PROGNOSIS IN COELIAC DISEASE

A REVIEW OF SEVENTY-THREE CASES *

BY

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Information as to the prognosis in coeliac disease is not abundant. Several series of cases have been reported, but the mortality given varies considerably; there are fewer records of the fate of those children who do not die of the disease.

Fifty years ago Gee (1888) wrote, 'death is a common end,' and Lehndorff and Mautner (1927) thought the prognosis was so hopeless that treatment was of little avail. Sauer (1927), however, recorded a series of twenty-five cases with one fatality. Evidence from another aspect was given by Bennett, Hunter and Vaughan (1932), who collected fifteen examples of the disease in adults, in most of whom the disorder dated from infancy. It would thus appear that though we may agree with Parsons (1932) and with Neale and others (1935) that coeliac disease responds remarkably well to treatment, yet there may be some cases that can run a protracted course. Such patients are not ill enough for their disorder to be recognized until adult age is reached, when, with the skeleton drained of calcium and crippled beyond repair, the disease declares itself. Facts in favour of this view will be given in this paper.

In the present investigation an attempt was made to learn the after-history of seventy-three cases of coeliac disease which had been in the Hospital for Sick Children, Great Ormond Street, London, between the years 1923 and 1938. The diagnosis of coeliac disease was made on the history of diarrhoea, anorexia and loss of weight, accompanied by the classical clinical features, and with the finding of an excess of normally split fat in the stools on more than one occasion. Only those patients have been included who were under observation long enough for an illness due to a transient digestive upset to be excluded.

Fifteen years have elapsed since the first patient was in the Hospital, and the oldest living subject is now sixteen-and-a-half years old. Twenty-two died in Hospital, and all but ten (fourteen per cent.) of the remainder have been

* Based on a Thesis submitted for the M.D. degree of the University of Cambridge. The work was done with the aid of a grant from the Medical Research Council.
traced. Those alive have been examined to determine if the disease was active, cured or quiescent, or if it had left any trace of its activity.

The cases

Age and sex incidence.—Of the seventy-three cases, forty-seven were girls and twenty-six were boys. This sex incidence agrees with that of all other published series in that the disease is almost twice as common in girls as in boys. The age of onset in those in whom it could be ascertained with any certainty is shown in the diagram (fig. 1). The age taken is that given by the parents as the date when symptoms were first noticed. Objection may be taken to this as in some instances the onset of the disease may be dated from some minor gastro-intestinal upset unrelated to coeliac disease; in others the disease may have been present for some time before it was noticed. But the figure shows that almost eighty per cent. of the cases occurred between six and twenty-one months; this again is in agreement with most authors. There was no difference between the number of patients who were breast-fed and those who were bottle-fed; but none of the very young ones was breast-fed.

General appearances.—The general appearance of the children varied with the severity of their disease and the stage in which they were seen. There is nothing to be added to the many admirable clinical descriptions which have already been given. The general wasting, with distension of the abdomen
PROGNOSIS IN COELIAC DISEASE

and deflation of the buttocks is well seen in the photograph of five children who were in the wards at one time (fig. 2).

![Photograph of five cases of coeliac disease showing the general clinical features.](image-url)

**Skin rashes.**—Five cases had rashes, which are described as being purpuric in two cases, psoriaform in one, mottled in one and as a sweat rash in one.

**Peristalsis.**—This was seen in three cases. It is observed no doubt owing to the thin abdominal wall. But a knowledge of its occasional occurrence is not without importance in that one child was subjected to a laparotomy as a consequence of its appearance.

**Ascites.**—Only one patient showed this, but here again it should be remembered, as the child was operated upon as a case of tuberculous peritonitis.

**Clubbing of the fingers.**—This occurred in two girls; both these were older than the rest when they came under observation and the disease had been present for some time.

**Laboratory investigations**

All the patients were investigated in various ways in the laboratory. The results would, in some instances, appear to have an important bearing on the
prognosis of the disease. They are therefore discussed in some detail in the section which follows.

**Fat metabolism.**—Only those have been included in this series in which the stools showed the characteristic abnormality—namely an increase in the total amount of fat with normal splitting on more than one analysis. Transitory steatorrhoea can occur in any form of gastro-enteritis in infancy. The amount of the fat in the faeces is not necessarily an indication of the severity of the disease; there was no difference between the average highest faecal fats of those who died and those who recovered. The highest values in the series, 75.6 per cent. and 73.9 per cent., were, however, given by patients who subsequently died. In most instances the faecal fat should fall within normal limits when a low-fat diet is introduced. After this it bears a strict relationship to the fat-content of the diet and to the condition of the patient. Any increase in intake of fat before the patient can tolerate it leads to an excess of the faecal fat and there is a similar rise if the patient suffers a relapse (tables 1 and 2).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>EFFECT OF DIET ON FAECAL FAT PERCENTAGE (FEMALE PATIENT AGED 2½ YEARS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LOW FAT DIET</td>
</tr>
<tr>
<td>Split</td>
<td>15·56</td>
</tr>
<tr>
<td>Unsplit</td>
<td>3·67</td>
</tr>
<tr>
<td>Total faecal fat</td>
<td>19·23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>EFFECT OF A RELAPSE ON THE FAECAL FAT PERCENTAGE (FEMALE PATIENT AGED 2½ YEARS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DATE</td>
<td>JUNE 7</td>
</tr>
<tr>
<td>Condition</td>
<td>On admission</td>
</tr>
<tr>
<td>Total faecal fat, per cent.</td>
<td>51·8</td>
</tr>
</tbody>
</table>

The response of the faecal fat to dietetic treatment is of some importance in estimating the prognosis of the disease. Of those who died, seven had three or more fat analyses done, and in five of these a normal result was not obtained, despite strict dieting.

**Carbohydrate metabolism.**—

**Oral Glucose Tolerance Curves.** The characteristic oral glucose tolerance curve in coeliac disease is flat, that is a rise of less than forty milligrams from the fasting value (Thaysen and Norgaard, 1929). Fourteen of the present series were investigated by this method. The curves are all abnormal
PROGNOSIS IN COELIAC DISEASE

Twelve of the curves are flat, the remaining two approach the normal, and both these patients were becoming convalescent. This has been shown by other workers (Thaysen and Norgaard, 1929; Macrae and Morris, 1931; Badenoch and Morris, 1936) and its value in prognosis is obvious (table 3).

**Table 3**

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>½ HR.</th>
<th>1 HR.</th>
<th>1½ HR.</th>
<th>2 HR.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nov., 1935</td>
<td>81</td>
<td>70</td>
<td>85</td>
<td>85</td>
<td>87</td>
</tr>
<tr>
<td>Feb., 1936</td>
<td>68</td>
<td>113</td>
<td>113</td>
<td>106</td>
<td>91</td>
</tr>
<tr>
<td>Mar., 1936</td>
<td>46</td>
<td>39</td>
<td>59</td>
<td>72</td>
<td>95</td>
</tr>
<tr>
<td>Apr., 1936</td>
<td>75</td>
<td>100</td>
<td>95</td>
<td>116</td>
<td>102</td>
</tr>
<tr>
<td>May, 1936</td>
<td>79</td>
<td>88</td>
<td>90</td>
<td>80</td>
<td>76</td>
</tr>
<tr>
<td>Feb., 1937</td>
<td>90</td>
<td>160</td>
<td>95</td>
<td>103</td>
<td>102</td>
</tr>
</tbody>
</table>

![Fig. 3.—Glucose tolerance curves in fourteen cases of coeliac disease.](http://adc.bmj.com/content/283/9148/283.b3)

The curves obtained differ from those previously published in that the fasting values are not low. In each case there had been a period of fasting of not less than eight hours before the test. The dose of glucose given was one gramme per kilogramme body weight.

**Intravenous Glucose Tolerance Curves.** Recently attention has been directed to the value of intravenous glucose tolerance curves in coeliac disease.
So far published results show no agreement and the need for the standardization of technique is marked. Thaysen (1929a) obtained flat curves, whereas Ross (1936) showed curves in which the first values after the injection were high. Crawford (1938) stressed the importance of considering the length rather than the height of the curves, whilst most recently Ross (1938) has advocated the measurement of the area of the curves. None of the present series was investigated by this method.

**Calcium, phosphorus and phosphatase.**—Sixteen out of twenty-seven cases investigated had a serum calcium below 9 mgm. per 100 c.c. Five of these had tetany, the lowest value recorded being 3.9 mgm. per 100 c.c.; two of these died. Nineteen had the inorganic blood phosphorus estimated and in fifteen of them it was below 4 mgm. per 100 c.c. The normal phosphatase is taken as 10–20 units up to two years and from 5–15 units after this. The low blood phosphatase in coeliac disease has already been demonstrated by Morris and Peden (1937). In only six out of sixteen cases was the phosphatase above the lower level of normal, in the remaining ten being of the order of two, three or four units. The low values are evidence of the almost complete cessation of growth which occurs in coeliac disease. A rise in the phosphatase to within normal limits is not necessarily a sign of good prognosis. The highest value obtained was 53 units in a patient who was in a quiescent phase of the disease, but who had active rickets. The possibility of this happening in a patient who would otherwise appear to be improving should be remembered.

**Fractional test meals.**—Eleven cases were investigated by this test; all were deficient in secretion of hydrochloric acid and four of them showed achlorhydria. No histamine test meals were done.

**Blood counts.**—Of thirty-three who were investigated, twenty-nine patients showed some degree of anaemia. In twenty-one of these the colour-index was low; in the remaining eight the anaemia was orthochromic or hyperchromic. Unfortunately no measurements were made of cell size so that it is impossible to say if the macrocytic anaemia found in other series occurred. The hypochromic anaemia is due to iron deficiency and is aggravated by the restricted diet, by the absence or diminution of the gastric hydrochloric acid, and by deficient absorption owing to the diarrhoea. The degree of anaemia in an untreated case is thus proportional to the severity of the disease and is of corresponding significance in prognosis.

**Radiology**

Skiagrams of the bones were taken in sixteen of the patients. Seven of them were reported as normal. One patient showed active scurvy. Four showed general decalcification. Four showed active rickets, the youngest being an infant of seventeen months; two of these, aged four-and-a-half and eleven-and-a-half years, showed pathological fractures. The process of healing when calcium, vitamin D and ultra-violet light are given is shown in the photographs (fig. 4). The rapid appearance of the missing centres of ossification is striking.
PROGNOSIS IN COELIAC DISEASE

Fig. 4.—To show the healing which occurs when coeliac rickets is treated. Note the rapid appearance of the centres of ossification and the disappearance of the Harris's line.
Course and treatment

The chronic nature of coeliac disease, the periods of rapid improvement and equally rapid deterioration, for either of which no cause can be found, are well known. They were seen in many cases in the present series, and fig. 5 shows the weight chart of two patients over a long period. These 'natural' fluctuations of the disease must be borne in mind in estimating the value of treatment, and any new remedy must be used consistently over a series of cases before it can be accepted.

The children were kept in hospital long enough for the diagnosis to be confirmed and a satisfactory response to treatment to be obtained. When it was judged safe they were transferred to the country branch at Tadworth, Surrey, or to their homes and their supervision was continued as out-patients. The preliminary period of hospitalization varied from two to fifteen months, and on an average was five months. Including the time they spent at Tadworth they were under direct observation for much longer; thus one boy spent five consecutive years either at the hospital or its branch.

The present series contains examples of practically every known form of therapy which has been suggested—bile salts, opium, insulin, pancreatic extracts, campolon and nicotinic acid were all included. The only common denominator in the treatment was a low-fat diet with added vitamins. This was given in some modification of the three-stage diet introduced by Howland (1921). Such a régime forms the best method of treatment, and has been universally recognized. The value of any other substance in the disease, whatever its claims theoretically or experimentally, has still to be proved.

Mortality

Twenty-two patients died during the period in the wards of the hospital or its country branch; to these may be added four who died subsequently,
as far as can be ascertained of the disease, a total mortality of thirty-six per cent. Compared with other published figures this is high (table 4).

**Table 4**

**MORTALITY IN COELIAC DISEASE**  
(Modified from Sauer, 1927)

<table>
<thead>
<tr>
<th>NAME</th>
<th>DATE</th>
<th>NUMBER OF CASES</th>
<th>MORTALITY PER CENT.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heubner</td>
<td>1909</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Still</td>
<td>1918</td>
<td>41</td>
<td>14</td>
</tr>
<tr>
<td>Lichtenstein</td>
<td>1921</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Howland</td>
<td>1921</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Hablützel-Weber</td>
<td>1923</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Pipping</td>
<td>1924</td>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>Schaap</td>
<td>1926</td>
<td>114</td>
<td>11</td>
</tr>
<tr>
<td>Sauer</td>
<td>1927</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Thaysen</td>
<td>1929b</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Parsons</td>
<td>1932</td>
<td>94</td>
<td>10.6</td>
</tr>
<tr>
<td>Neale</td>
<td>1935</td>
<td>93</td>
<td>12</td>
</tr>
<tr>
<td>Hardwick</td>
<td>1939</td>
<td>73</td>
<td>36</td>
</tr>
</tbody>
</table>

In the four in whom death was not directly attributable to the disease, it was due to intussusception, measles, diphtheria and influenzal bronchopneumonia. Excluding these the mortality is thirty per cent. To some extent this high figure may be explained by the fact that the Hospital for Sick Children has a more than parochial reputation and not only do the patients come from a wide area, but also the more severe cases tend to gravitate there.

It is usually said that death in coeliac disease is due to an intercurrent infection, but in seventeen of the twenty-six fatal cases it was directly due to an exacerbation of the disease. The diarrhoea was increased, dehydration became intense, and the final picture was that of death from a severe enteritis. In only four did bronchopneumonia play a leading part.

Table 5, showing the age at which death occurred, emphasizes the danger of the disease in its early stages and the need for adequate treatment once it has been recognized:

**Table 5**

<table>
<thead>
<tr>
<th>YEARS</th>
<th>0-1</th>
<th>1-2</th>
<th>2-3</th>
<th>3-4</th>
<th>4-5</th>
<th>5-6</th>
<th>16-17</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEATHS</td>
<td>0</td>
<td>11</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

**Results of the Investigation**

A case of coeliac disease can only be said to have recovered when he passes normal motions on a normal diet and maintains this state. Remissions in the course of the disease are common, but in the present series no one who was
symptom-free for three years had a relapse. Of the original seventy-three cases twenty-two died in the hospital, leaving fifty-one to be accounted for. All but ten of these (fourteen per cent.) were traced. As has been said, four of them had died. Seventeen out of thirty-seven living patients who were traced appeared to have recovered. Their physical condition showed no signs of activity, they ate a normal diet and they passed normal motions and had been doing so for more than three years. A further ten were in a similar condition, but three years had not elapsed since the disease became inactive. Together these form a group of twenty-seven patients or thirty-seven per cent. of the whole. In six the disease is still active. Four have not yet become sufficiently well to leave the hospital or its country branch. Two are at home, but on a strict diet, any indiscretion causing a return of steatorrhoea.

Latent coeliac disease.—There remain four patients who have relapsed after having been well for as long as fifteen months, or who were thought to be well until analysis of their stools showed abnormal figures. To these the name latent coeliac disease is applied. This term was first used by Bennett, Hunter and Vaughan in describing fifteen cases of steatorrhoea in adults; all except one of these gave a history of diarrhoea in childhood, had apparently enjoyed normal health for some time and had then presented themselves with advanced disease. Details of the four cases are given in the table, and the following is the history of one of them:

A.M., female, aged six years, was in the hospital from July, 1935, to January, 1937, with coeliac disease which had been present since she was eighteen months old. She was again seen in August, 1938, when her parents said she had quite recovered and was eating a normal diet and passing normal motions. She had grown, was no longer wasted (height 41½ in., weight 39½ lb.), the rickets which had been present was healed (see fig. 4), but an analysis of her faeces showed:

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Split fat</td>
<td></td>
<td></td>
<td>30·10 per cent.</td>
</tr>
<tr>
<td>Unsplit fat</td>
<td></td>
<td></td>
<td>16·65 per cent.</td>
</tr>
<tr>
<td>Total fat</td>
<td></td>
<td></td>
<td>46·75 per cent.</td>
</tr>
</tbody>
</table>

**Table 6**

<table>
<thead>
<tr>
<th>PATIENT AND SEX</th>
<th>AGE IN YEARS</th>
<th>TOTAL FAECAL FAT PER CENT.</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.B., Female</td>
<td>16</td>
<td>33·00</td>
<td>Undersized. Amenorrhoea.</td>
</tr>
<tr>
<td></td>
<td>7½</td>
<td>46·75</td>
<td>Growing and gaining weight.</td>
</tr>
<tr>
<td>A.M., Female</td>
<td>14½</td>
<td>30·27</td>
<td>Rickets healed.</td>
</tr>
<tr>
<td>O.W., Female</td>
<td>5½</td>
<td>43·75</td>
<td>Apparently in good health though undersized.</td>
</tr>
<tr>
<td>C.B., Female</td>
<td></td>
<td></td>
<td>Relapse after 15 months. Flat glucose tolerance curves.</td>
</tr>
</tbody>
</table>
PROGNOSIS IN COELIAC DISEASE

Parsons (1932) suggests that clinical recovery precedes biochemical recovery, meaning that the patient's physique is restored to normal before the fat-content of the stools. This condition cannot be regarded as a true recovery, but as a quiescent stage of the disease. Further evidence of the existence of such a condition may be adduced from a comparison of the frequency of the disease in children and in adults. The present seventy-three cases were collected over a period of fifteen years, yet in adults the condition is so uncommon that isolated examples are still being recorded (Mogensen, 1937; Riley, 1939). Though most patients probably recover or die there remain a few in whom the disease is long continued.

The absence of any story of diarrhoea when young in a case of adult steatorrhoea does not necessarily mean that the disease has arisen de novo and is not an example of latent coeliac disease. Such histories are based on the lay conception of diarrhoea and it is noteworthy that the parents of the patient A.M. above, strenuously denied that she had any abnormal motions, when actually she had copious steatorrhoea. Furthermore, Miller and Perkins (1923) have called attention to the occurrence of periods of apparent constipation in coeliac disease. Finally, skiagrams in long-continued cases show that the large bowel dilates, holding the bulky motions more easily, so that evacuation becomes less frequent.

The possible fate of a young child who develops coeliac disease may include years of illness and may be represented schematically thus:

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INSIDIOUS ONSET

DISEASE BECOMES APPARENT

Severe illness with possible complications

DEATH QUIESCENCE RECOVERY

RECRUDESCENCE
```

Size of those followed up.—It is to be expected that such a severe and long-continued disease would leave lasting effects on the physique of the recovered patient. This has been shown to be so by other workers and Hablützel-Weber (1923) found forty per cent. of his living patients to be below the average physique. Schaap (1926), too, was of opinion that if the patient recovered he always bore traces of his illness, even when grown up. In the two diagrams the relation of the height and weight of thirty of the patients traced in relation to the average for their age is plotted. The six active patients have been excluded (figs. 6 and 7). Five of the patients were above the standard
height for their age. Three of these were over the standard weight, one was three-and-a-half pounds and one six-and-a-half pounds below the standard. Fifteen patients were more than two inches under height and five pounds under weight. Eight of these were more than ten, and four more than thirty pounds under weight. Two patients were within one inch in height, but more than ten pounds below weight. Six patients approximated to both standard height or weight.

Two patients were under height, but were five or more pounds over weight.

These patients thus appeared excessively fat, and this tendency for them to gain too much weight and so have the appearance of Fröhlich's syndrome has been thought by Parsons to be further evidence of the instability of their fat regulating mechanism. It is well shown in the photograph of a patient who subsequently died from influenzal bronchopneumonia (fig. 8). Eventually the condition rights itself as is shown by a boy who now, at the age of fourteen, is above both the standard height and weight; a photograph of him at the age of six-and-a-half is most suggestive of Fröhlich's syndrome.

The imprint of coeliac disease is thus heavily written upon the stature of the child. As time goes on, and particularly as puberty is passed, this may get fainter, but in most cases it is probable that permanent record is left.
Haematology.—Blood counts upon those followed up showed only four with haemoglobin levels below 70 per cent. The anaemia was of a low colour index type and only one of them had steatorrhea indicative of activity. Eight had haemoglobin values between 70 per cent. and 75 per cent., four between 75 per cent. and 80 per cent. and eight were over 80 per cent. No hyperchromic anaemias were discovered, thirteen patients had a colour-index between 0·9 and 1·1 and the remainder a low colour-index anaemia.

Other features.—Teeth: It might be thought that the teeth would show evidence of a disease which has such a profound influence on the metabolism of calcium. Unexpectedly most of the patients had good teeth; there was only one with gross caries and one other with a mild degree.

Mentality: There appeared to be no serious retarding of the mentality of the patients. Those who had missed many terms at school would have compared badly with their more fortunate fellows, but this was due to lack of education and not of capacity to learn. This is in keeping with the behaviour of the children when they are in the acute phases of the disease and their precocity is so well marked.
Fig. 8.—Two photographs of the patient T. M. age 15 mth., and 5 yr. 4 mth. Note the tendency to obesity which may occur when recovery from coeliac disease takes place.
PROGNOSIS IN COELIAC DISEASE

Summary

(1) Seventy-three cases of coeliac disease who had been patients at the Hospital for Sick Children, Great Ormond Street, London, for more than two months between 1925 and 1938 have been analysed and followed up, all but fourteen per cent. of the living patients having been traced.

(2) Twenty-six patients died. Excluding four who died when the disease was not active, the mortality was thirty per cent. This is high when compared with other series.

(3) Death was usually due to an exacerbation of the disease, the diarrhoea increasing and dehydration and intoxication becoming marked. Only four children died from bronchopneumonia.

(4) Seventeen patients appeared to have recovered clinically and biochemically for more than three years, ten had been in a similar condition for less than three years. Together these form a group of thirty-seven per cent. of the whole.

(5) Six patients are still in the first phase of activity of the disease.

(6) Four patients were thought to be well until stool analyses showed steatorrhoea. These patients are in a quiescent phase of the disease, which, if in adult life it becomes reactivated, is usually diagnosed as idiopathic steatorrhoea. To such the name latent coeliac disease should be given.

(7) Patients who have had coeliac disease tend to remain dwarfed, but their intellect is not affected and their teeth remain good. Anaemia does not as a rule persist.

Thanks are due to the Honorary Staff of the Hospital for Sick Children, Great Ormond Street, for providing access to the notes of these patients and allowing them to be investigated, to Dr. D. N. Nabarro, late Director of the Pathological Laboratory, for facilities to work in the laboratories, to Dr. Bertram Shires for permission to reproduce the skiagrams and to Mr. Deryck Martin for taking the photographs.

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Prognosis in coeliac disease: A Review of Seventy-Three Cases

Christopher Hardwick

*Arch Dis Child* 1939 14: 279-294
doi: 10.1136/adc.14.80.279

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