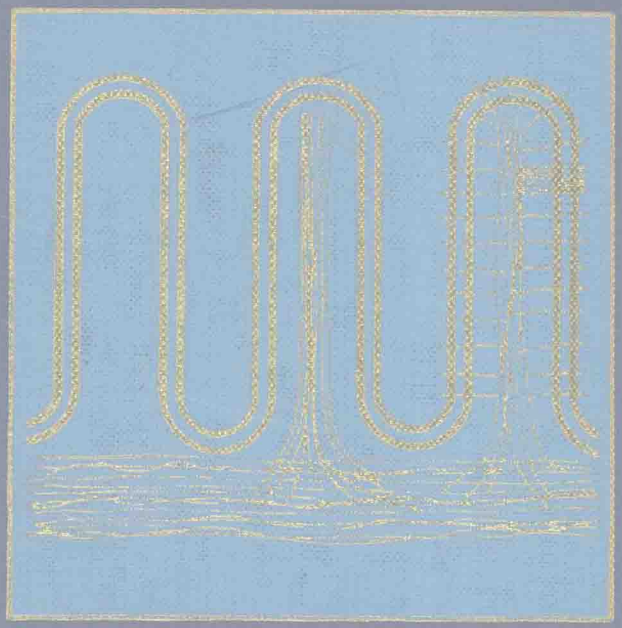
COELIAC DISEASE



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CHURCHILL LIVINGSTONE

Coeliac Disease

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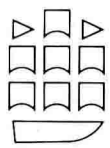

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Preface

Coeliac disease was introduced to one of us almost 50 years ago by Sir Leonard Parsons FRS and has remained an enduring source of clinical and research interest. During this period the disorder has been differentiated from tropical sprue, the benefits of a gluten free diet have become evident and the characteristic jejunal biopsy appearances recognized. However, despite the increasing clinical recognition and study of coeliac disease involving many disciplines, its secrets have not been fully unravelled, and it continues to stimulate research into many areas of human metabolism and pathophysiology. The greater ease of investigation has not clarified the aetiology and in some respects we are little further forward than when the search was commenced by the classical experiments carried out in Holland over 30 years ago.

We have followed some 500 patients closely through the years who have been a constant source of stimulation and have helped us crystallize our views of this fascinating disorder.

It has become clear that patients differ widely in their sensitivity to gluten and at some stage in life may ingest a high gluten load without developing symptoms and may not even have a flat jejunal biopsy. These considerations have made a definition of coeliac disease difficult. The disorder should not be missed for it is eminently treatable and fortunately in the majority of cases the diagnosis presents little difficulty. Whether a gluten free diet prevents the development of the most serious complication, malignancy, is not known, but a diet for life should be strongly advised for all patients. Many other questions also remain unanswered and await further study.

Our aim in writing this book has been to present a comprehensive account of coeliac disease which we hope will be of value not only to gastroenterologists but also to others who may encounter the disorder in their practice and research. An extensive bibliography has been included for those who may wish to consult the original texts. It is also written in the hope that some of the early work containing so much truth will not be forgotten.

We are indebted to Professor I.M.P. Dawson for supplying the scanning electron micrographs and Figure 3.19. Mr A.D. Phillips, Electron Microscopist at the Queen Elizabeth Hospital for Children, London, kindly produced Figures 3.17a, 3.20 and 4.6; Dr M. Lucas generously supplied Figures 3.17b and 4.4, Dr R. Montgomery Figure 3.29 and Dr R. Cockel Figure 6.23. Mr Barry Wilkes and Miss Jane Wain of the Department of Medical Illustration at the Derbyshire Royal Infirmary prepared many of the diagrams and photographs and their contribution is gratefully acknowledged. Dr Rosemary Guy gave invaluable help checking the references and proof reading the text. We are particularly grateful to Mrs Deborah Foweather and Mrs Sylvia Thomas for cheerful and expert secretarial assistance.

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1983

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Historical background

The first acceptable description of sprue is attributed to Aretaeus, the Cappadocean, who lived in the First or Second Century AD [3]. He described the characteristic stool and recognised the chronicity of the condition, noting that the disorder was rather more common in women than men and that children could also be affected. Vincent Ketelaer, a Dutch physician, is particularly remembered for his book *De aaphthis nostratibus, seu Belgarium Sprouw*, which first appeared in 1669 [32]. He described mainly the oral aphthous ulceration associated with sprue, and concerned himself little with intestinal manifestations, although he did state that the faeces could be so voluminous that, 'several basins or pots scarcely hold these accumulations'. John Brickell in his work *Natural History of North Carolina*, written in 1737 mentioned patients suffering from 'White Flux' [12]. Both Ketelaer and Brickell may well have been describing coeliac disease.

The first description of tropical sprue is usually attributed to William Hillary, a Yorkshireman, whose best known work, *Observations on the changes of the Air and the Concomitant Epidemical Diseases of the Island of Barbadoes*, was published in London in 1759 [25]. In 1880 Manson [37] in China and Van der Burg [72] in Java made major contributions by delineating the clinical features of tropical sprue.

In 1888, Samuel Gee, having drawn attention to the disorder in a lecture delivered on 5 October 1887, at the Hospital for Sick Children, Great Ormond Street, London, produced his classical paper, *On the Coeliac Affection* [17]. Gee clearly regarded tropical sprue and non-tropical sprue as the same disease, although his was the first description of the disorder occurring among those who had never left the British Isles. In this short publication, which always repays reading and re-reading, he described the features of the condition with remarkable accuracy and even suggested that the cure might be found in the diet:

> There is a kind of chronic indigestion which is met with in persons of all ages, yet is especially apt to affect children between one and five years old. Signs of the disease are yielded by the faeces; being loose, not formed, but not watery; more bulky than the food taken would seem to account for; pale in colour, as if devoid of bile, yeasty, frothy, an appearance probably due to fermentation; stinking, stench often very great, the food having undergone putrefaction rather than concoction.
>
> *'His stomack is the kitchin, where the meat*
> *Is often but half sod, for want of heat.'*
>
> The pale loose stool looks very much like oatmeal porridge, or gruel. The hue is somewhile more yellow, otherwhile more drab. The paleness is commonly supposed to signify lack of bile; but the colour of faeces is a very rough measure of the quantity of bile poured into the duodenum; nay, more, the colour of faeces is a very rough measure of the quantity of bile which they contain. Whitish stools are not always so wanting in bile as they seem to be; in particular, opaque white food, such as milk-curd, undigested, will hide the colour of much bile.
>
> Diarrhoea alba is a name employed in India to denote the coeliac affection; not that it is always a coeliac flux, a diarrhoea strictly speaking. True the dejections are faecal, more liquid and larger than natural, but they are not always more frequent than natural; it may be that the patient voids daily but one large, loose, whitish stinking stool. Diarrhoea chylosa is another name used formerly, and which seems to mean that the faeces consist of chyle unabsorbed. Aretaeus and Aurelian speak of the coeliac diathesis, ventriculosa passio (as who should say in English, wambecothe or belly sickness), names which are to be preferred, inasmuch as they connote nothing relative to the precise seat or nature of the disorder. It is one of a few diseases called by the common people consumption of the bowels, a phrase similar to that of pulmonary consumption; the term consumption referring to the wasting of the whole body, and the qualifying words, bowels or lungs, signifying the parts affected first and foremost.

The coeliac disease is commonest in patients between one and five years old: it often begins during the second year of life. Sometimes from India Englishmen return sick with the coeliac affection: seldom is it met with in adults who have never left our island.

The causes of the disease are obscure. Children who suffer from it are not all weak in constitution. Errors in diet may perhaps be a cause, but what error? Why, out of a family of children all brought up in much the same way, should one alone suffer? This often happens. Nor can we deem the coeliac passion always a consequence of accidental diarrhoea, for costiveness is sometimes a forerunner of the disorder. Nor need we call upon teething and worms to explain this, more than every other disease of childhood.

Naked-eye examination of dead bodies throws no light upon the nature of the coeliac affection: nothing unnatural can be seen in the stomach, intestines, or other digestive organs. Whether atrophy of the glandular crypts of the intestines be ever or always present, I cannot tell.

The onset is usually gradual, so that its time is hard to fix: sometimes the complaint sets in suddenly, like an accidental diarrhoea; but even when this is so, the nature of the disease soon shows itself.

The patient wastes more in the limbs than in the face, which often remains plump until death is nigh. In the limbs, emaciation is at first more apparent to hand than to eye, the flesh feeling soft and flabby. Muscular weakness great: muscular tenderness often present.

Cachexia, a fault of sanguification, betokened by pallor and tendency to dropsy, is a constant symptom: the patients become white and puffy; the loss of colour sometimes such as to resemble the cachectic hue of ague or splenic disease: the spleen sometimes enlarged. Examination of the blood by the microscope shows nothing noteworthy, unless much molecular matter in form of clear distinct particles or aggregated masses: but in this is no peculiarity.

The belly is mostly soft, doughy, and inelastic; sometimes distended and rather tight. Wind may be troublesome and very foetid. Appetite for food differs in different cases, being good, or ravenous, or bad. Heat of the body mostly natural; sometimes children are said to be hot at night, and especially so over the belly.

To diarrhoea alba add emaciation and cachexia, and we have a complete picture of the disease. At times the bowel complaint is overlooked: the wasting, weakness, paleness are what is noticed, and are thought to be due to another than the true cause. Ulceration of the intestines may be attended by all the symptoms of coeliac affection. In children, chronic ulceration of the intestines is often tubercular, sometimes syphilic, seldom dysenteric. The diagnosis of ulceration turns upon a diarrhoea purulenta: the microscope discovers pus globules in the faeces. In rare cases the pus is so abundant that the stools consist of hardly anything else. But pus in the stools is not quite pathognomonic of ulceration; an abscess may open into the bowel: even apart from ulceration or abscess, a few pus globules may sometimes be found in the stools: still, for all practical purposes, the presence of pus in faeces may be deemed indicative of ulceration.

The course of the disease is always slow, whatever be its end; whether the patient live or die, he lingers ill for months or years. Death is a common end, and is mostly brought about by some intercurrent disorder; for instance, choleraic diarrhoea. Recovery is complete, or incomplete. When recovery tends to be complete, a peculiar weakness of the legs is left long after all other tokens of disease have passed away, a weakness which shows itself in that the child is unable to jump. When recovery is incomplete, the illness drags on for years; the patient getting better on the whole, but being very subject to relapses of his complaint. While the disease is active, children cease to grow; even when it tends slowly to recovery, they are left frail and stunted.

To regulate the food is the main part of treatment. Cows' milk, which is recommended by Aurelian and some modern physicians in the case of the coeliac passion of hot climates, is not only not suited for children suffering from that disease, but is the least suited kind of food for them. Nothing more certain than that coeliac children cannot digest the hard curd of ruminants' milk. Asses' milk agrees with these patients very well, and they may have two, three, or four pints of it daily. If asses' milk cannot be procured, we must make shift with cows' milk from which most or all of the curd has been removed: we must try whey, or cream mixed with water or scalded whey. The allowance of farinaceous food must be small; highly starchy food, rice, sago, corn-flour are unfit. Malted food is better, also rusks or bread cut thin and well toasted on both sides. No kind of fruit or vegetables may be given, except a tablespoonful or two of well-boiled mealy potatoes, mashed or rubbed through a sieve. Mutton and beef, raw or very underdone, pounded and rubbed through a wire sieve, should be given at the rate of from four to six tablespoonfuls daily. Even English beef, eaten raw, is now and then a cause of tapeworm, much more so foreign beef. Broths and meat juices are allowed, also lightly boiled eggs and good fresh butter. A child, who was fed upon a quart of the best Dutch mussels daily, throve wonderfully, but relapsed when the season for mussels was over: next season he could not be prevailed upon to take them. This is an experiment which I have not yet been able to repeat. The disease being a failure of digestion, nothing seems more reasonable, at first sight, than to digest the patient's food artificially before it is given; but my experience has shown that peptonised milk and gruel are of little or no use in the treatment of the coeliac affection.

The diet recommended may seem to be scanty, but we must never forget that what the patient takes beyond his power of digestion does harm. The skin must be kept clean and warm; fresh air is necessary, muscular exercise not so. For drugs, carbonate of bismuth and aromatic chalk powder may be prescribed; also a small dose of compound decoction of aloes now and then. But if the patient can be cured at all, it must be by means of diet.

Parsons [49] paid tribute to this paper: 'certainly it is true that whenever people believe that they have discovered some new fact in coeliac disease, a reference to this classical cameo has a chastening effect, for time after time, they will find that their discovery has been forestalled'.

Gibbons [19], who was introduced to the coeliac disorder by Gee, reported four cases, all in children in 1889. Three of these children made a partial recovery on non-specific treatment, while a fourth, after an initial remission of symptoms, died of acute haemorrhagic purpura; the postmortem

findings of this child had been published earlier [18]. Gibbons, like Gee, noted no distinctive pathological changes: 'examination of the bowel after death has led to the discovery of nothing'. However, Manson in 1880 [15] and Fayrer in 1881 [37] had described marked pathological changes in the intestines of patients dying of sprue in the tropics. Consequently, Gibbons [19] thought it inconceivable that any pathological changes in the disease he was describing would have been missed for so long and on this tenuous evidence differentiated the two conditions. He argued that since nothing could be found pathologically the disease depended upon a functional disturbance of the nervous supply of the various digestive organs, with the absorption of toxic food products contributing to the ill health of the patients. He also considered that the signs and symptoms were quite clear cut and different from dysentery and drew particular attention to the soft fleshy musculature, reflected in loss of muscle power and an unwillingness of the patients to climb stairs. He exhorted, 'it is however of the greatest importance to examine the motions for oneself', and pointed out that while the stools are very large, soft, whitish in colour and frothy, diarrhoea is not an essential part of the disease. He also thought that manipulations of the diet were the only useful form of treatment and considered the prognosis to be very poor.

Interest in the condition lapsed until Cheadle [13] produced his paper on acholia in 1903 which he defined as the absence of bile in the stools, but without jaundice, or signs of obstruction to the biliary outflow into the upper bowel. Thus he classified the cases described by Gee [17] and Gibbons [19] as well as the conditions of white diarrhoea of the tropics [15] and of sprue [37] as examples of acholia. Cheadle [13] described five cases of acholia in childhood, and one in a 60-year-old man and for the first time excess fat in the stools of some of the patients was estimated chemically by Willcox.

Cheadle also encountered one fatal case in a child, but he too had not observed any distinctive changes at the postmortem: 'the liver where one would expect the secret to lie hidden is normal in appearance'. He agreed with Gibbons [19] that the clinical picture could be attributed to a nervous disturbance altering hepatic function and that teething, or a chill might be the triggering mechanisms. However, following the publications of Van Praagh [73] in 1904 and May [38] in 1905, the term acholia disappeared from the literature.

In 1901 Bramwell [7] published his case of infantilism which he believed was of pancreatic origin, basing this assumption on an abnormal Sahli test and a good response by the patient to the ingestion of pancreatic extract. In several later papers [8–10] he reviewed his experience and in 1915 his final publication on this subject appeared [11] gathering together his own cases and those of Rentoul [57], Thomson [71], Mumford [47] and Freeman [16]. He also described two patients who were not improved by the administration of pancreatic extract and claimed these as 'intestinal infantilism' or 'gastro-intestinal infantilism' as originally described by Herter in 1908 [23].

Herter [23] seems to have genuinely rediscovered the coeliac affection, for he appeared unfamiliar with the writings of Gee [17], Gibbons [19] and Cheadle [13]. His book, published in 1908, *Infantilism from Chronic Intestinal Infection*, became widely known. In this he described five children with chronic fatty diarrhoea and infantilism and by metabolic studies was able to show that they had virtually no positive calcium balance. He also demonstrated that the greater part of the fat present in the faeces was in the form of fatty acids and contended therefore that the loss was due to malabsorption of fat and not to failure of fat splitting. He attributed this malabsorption to an enteritis caused by an overgrowth of gram positive bacteria, particularly B. bifidus. Heubner [24] in 1909 produced one of the first important German contributions to the literature on this subject entitled *Uber Schwere Verdaunngsinsuffizienz beim Kinde jenseits des Sauglingsatters*.

In 1914 Poynton, Armstrong & Nabarro [56] presented in detail the case histories of nine patients, all children, with chronic recurrent diarrhoea. It is noteworthy that while both Still [67] and Miller [40] accepted the non-fatal cases as examples of coeliac disease, Armstrong [2], an author of the original paper, in a letter to the Lancet, pointed out that this term (coeliac) had been purposely avoided in the diagnosis because it was felt that the alterations

in gut function might have resulted from diarrhoea rather than vice-versa. The principal importance of this paper centres on the postmortem findings in the first and only fatal case in the series. This boy (case 1), 9 years old at the time of his death, had an attack of diarrhoea and abdominal distension which began when he was 1 year old and lasted for eight months. From 5 years of age to his death four years later, he was again troubled with these symptoms together with wasting and weakness. At autopsy performed 24 hours after death, there was no evidence of tuberculosis, but the walls of both the large and small bowel were thickened, with thickened and congested mucosa. The liver showed fatty change, but the pancreas appeared normal whilst microscopically the 'jejunum showed marked small round celled infiltration, prominence of solitary lymph follicles, and congestion and haemorrhage onto the free surface of the section'. The colon also showed cellular infiltration though less marked than the small intestine. Still [67], under whose care this boy had been for some time, accepted him as a case of coeliac disease, although Miller [40] thought he was probably an example of dysentery of the 'asylum' type. Although the diagnosis in this particular case remains doubtful and the postmortem findings essentially of little value, a systematic attempt had been made, probably for the first time, to relate pathological and clinical findings in the coeliac disorder.

Poynton and his colleagues [56], in common with other workers at that time, realised the value of diet in management, but were unable to incriminate any particular item of food. Nevertheless one of their cases (Case VIII) found it quite impossible to add bread and butter to the diet without causing an exacerbation of symptoms. The authors speculated that the clinical picture could occur as 'a result of an unsuitable diet in a disease which in itself still persists, although the special symptoms may disappear when the diet is corrected'. They also pointed out that constipation rather than diarrhoea may be troublesome, and that the disorder has a natural tendency to remit in early adolescence.

The next series of publications of importance were the Lumleian Lectures given by Still in 1918 [67]. In the first lecture he reviewed the symptomatology of coeliac disease, drawing on his experience of 41 cases, and obviously accepting the cases of Gee [17], Gibbons [19], Cheadle [13], Herter [23] and Poynton [56] as examples of the disorder. Up to this time all authorities with the notable exception of Gibbons [19] had taken the view that coeliac disease and tropical sprue were identical. Thus Gee [17] had commented, 'Sometimes from India Englishmen return sick with the coeliac affection', while Cheadle [13] had written 'the condition of the stools in the two forms is absolutely identical'. However, Still thought that there was insufficient evidence on which to decide this issue and remained non-commital, for he acknowledged that he did not have the necessary experience to make a judgement.

The second lecture was devoted to pathological considerations of coeliac disease, although morbid anatomical studies to that date had been very few. Still also noted that Gee [17], Gibbons [19] and Cheadle [13] had been unable to find any helpful pathological changes in their fatal cases. The only detailed record of a postmortem which he could discover was that reported by Poynton and his colleagues [56]. Still did, however, report the autopsy findings in one case of his own in which there was no evidence of tuberculosis, or ulceration of the bowel: 'Microscopic examination of the duodenum, ileum and colon, showed much small round cell infiltration of the mucosa and submucosa and this was most marked in the duodenum'. He went on to state that in children dying from acute, or chronic gastroenteritis, these appearances were not seen and suggested that the inflammatory changes in the bowel wall might not have been merely a terminal event, for 'the first step in the disease may well be a catarrhal condition of the mucosa of the small intestine'.

The third and final Lumleian Lecture was concerned with treatment, and as might be expected Still's main pre-occupation was with diet. He thought it best to reduce the intake of fats to a minimum and advised that cows' milk should be rigidly excluded from the diet. He noted that starch in some cases exacerbated symptoms: 'One form of starch which seems particularly liable to aggravate symptoms is bread'.

In 1920 Moorhead [46] reported two cases of infantilism. The first which came to autopsy

showed no response to pancreatic extracts and was considered an example of the intestinal infantilism of Herter [23]. At postmortem the pancreas was normal. Of particular interest was the report on the small intestine which stated that the villi were abnormal, but this was attributed to autolytic change. The second case was labelled pancreatic insufficiency as described originally by Bramwell [11].

Beginning in 1920 Miller published a series of papers dealing with coeliac disease [40–45]. In his first paper [45] he described three cases of coeliac infantilism treated with bile salts. Although an improvement in the absorption of fat occurred, he was reluctant to suggest that the fatty diarrhoea was due to a failure of bile. However, in a subsequent letter to the *Lancet* [43] he proposed that coeliac disease was a functional disorder probably of bile salt secretion. Armstrong [2] pointed out that bile salts had been given to a patient by his group, but without any success [56].

In 1921 Miller [40] reported the autopsy findings of a child who had died of coeliac infantilism, but the postmortem was not done until 60 hours after death. There were no chronic changes to be seen in any of the organs. Microscopically, 'the mucosa shows much superficial postmortem desquamation, and no opinion can be given on its condition at death, the deeper layers show no evidence of cell infiltration or fibrosis, and the examination satisfactorily excludes the presence of chronic inflammatory changes in the small intestine or colon'. Autolytic changes must have been advanced after 60 hours making these findings virtually valueless. However, Miller considered that his own viewpoint on the cause of coeliac disease had been strengthened and concluded that since no organic changes were evident, the disorder must be due to a digestive fault. He reviewed, but tended to dismiss, earlier postmortem reports on fatal cases on the grounds that these patients were either not suffering from coeliac disease (the case of Poynton et al [56]) or had an atypical form (such as the cases of Still [67] and Moorhead [46]).

Miller also made notable contributions to the clinical understanding of the disorder and wrote on several features including fatty stools, enlargement of the abdomen, retardation of growth and development, anorexia, fever, tetany, convulsions, megacolon and late rickets [41, 42]. He recognised that fat absorption may be abnormal even in the absence of symptoms, while adults could remain well on a full, normal diet. He also observed spontaneous remissions during adolescence. He devoted a further publication to a non-diarrhoeic form of the disease noting that normal appearing stools did not necessarily indicate normal fat absorption [44].

In this same year, 1923, Miller [42] continued to advance his theory that the illness was a digestive fault and not an organic disorder and in support of this idea reported an autopsy on a child with both coeliac disease and megacolon. He stated that 'no chronic enteritis or other organic cause for the chronic fatty diarrhoea could be found', although no histological studies of the small bowel were reported. Langmead [34] in 1911 had earlier studied a group of cases with colonic tetany, some of whom were accepted by Miller as having coeliac disease.

Over the 35 years following the original publication by Gee [17] in 1888, the clinical picture of coeliac disease gradually became better defined. A few biochemical tests were available and physicians were appreciating the value of postmortem studies. Although there was no specific treatment, most patients could be maintained in reasonable health by a suitable diet [67].

Most authors, whilst recognising that dietary control was relevant to the management of coeliac disease, had failed to recognise the importance that wheat-containing foods might have. Howland [29] in 1921 described two types of carbohydrate intolerance, the first occurring in very young infants, most of whom had not been weaned, while the second type was found in children of all ages. Such children were designated as having intestinal infantilism according to the American terminology, or coeliac disease in the English terminology. 'From clinical experience it has been found that of all the elements of the food carbohydrate is the one which must be excluded rigorously'. His dietary regime allowed milk only at first, to which was added cheese and eggs and lastly vegetables. 'Bread, cereals and potato are the last articles that can be allowed'.

Until this time all the authorities had considered coeliac disease and tropical sprue as either iden-

tical, or closely related conditions. Although Miller thought that more evidence was needed to settle the issue, on clinical grounds he considered it unlikely that the two conditions would prove to be identical [43, 58]. Still [67] had taken a similar position. It is of interest that Scheel [62] in 1905 had described a 35-year-old woman who had never left Holland and who developed a disorder resembling tropical sprue. Wood [74] in 1915 had recognised sprue in America and by 1925 [75] was aware of a syndrome like tropical sprue occurring in people who had never left the northern states of that country. Nevertheless he felt that the correct diagnosis in these patients was most likely pernicious anaemia, writing, 'one feels that the diagnosis was largely a matter of geography. In the tropics it would be called sprue, while out of the tropics it would be called pernicious anaemia', but he made no mention of non-tropical sprue as a separate disease.

Lambright [33], in 1926, in a publication entitled *Sprue in the Temperate Zone*, presented the case history of a young woman with a sprue-like illness who had never left North America. At the age of 3 years she had a prolonged attack of diarrhoea and was in poor health until puberty when her condition improved. At the age of 16 years she became anaemic, lost weight and passed large odorous stools. Pernicious anaemia was diagnosed and a splenectomy performed. No treatment was found to be of any avail and blood transfusions were regularly required to alleviate the anaemia. This patient almost certainly had coeliac disease, but Lambright thought that she had contracted tropical sprue in a temperate climate.

In 1929 Holmes & Starr [27] described a nutritional disturbance in adults resembling coeliac disease and sprue. They classified five patients with emaciation, diarrhoea, fatty stools, anaemia and tetany as having non-tropical sprue. This contribution is noteworthy because barium studies were carried out, and although small bowel abnormalities were not reported as occurring, a distended colon was commented on in all the cases. Porter & Rucker [55] in 1930 also used the term 'non-tropical sprue' in describing their two patients, both with a megaloblastic anaemia which responded to liver extracts. There were no neurological signs and free hydrochloric acid was found in the gastric juice. Thus by 1930, reports of a sprue-like illness occurring in adults who had never visited the tropics were appearing and the new diagnosis of non-tropical sprue was being used to describe this syndrome.

Thaysen produced his monograph on non-tropical sprue in 1932 [70] which was widely referred to in the following years, but was in fact only an incomplete review of the literature of the disorder to that date. In 1929 Thaysen [69] had taken the position, which he developed in his monograph, that tropical sprue, non-tropical sprue, and Gee-Herter's disease should be grouped under the term 'idiopathic steatorrhoea' and were either identical, or nearly identical conditions. He discovered 34 cases of non-tropical sprue in the literature and an analysis of these patients revealed that 16 had a history of chronic intestinal disease in infancy, adolescence, or later life of several years duration. It is surprising that, since he recognised adults could have symptoms dating back to childhood, and in view of the reports of children with 'infantilism', or the 'coeliac affection', he only included one child among these cases, the majority of which were between 41 and 50 years of age at diagnosis. Aphthous stomatitis was recognised as being common, occurring in 26 of the 34 cases and often preceding the onset of diarrhoea. Of great interest are his descriptions of the psychiatric and neurological abnormalities he encountered.

Autopsy reports were available on six of the 34 patients reviewed in Thaysen's series. In 1923 Blumgart [6] described three fatal cases of malabsorption of fat, one being that of a 42-year-old Swede who had never visited the tropics and had lived in Boston for 25 years. At the age of 40 years he developed symptoms and signs of malabsorption leading rapidly to death within two years. A postmortem limited to the abdomen was carried out six hours after death and revealed large mesenteric nodes. Histological examination of the small bowel wall showed a thin atrophic mucosa with short villi and lymphoid cell infiltration. Holst [28] in an attempt to overcome postmortem autolysis, injected formalin into the abdominal cavity immediately after death in order to facilitate tissue preservation, but failed to find atrophy, or inflammation of the jejunum, or colon. In Thaysen's [68] own patient also, there were said to be no definite

histological abnormalities in the small intestine, but Rosendahl [59] did report inflammatory changes in the small bowel, but since the patient had received X-irradiation for a breast tumour Thaysen was sceptical about this finding. Starr & Gardener [66] found 'marked atrophy, moderate dilatation, and passive congestion of the small and large intestine', but no microscopy was reported. Autolytic changes made interpretation of autopsy findings difficult and on balance the reports were not of great value at that time. It is not surprising perhaps that Thaysen concluded that these findings in non-tropical sprue by many workers were variable and insignificant and threw no light on the aetiology of the condition. Even so, the six autopsies he cited were not the only ones which had been performed on patients with non-tropical sprue to that date.

Parsons had reported a case of intestinal infantilism as early as 1913 [48] and in later years discussed both bone changes and the pathology of the disorder [50]. In 1932 there appeared his important publication on coeliac disease [49] in which he reviewed the clinical presentation of 94 cases occurring in children. He recognised that coeliac disease was not seen in infants still being breast fed, that it could occur in one, or both homologous twins and also in more than one instance in sisters and cousins, commenting: 'there can be no doubt that coeliac disease is more common than these statistics represent and that the number of cases particularly of the less severe varieties will increase with the dissemination of knowledge regarding it'. He presented some postmortem findings, but was only able to conclude: 'there is no known morbid anatomy of coeliac disease'. In contradistinction to Thaysen [70], Parsons believed that coeliac disease and sprue were different conditions [49, 50].

During a discussion following a paper given by Ross [60], Parsons recalled nine cases of coeliac disease occurring in adults and mentioned in particular two patients, one of whom developed the condition late in life at the age of 72 years, and the other following a partial gastrectomy. He maintained that coeliac disease occurring in children or in adults was basically the same disorder. He recognised that certain deficiencies could occur in one case and yet not in another and drew attention to the role of carbohydrate in the disease, citing the work of Howland [29]. Parsons had found that if carbohydrate was rigorously excluded from the diet other foods were almost always well digested, although fat absorption might not return completely to normal.

Bennett and his colleagues [5] in 1932 wrote their review of idiopathic steatorrhoea in which they described fifteen patients with fatty stools, tetany, osteomalacia, anaemias of various types, skin lesions and frequently infantilism, all of them adolescents or adults. Diarrhoea, however, was not a constant feature. They noted the occurrence of finger clubbing, an observation also made by Fanconi [14]. All had been born in Britain and had never resided abroad. The authors commented, 'we feel they cannot be classed with patients having tropical sprue'. Also at about this period other metabolic [4, 35, 36, 49] and haematological studies [20, 49, 70] in the disorder were appearing.

In 1934 Snell & Camp [65] described the radiological findings of the gastrointestinal tract of seven patients with idiopathic steatorrhoea, including delayed intestinal motility, alterations in the mucosal pattern, particularly in the jejunum, and clumping of the barium. These changes were considered characteristic of the disorder, but probably not specific. In addition for the first time particular attention was paid to the skeletal system radiologically. Of three such patients no abnormality was detected in one, in the second osteoporosis, while in the third severe osteomalacia with deformities of the long bones and pelvis, together with pseudofractures, were observed. Other early roentgen studies were made by Kantor [31] who described dilatation and segmentation in a smoothly outlined small bowel as the important radiological features of idiopathic steatorrhoea.

Of incidental interest, Mendez Ferreira & Bargen [39] had found about 150 well-documented cases of sprue in the literature up to 1937 and in 1939 Snell [64] reviewed his series of six cases of tropical sprue and 32 cases of non-tropical sprue. He claimed that no fundamental differences between these two groups of cases could be demonstrated, concluding, 'If sprue is sought for as vigorously in Northern climates as it is in the tropics, it seems certain that the artificial distinc-

tions which have been set up between tropical and non-tropical sprue will soon be regarded as unimportant'. Three of his patients with non-tropical sprue had died and postmortems had been performed. In one case the intestinal tract was reported as entirely normal. At the second autopsy, which had also been published by Mendez Ferreira & Bargen [39] a chronic, atrophic gastroenteritis was noted. Although pulmonary tuberculosis was present, it was considered merely as a complication of the underlying idiopathic steatorrhoea since there was no involvement of the mesenteric nodes. The third postmortem also showed mucosal atrophy and ulcerations in the digestive tract, although no further details were given. He considered these changes were neither specific nor characteristic and discounted them as being of significance. In 1936 Hanes & McBryde [22], in describing nine adults with steatorrhoea and a macrocytic anaemia, had also proposed that sprue, non-tropical sprue and coeliac disease were identical conditions.

This difficulty in differentiating tropical from non-tropical sprue and coeliac disease continued until relatively recent years. In 1942, Hurst [30] wrote, 'Tropical sprue, non-tropical sprue and coeliac disease are varieties of the same disorder, the sprue syndrome, which differs only in the part of the world in which the disorder originated and in the age of the patient'. In 1957, Perez-Santiago & Butterworth [54] created more difficulties by recommending that 'patients with malabsorption and megablastic marrow be considered in the same category as sprue regardless of geographical location'. In 1960 Green & Wollaeger [21] from the Mayo Clinic endorsed these views: 'if not identical, they may at least stem from the same basic defect which has been influenced by different environmental factors such as climate, infection and diet'. However, with better understanding tropical sprue and non-tropical sprue are now regarded as separate and distinct entities.

Studies during the late 1940s and 1950s established that pathological changes were to be found at autopsy in patients with idiopathic steatorrhoea, or non-tropical sprue. In 1947 Schein [63] described the postmortem findings in a 15-year-old boy with idiopathic steatorrhoea who had died at the Mount Sinai Hospital. The autopsy was carried out two and a half hours after death and all tissues were fixed immediately in formalin. Autolytic changes were said to be slight and histological examination of the small intestine revealed that the normally found elongated villi had been replaced by 'broad based, squat, bulbous and plump villi'. In addition a hyaline material was found deposited beneath the basement membrane at the apices of the villi. In a further publication Adlersberg & Schein [1] confirmed this finding in six patients dying with primary sprue and described clubbing of the villi, atrophy of the intestinal mucosa and increased cellularity of the lamina propria in the upper small bowel. Paulley [51] in 1949 questioned Thaysen's views [70] that all postmortem findings in the small intestine in non-tropical sprue were due to autolytic change and in 1952 and 1954 described the appearance of jejunum biopsies taken at laparotomy from three cases of idiopathic steatorrhoea and a doubtful fourth case [52, 53]. Histological examination of the mucosa showed broadened villi with a dense, chronic inflammatory cell infiltration in the lamina propria. Similar observations were made by Himes & Adlersberg [26] in 1957 who reported the postmortems of 11 patients with idiopathic steatorrhoea, in several of which there was marked atrophy of the small intestinal mucosa with morphological changes in the villi. (Four of the patients had been subjected to a jejunal biopsy during life and the same changes were noted.) No other organs were significantly abnormal. They concluded that 'the major pathological alterations in sprue are to be found in the small intestine'.

Salvesen & Skogrand [61] in 1957 described the autopsy findings in a fatal case of idiopathic steatorrhoea, having injected the body immediately after death with formalin intraperitoneally to offset postmortem autolysis. Histologically there was chronic inflammation of the mucosa with atrophy and degeneration of the villi.

The stage was set for the introduction of the two most important advances in the understanding of coeliac disease — the use of the gluten free diet and the technique of jejunal biopsy.

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2

Definition and epidemiology

Definition
Geographical distribution and incidence
Sex incidence
Age incidence
Blood groups
Familial incidence
Studies of twins
Mortality rate

DEFINITION

Coeliac disease requires definition in order to allow analysis and evaluation of clinical data, diagnostic methods, treatments and research results. Definitions will in themselves require revision periodically as new knowledge becomes available. For the past 25 years definitions have revolved around the findings in the jejunal mucosa and the responses to gluten withdrawal and challenge and the associated clinical reactions. From the practical point of view the diagnosis in the majority of patients is relatively simple and made on the presence of a characteristic jejunal biopsy and a satisfactory clinical response to gluten withdrawal. There remain, however, many patients in whom the diagnosis is not easy and with increased understanding of disorders of the small intestine, definition has, if anything, become more difficult. Accordingly, it is worthwhile considering some of the definitions that have been put forward and the problems they raise.

1. 'The demonstration of a characteristic flat mucosal lesion by suction biopsy of the proximal small intestine' and secondly, 'the demonstration of a dramatic clinical response to the removal of gluten from the diet' [91].

2. 'The condition in which there is an abnormal jejunal mucosa that responds morphologically to treatment with a gluten free diet' [10] 'and which again shows abnormalities when gluten is reintroduced' [11].

3a. It is a permanent condition
b. There is a flat mucosa in the upper small intestine
c. A gluten free diet results in complete restoration of normal mucosal architecture
d. Reintroduction of gluten into the diet will be followed by recurrence of mucosal abnormalities' [74].

4. 'The disease in which there is an abnormality of the small intestinal mucosa provoked by the gluten fraction of wheat' [93].

5. 'The criterion for diagnosis of coeliac disease should be the demonstration of an unequivocal improvement of any mucosal abnormality in response to a gluten free diet, or deterioration in response to gluten' [94].

6a. The disease must be suspected on clinical grounds
b. A small bowel biopsy must be obtained showing the typical lesion
c. A gluten free diet must be instituted after which clinical remission and improvement must occur
d. A gluten challenge must be done and objective features such as changes in the small bowel biopsy or onset of diarrhoea with steatorrhoea must be shown before definitive diagnosis can be accepted. In some instances, in vitro demonstration of gluten induced toxicity may establish the diagnosis, obviating the need for further biopsy [36].

7a. A structurally abnormal jejunal mucosa on a gluten containing diet
b. A clear improvement of villous structure on a gluten free diet