also to the presence of chronic inflammatory cells in the stroma and degenerative changes in the surface epithelium with lymphocytic infiltration. Most of the cases described here had a flattened appearance on examination with the dissecting microscope, and all showed the changes of inflammation and epithelial degeneration. This we call a flat mucosa.

*Disease entity.*—Under the labels of idiopathic steatorrhoea, adult coeliac disease, and non-tropical sprue, a disease is recognized which may be linked with coeliac disease of childhood

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but more often begins in adult life and is defined by a flat mucosa. While no aetiological agent is identified by these terms the presumption is that this is a single disease. The term "gluten-sensitive enteropathy," however, defines a group with a known mechanism but excludes a certain number of patients with a flat mucosa. As will be argued, many causes seem likely and gluten-sensitivity is independent of this. Therefore we prefer the term "coeliac syndrome" to include all cases with a flat mucosa without implying a single cause or gluten-sensitivity.

## Cases

There were 50 patients selected for study; they were all those seen during a four-year period in whom a typically flat small-intestinal mucosa was found and of whom full clinical and investigative details were available. There were 26 males and 24 females, their ages varying from 15 to 74 years. In 49 cases the biopsy specimen was obtained perorally, and in one case it was a surgical biopsy.

The patients were fully investigated, and the results are presented and analysed in another communication (Hindle and Creamer, 1965).

## Results

Three groups of cases can be distinguished. Firstly, those with a history of coeliac disease; secondly, those developing a malabsorption syndrome in adult life but without any other disease which could be regarded as primary; and, lastly, those with another disease preceding or presenting soon after the development of malabsorption.

### Group I. Coeliac Disease

Nine patients (18%) had a history of coeliac disease, and in two of these a sibling was also affected (Fig. 1). One of these patients had congenital aortic stenosis but without any symptoms of heart disease or evidence of cardiac failure. One other patient developed a severe megaloblastic anaemia with glandular fever, but apart from this there were no other associated diseases in this group.

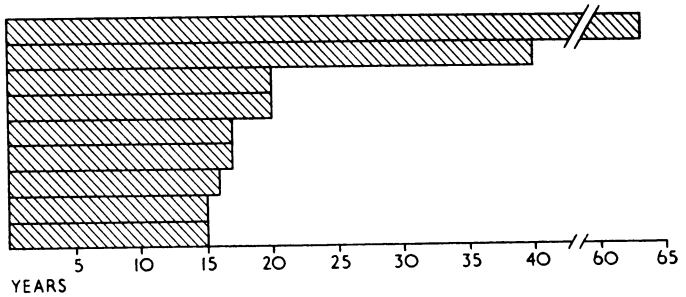


FIG. 1.—Diagram of the duration of malabsorption before biopsy in nine patients who began with coeliac disease in infancy (group I).

### Group II. Patients with a Flat Mucosa without Other Associated Disease

Twenty-three patients (46%) fell into this group. The duration of malabsorption before biopsy is shown in Fig. 2. Apart from three cases detailed below, there were no other associated diseases. One patient had a familial myelopathy which was thought to be unrelated to malabsorption. Another patient developed dermatitis, but this appeared to be a complication of his malabsorption syndrome. A third patient presented with a severe megaloblastic anaemia during an attack of glandular fever. He was later found to have steatorrhoea and folic-acid deficiency. In view of the other similar case with a coeliac history the glandular fever was thought to be a revealing stress rather than a primary event.

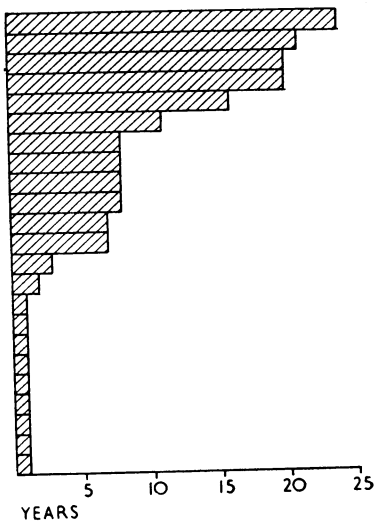


FIG. 2.—Diagram of the duration of malabsorption before biopsy in 23 patients who had no associated disease (group II).

### Group III. Patients with a Flat Mucosa and an Associated Disease

There were 18 patients (36%) in this group. The relation of the onset of the associated disease to the onset of malabsorption and the timing of the jejunal biopsy are shown in Figs. 3 and 4. These cases appear to fall into two subgroups. In seven patients (Group IIIa, Fig. 3) the associated disease preceded the onset of malabsorption, while in 11 (Group IIIb, Fig. 4) the symptoms of malabsorption were the first indications of disease.

Two patients in Group IIIa were diabetic since childhood, the diabetes preceding the onset of malabsorption by 14 and 13 years respectively. Three patients in this group had dermatitis of 22, 17, and 10 years' duration before any evidence of diarrhoea or deficiencies developed. One of the patients with dermatitis subsequently developed Hodgkin's disease and appears to occupy a position halfway between Groups IIIa

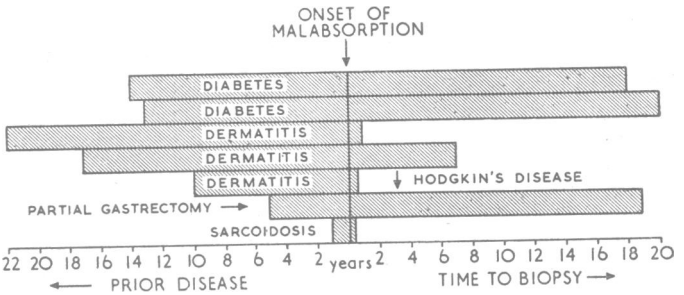


FIG. 3.—Diagram showing the duration of the disease preceding malabsorption and duration of malabsorption before biopsy in seven patients (group IIIa). In one patient dermatitis preceded the malabsorption by 10 years, and two years after the jejunal biopsy a gland biopsy showed Hodgkin's disease.

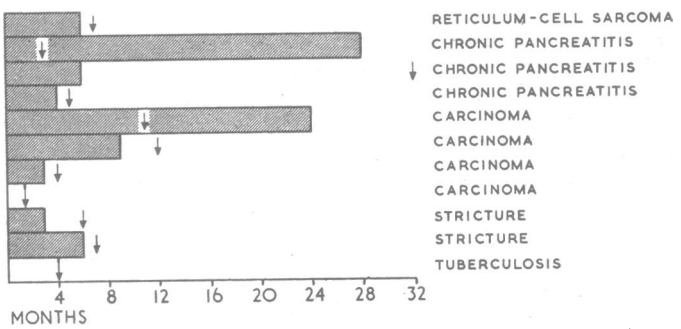


FIG. 4.—Diagram showing the duration of malabsorption before biopsy in 11 patients (group IIIb). The arrow marks the point in time where the associated disease was diagnosed.

and IIIb. One patient had a long history of peptic ulceration, and five years after partial gastrectomy he developed malabsorption; many years later a totally flat jejunal biopsy was obtained from a site well distal to the stoma. The seventh patient presented with generalized lymphadenopathy, and gland biopsy showed sarcoidosis. Later he developed hypercalcaemia, and at this time a flat intestinal mucosa was found. After successful treatment of the hypercalcaemia with prednisone his intestinal mucosa reverted towards normal.

Four of the patients in Group IIIb, whose first symptoms were those of malabsorption, had a carcinoma, the primary sites being ovary, cervix, adrenal, and malignant small-intestinal polyps. These cases have already been reported (Creamer, 1964b). One patient had a reticulum-cell sarcoma. Three patients had good evidence of chronic pancreatitis, with an abnormal secretin test in all, pain in two, and pancreatic calcification in one. Two patients presented with severe abdominal colic and malabsorption; both had multiple simple ulcers in the jejunum with stricture formation, but there was no evidence of Crohn's disease. After resection recovery was rapid, although in addition both were treated with a gluten-free diet. The final patient in this group had generalized lymphadenopathy and malabsorption. Biopsy of an axillary gland on two occasions showed caseating tuberculosis.

## Discussion

It is clear from these findings that many patients with a flat jejunal mucosa—36% in this series—have some associated disease in addition to the symptoms of malabsorption. There would seem to be three possible explanations for this: firstly, the association may be fortuitous; secondly the flat mucosa may have been present for a varying period without symptoms and be the cause of the associated disease; or, thirdly, the associated disease may be the cause of the flat mucosa. Two separate diseases in one patient are not infrequently seen, but an incidence of 36% is very high and makes this explanation seem extremely unlikely.

In the 18 cases in Group III the problem is straightforward: Is the mucosal change primary or secondary? Some evidence can be obtained from within the whole series of 50 cases. If the flat mucosa were the primary condition it would be expected that the longer a patient suffers from it the greater would be the risk of his developing another disease. In fact the reverse seems true. In Group I the patients with a coeliac history had an average "exposure time" of 25 years, and in Group II an average "exposure time" of seven and a half years, yet none of these patients developed any of the associated diseases found in Group III. On the other hand, in Group IIIb the associated disease was diagnosed in an average time of only eight months from the onset of malabsorption, while in Group IIIa the preceding disease had been present for many years before malabsorption developed. Therefore there seems to be a strong suggestion that the flat mucosa is a result of the associated disease.

Somewhat the opposite conclusion, that a flat mucosa may be a premalignant condition, was advanced by Gough *et al.* (1962). They reported three cases of reticulum-cell sarcoma in which jejunal biopsy showed an abnormal mucosa. One of these patients had a history suggestive of coeliac disease, but in the other two the history was not so long as to preclude the possibility that the whole illness was due to reticulum-cell sarcoma. They gathered a further 16 cases of reticulum-cell sarcoma and malabsorption from the literature, but the duration of the disease in at least 10 of these was again compatible with the whole illness being due to lymphoma. Eakins *et al.* (1964) reported a further six cases of reticulum-cell sarcoma of the small bowel and steatorrhoea with an abnormal jejunal biopsy. In their search of the literature they found only three cases of small-intestinal reticulosis occurring in patients with the clinical features of coeliac disease, and only two further cases in patients known to have had idiopathic steatorrhoea for more than 10 years. While it is possible that in some cases an intestinal reticulosis may arise as a complication of idiopathic steatorrhoea, much of the evidence suggests that the flat mucosa develops as a result of the reticulosis.

The patients with dermatitis present a difficult problem, as it has been recognized for some years that dermatitis may be a complication of idiopathic steatorrhoea or coeliac disease (Wells, 1962). In the cases described in Group IIIa the dermatitis antedated malabsorption by many years and there seems to be no reason why the dermatitis should be regarded as a complication of the malabsorption. It seems more logical to regard the flat mucosa as secondary to the dermatitis.

The two patients with a flat mucosa, jejunal ulceration, and stricture formation are difficult to classify. There was no evidence of lymphoma or Crohn's disease, and the nearest description available seems to be a brief report by Goulston (1964) of four cases with similar features.

Astaldi *et al.* (1964) have recently shown that abnormal jejunal biopsy appearances, including atrophy of the villi similar to those found in idiopathic steatorrhoea, can occur in association with infective hepatitis and that after recovery from the hepatitis the mucosal appearances return to normal.

Salem *et al.* (1964) reported abnormal jejunal biopsy appearances in ulcerative colitis. Although the changes they described were less severe than those under discussion in this paper, more than half of the 25 patients studied had abnormal biopsies. The degree of abnormality was related to the severity of the ulcerative colitis, but as repeat biopsies were not performed it is uncertain whether the changes in the mucosa improved during remissions in the ulcerative colitis. They found only one completely flat jejunal biopsy, and it is of interest that this patient also had cirrhosis.

Ellenberg and Bookman (1960) described the cases of two patients with diabetes, steatorrhoea, and a full malabsorption syndrome, one of whom had atrophy of the jejunal mucosa such as is found in idiopathic steatorrhoea. They suggested that the mucosal change should be regarded as a complication of long-continued diabetes. Mailman (1958) also reported a case of steatorrhoea, diabetes, and neuropathy. This patient was later studied by Grossman, who found that the jejunal mucosa showed an almost total lack of villi. Vinnik *et al.* (1962) described seven cases of diarrhoea and diabetes, in three of which the laboratory and histological findings were those of idiopathic steatorrhoea. They assumed that these three patients had coincident diabetes and idiopathic steatorrhoea. In their patients, as in ours, diabetes preceded the onset of diarrhoea by many years, and in those with a flat jejunal biopsy there was a prompt response to a gluten-free diet.

There are now a considerable number of case reports in the literature of diseases associated with malabsorption and a flat jejunal mucosa (see Table). In some instances there is also evidence that the mucosal changes are reversible with improvement of the underlying disease. It is therefore suggested that in some patients a flat intestinal mucosa may be due to an

*Reported Cases of Diseases Associated with Malabsorption and Flat Jejunal Mucosa*

| Disease | No. | Author |
|---|---|---|
| Carcinoma | 4 | Creamer (1964b) |
| Malignant lymphoma | 2 | Gough *et al.* (1962) |
| | 2 | Present series (1965) |
| Diabetes mellitus | 1 | Mailman (1958) |
| | 1 | Ellenberg and Bookman (1960) |
| | 3 | Vinnik *et al.* (1962) |
| | 2 | Present series (1965) |
| Chronic pancreatitis | 3 | " " (1965) |
| Post-gastrectomy | 1 | " " (1965) |
| Ulcerative jejunitis and stricture | 4 | Goulston (1964) |
| | 2 | Present series (1965) |
| Ulcerative colitis (also cirrhosis) | 1 | Salem *et al.* (1964) |
| Infective hepatitis | ? | Astaldi *et al.* (1964) |
| Tuberculosis | 1 | Present series (1965) |
| Sarcoidosis | 1 | " " (1965) |
| Dermatitis | 3 | " " (1965) |

intrinsic defect, as in coeliac disease and a fair proportion of adult cases, but that in others it may be secondary to some other disease. The list of causative diseases is already long and probably others will be added. The implication to be drawn from the patients in Group III is that the primary disease may either be well established years before the mucosal change or that the malabsorption and mucosal abnormality present shortly beforehand. With this in mind it is suggested that all patients with a short history of malabsorption should be suspected of an underlying disease which may be excluded only by observation over a period of time.

The terminology of this condition has never been satisfactory, and the label "idiopathic steatorrhoea" has long been challenged. We would suggest the substitution of coeliac syndrome, which may be primary or secondary, as being accurate and euphonious, until more definite knowledge is available.

## Summary

Fifty patients with a flat small-intestinal mucosa have been reviewed. Eight (16%) had coeliac disease and 24 (48%) had no disease other than a malabsorption state. The remaining 18 (36%) had some other disease which either antedated the onset of malabsorption by many years or succeeded it by a relatively short interval. It is suggested that in this last group the flat mucosa was a complication of the associated disease. If this explanation is correct then the finding of a flat jejunal mucosa on biopsy can no longer be regarded as diagnostic of idiopathic steatorrhoea.

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# Clinical Picture Accompanying a Flat Small-intestinal Mucosa

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The diagnostic significance of a flat jejunal mucosa and its relation to other diseases has been discussed in a previous paper (Hindle and Creamer, 1965). It was suggested that those patients in whom there was no associated disease should be regarded as having a primary coeliac syndrome, whereas in those in whom certain other disease was present the coeliac syndrome should be regarded as a secondary manifestation. In this article the clinical and investigative findings in the same 50 patients with flat jejunal mucosa are described, and an attempt is made to see if primary and secondary coeliac syndromes can be distinguished on these grounds.

## Cases and Investigations

The case records of 50 patients with an unequivocally flat jejunal mucosa were examined. There were 26 males and 24 females, their ages ranging from 15 to 74 years. In 49 cases the biopsy specimen was obtained perorally, and in one case it was taken at operation. All patients were fully investigated at the time of biopsy. The range of investigations used is listed below, although not every patient had all the tests performed.

*Haematology.*—Full blood count, E.S.R., serum iron, serum folate, Figlu test, serum vitamin $B_{12}$, Schilling test, and sternal-marrow examination.

*Biochemistry.*—Five-day faecal fat excretion, xylose excretion, glucose-tolerance curves, serum potassium, serum calcium, serum phosphorus, alkaline phosphatase, and plasma proteins.

*Radiology.*—Small-bowel meal.

*Histology.*—The biopsy specimens were examined under the dissecting microscope. They were accurately orientated and after section were examined by conventional microscopy.

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## Results

For the purpose of analysis patients with coeliac disease have been grouped with those who developed symptoms of malabsorption in adult life but had no evidence of any other disease (primary coeliac syndrome). There were 32 patients in this group (16 males and 16 females); 18 (10 males and 8 females) had a secondary coeliac syndrome.

Fig. 1 contrasts the incidence of various symptoms in the patients with primary and secondary coeliac syndromes. It is clear that in the two groups there is no difference in the frequency of occurrence of diarrhoea, loss of weight, or reduction in appetite. Patients with a secondary coeliac syndrome complained of abdominal pain and oedema almost twice as often as did those with a primary coeliac syndrome. However, the number of patients with these complaints was small and the difference between the two groups may not be signifi-

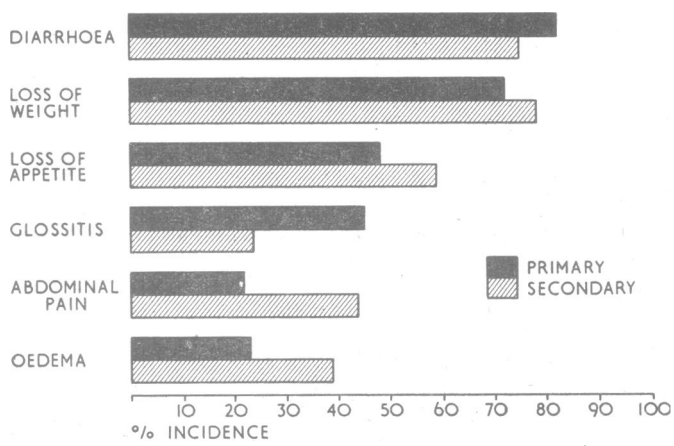


FIG. 1.—Diagram showing the incidence of symptoms in the primary and secondary coeliac syndromes.