Papers and Originals

Prognosis in Early Adult Life of Coeliac Children Treated with a Gluten-free Diet *

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Summary: Long-term follow up of 57 young adults with coeliac disease diagnosed in childhood showed that 13 had relapsed clinically and had resumed a gluten-free diet. Of the remainder, who were taking a normal diet and were apparently normal, 19 had low serum folate levels and 11 low serum iron levels. Pregnancy was found particularly likely to provoke an overt relapse.

Only six patients were found to be stunted in height, while the menarche had occurred within the average range. The study also confirmed the very low present-day mortality rate of coeliac disease in childhood, which at the Hospital for Sick Children in London has been 0·4% between 1951 and 1968. In view of the finding that childhood coeliac disease usually persists, even though not causing symptoms, it is suggested that the use of a gluten-free diet should be lifelong.

Introduction

The purpose of this communication is to record the progress of 57 children with coeliac disease who were treated by a gluten-free diet during the years immediately following the description by Dicke (1950) of the role of gluten. These children are now young adults, and their experiences offer a basis on which to judge the longer-term benefit of treatment in childhood with a gluten-free diet, and to consider whether their management requires modification. All the children were under my observation at the coeliac clinic at the Hospital for Sick Children, Great Ormond Street, where they continued to attend until puberty. By that age all but three were on a normal diet, and seemingly healthy; three had been unable to tolerate gluten throughout their attendance, and at the ages of 18, 18, and 24, respectively, were still taking a gluten-free diet.

The period during which the children remained on a gluten-free diet varied, but in general it was our practice to try a normal diet after two years of treatment, intolerance to gluten being recognized by a return of abdominal symptoms with loose pale motions, anaemia, failure to maintain the gradient of growth that had been established during treatment, a deterioration of temperament, or a combination of these. Evidence of intolerance was sometimes apparent within a few weeks, in others it might be delayed for two or three years, but when it appeared the gluten-free diet was reintroduced for a further period of about two years before a fresh trial of a normal diet was made. Thus some of the children did well after one course of treatment, others required two or more courses before they were able to tolerate gluten. Sheldon and Tempany (1966) pointed out that improvement of the jejunal mucosa, even if virtually to normal, during gluten-free treatment is no guarantee that gluten will then be tolerated, for the mucosa may rapidly go back to a flat appearance in the presence of gluten. Tolerance towards gluten by coeliac children is a matter of trial and error, and requires careful and persistent observation after reverting to a diet containing gluten.

The method of conducting this follow-up was to invite each patient to return a questionary concerning his or her health. Each patient was then interviewed and examined by me, the haemoglobin was estimated, and a blood film examined. The following serum determinations were made: iron, method of Bothwell and Mallett (1955), the normal range being 80–150 μg./ml.; folic acid, method of Waters and Mollin (1961), the normal range being 5·9–21 mμg./ml.; vitamin B_{12}, method of Matthews (1962), the normal range being 170–950 $\mu\mu$g./ml.; and calcium on an Eppendorf flame photometer, the normal range being 8·5–10·3 mg./100 ml. Questionaries were in fact returned by 65 patients, but for various reasons (a fatal accident, emigration, inability to attend for interview) eight were unable to complete the follow-up. It was decided that the information from the questionary was not reliable enough by itself to include these patients in this review, though it is tolerably certain that one of them had relapsed.

For three years before the gluten era the coeliac children attending Great Ormond Street were given a normal diet except that all flours were withheld. They benefited in the same way as the children who were later started on a gluten-free regimen, because withholding all flours did in fact entail the withdrawal of gluten. When the importance of gluten was realized these children were transferred from what had been a needlessly restricted diet to a gluten-free diet. Twenty-five of the patients in this series began their treatment in this way.

Results

The results are set out in Table I. The average age of the 57 patients (23 males, 34 females) is 21½ years, ranging between 16 and 27 years. Since leaving the clinic 13 have already undergone a clinical relapse and have had to revert to a gluten-free diet. Eleven of these are females. The relatively high proportion of relapses in women is probably connected with pregnancy, which, as mentioned below, is apt to precipitate a relapse. The remaining 44 regarded themselves as healthy, and are leading normal lives, but 19 of them have a serum folic acid below 5 mμg./ml., ranging from 0·6 to 4·8,

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with an average of 2·6 mμg./ml. Four of these also have an abnormally low serum iron, the levels being 32, 45, 50, and 68 μg./100 ml. Hepner *et al.* (1968) showed that absorption of folic acid takes place principally in the proximal part of the small intestine. The reason why these patients have so low a folic acid is almost certainly associated with defective absorption arising from an unhealthy jejunal mucosa, and it may well be that at a later date they will experience a more severe relapse of their disease—indeed, one young woman with a folic acid deficiency at the time of investigation has since undergone a more complete relapse, including symptoms of tetany.

TABLE I.—*Progress of 57 Patients (23 Males, 34 Females)*

	No.	Males	Females
Relapsed	13 (23%)	2	11
Not clinically relapsed, but low serum folic acid	19 (33%)	10	9
Not clinically relapsed, folic acid normal, but low serum iron	11 (19%)	4	7
Healthy, normal serum folic acid and iron	14 (25%)	7	7

In these 19 patients there was nothing on clinical examination to suggest that the folic acid level would be low. The patients did not look anaemic and their haemoglobin averaged 94%, ranging between 81 and 111%, nor did their blood films show macrocytes. In children with untreated coeliac disease the folic acid level is almost invariably below normal, though it picks up when folic acid is administered and they are on a gluten-free diet. The results reported here suggest that when checking the health of adults who give a history of coeliac disease during childhood a folic acid estimation may be of value as an indication of the absorptive capacity of the small-intestine mucosa.

We are left with 25 patients who have not as yet relapsed and whose folic acid level is within normal limits. Eleven of these, four men and seven women, have a serum iron below 80 μg./ml., the figures ranging between 26 and 75, with an average of 53 μg./ml. Iron is absorbed principally from the duodenum, and Badenoch and Callender (1954) showed that absorption of iron in idiopathic steatorrhoea is deficient. Although other factors such as dietetic deficiency, intermittent or occult bleeding, or leakage through the intestinal mucosa may contribute to a low serum iron, for 11 out of 25 patients to have a low iron level is a big proportion, and it is difficult to escape the conclusion that defective absorption because of an atrophic mucosa is operating in some of them.

If to the 19 patients with a low folic acid we add 11 with a low serum iron, there remain only 14 coeliac children who have entered young adult life on a normal diet and who have so far kept healthy.

Biopsy

The children in this series had started their gluten-free treatment a few years before Sakula and Shiner (1957) introduced their technique of small-intestine mucosal biopsy and therefore could not undergo this method of investigation during the early years of their disease. Subsequently 13 have undergone biopsy. Of these, seven are in the group who have experienced a relapse, biopsy was carried out between the ages of 11 and 24 years (four biopsies were performed at St. Thomas's Hospital) and all showed mucosal atrophy. Three are in the group with a low folic acid or iron level in their sera, biopsy was carried out when they were 13 years old and showed varying degrees of mucosal atrophy. Three are in the group of healthy young adults, two were examined at 11 years of age and showed atrophy, in one aged 10½ the mucosa was regarded as normal.

A flat mucosa at biopsy does not preclude the patient from remaining symptomless and thriving satisfactorily on a normal diet (Cooke *et al.*, 1963), because the total area of unhealthy mucosa is of greater significance than the degree of change in the small biopsy specimen. Nevertheless, an atrophied mucosa in a biopsy from a seemingly healthy patient who has had coeliac disease implies that a relapse will come about if the area of unhealthy mucosa increases sufficiently and must indicate at least a potentiality towards relapse. This is supported by the subsequent history of those in this series who underwent biopsy in early adolescence.

As regards the remaining investigations one of the blood films showed an occasional macrocyte, from a woman who had relapsed following a visit to U.S.S.R., where she consumed a quantity of rye bread. The serum vitamin B_{12} level was within normal limits in all patients. The serum calcium was low in two—8·2 mg./100 ml. in a woman of 24 who also had a low folic acid level and 8·1 mg./100 ml. in a man of 20 who was otherwise healthy.

Analyses have been carried out to look for any factors during childhood which could demarcate those who in young adult life have remained healthy from those who have either relapsed or have low levels of folic acid and/or iron. This might enable a more accurate long-term prognosis to be given at a time when the children are still under observation. The results are set out in Table II. The analyses concerned the age of onset of the disease, the interval between the onset and the beginning of a gluten-free diet, the total period in childhood of a gluten-free diet, a family history of coeliac disease, and whether a relapse occurred in childhood when a trial of a normal diet was made. The results indicate that none of these criteria will serve to separate those who have so far remained healthy. The likeliest explanation is that though a quarter of the patients have attained young adult life in a healthy state they differ in no other respect from the remainder. They have until now been fortunate, but they are still relatively young, and in the years ahead circumstances may arise which will precipitate them into a return of coeliac symptoms. This would be consistent with the picture of idiopathic steatorrhoea in adults, which may first show itself much later in life than the early twenties.

TABLE II.—*Factors Analysed to Seek Differences Between the Healthy Group, the Biochemically Abnormal Group, and the Relapsed Group. The Range for Each Average Figure is Given in Parentheses*

	Healthy Group	Group with Low Serum Folic Acid and/or Low Serum Iron	Relapsed Group
No. of cases	14 (M 7, F 7)	30 (M 14, F 16)	13 (M 2, F 11)
Average age at onset	1½ years (2 mth–4 yr)	1½ years (5 mth–3½ yr)	2 years (12 mth–6 yr)
Average interval between onset and institution of gluten-free diet	3 years (3 mth–6½ yr)	2½ years (2 mth–8½ yr)	3½ years (6 mth–6 yr)
Average duration of gluten-free diet	4 years (15 mth–7 yr)	4 years (14 mth–8 yr)	4 years (15 mth–8½ yr)
Family history of coeliac disease	4 families	3 families	None
Relapse in childhood after one period on a gluten-free diet	5 out of 14	13 out of 30	7 out of 13

Pregnancy

Mention has already been made of the stress of pregnancy for these patients. It must be remembered that the majority of pregnant women receive a supplement of iron as well as vitamins, but additional folic acid is not given as a routine.

Ten of the women in this series have had 13 pregnancies, resulting in 13 healthy offspring. The details are set out in Table III. Three women began their relapse during pregnancy; four volunteered the information that pregnancy was accompanied by anaemia or by an increase of a pre-existing anaemia, one being given intramuscular iron; three reported healthy pregnancies. The pregnant woman is exposed to an increased demand on her nutritional economy and needs an efficient absorption of the products of digestion. It is perhaps to be expected that if the absorbing surface in the proximal small intestine is reduced owing to diminution of the villous surface the extra demands of pregnancy may be sufficient to convert what had been an adequate absorption into a deficiency. When patients who have been on a normal diet for some years find themselves pregnant it is understandable if they do not inform their doctor that they had had coeliac disease during childhood; but when this knowledge is forthcoming the increased liability to anaemia, involving folic acid as well as iron, and the possibility of a more complete relapse have to be taken into account. The best way to keep these women healthy during pregnancy would be for them to revert to a gluten-free diet. Although the number of women involved in the present series is small, it is probable that reversion to a gluten-free diet would have saved seven of them a good deal of ill-health.

TABLE III.—*Effect of Pregnancy*

	Patient No.	Patient's Statement
Relapsed group ..	1	Relapsed towards end of second pregnancy
	2	Relapsed during second pregnancy
	3	Relapsed during pregnancy. Very anaemic
Low folic acid group	4	Often anaemic, especially during pregnancy
	5	Anaemic during pregnancy
	6	Normal pregnancy
Low iron group ..	7	Anaemic during pregnancy. Given intramuscular iron
	8	Treated for anaemia from third month in both pregnancies
Normal group ..	9	Normal pregnancy
	10	Normal pregnancy

Height

Regular measurements of height are of great help in the supervision of coeliac children. Growth fails from the time the disease begins but tends to catch up during the period of a diet without gluten. When at a late stage an attempt is made to resume a normal diet it is essential that the gradient of growth should not falter; if it does so, a return to a gluten-free diet must be made. It is customary at the Great Ormond Street clinic to record the heights of the parents, because this affords a guide to whether the child might be expected to be tall or short, and prevents an expectation of growth which the family growth pattern would not justify. Parental height also enables a forecast to be made of the expected final height of the child, by using a formula which averages the height of the parents and then adds 2½ in. (6·3 cm.) for a male and subtracts this amount for a female.

Diminution of height in coeliac children becomes increasingly noticeable as the interval between the onset of the illness and the beginning of treatment lengthens, the most severely affected children being sometimes described as coeliac dwarfs. It has generally been accepted that the disease leaves a legacy of stunting in adults, but our figures show that in general the recovery in height by adult life has been remarkably good (see Table IV). Permanent interference with height was found in only six patients, and for them there had been a delay of seven years or more between the onset of their disease and the institution of a gluten-free diet. Table V compares the average height attained by all the patients in this series with a comparable group, reported by Lindsay *et al.* (1956), who had been treated by older methods. Although the numbers are small, it would appear that the children treated by the exclusion of gluten grew more satisfactorily.

TABLE IV.—*Relation Between Height and Delay in Treatment*

Time Between Onset of Disease and Beginning of Gluten-free Treatment	No. of Cases	Average Deficiency Below the Mean at Onset of Treatment	Average Adult Height Compared with National Mean Height	Average Adult Height Compared with Expected Height Gauged from Parental Height
2–4 years ..	5	4 in. (10·1 cm.)	At mean	+ ½ in. (1·25 cm.)
4–7 years ..	6	4 in. (10·1 cm.)	At mean	+ ¼ in. (0·8 cm.)
7–10 years ..	6	7 in. (18 cm.)	− ½ in. (1·25 cm.)	− 1½ in. (3·8 cm.)

TABLE V.—*Comparison of Adult Heights Between the Present Series and Those Reported by Lindsay et al.* (1956)

	Males		Females	
	No.	Average Adult Height	No.	Average Adult Height
Present series ..	23	68½ in. (174 cm.)	34	63½ in. (160·5 cm.)
Series of Lindsay *et al.* (1956) ..	8	66¾ in. (169·5 cm.)	9	62½ in. (158·75 cm.)

Discussion

How do the total findings in this series compare with those obtained before the role of gluten was established? Hardwick (1939) reviewed 73 children who had attended Great Ormond Street between 1923 and 1938. His series is particularly valid for comparison because 25 of his cases were followed up and reported by Lindsay *et al.* (1956). Reference to these has already been made. The average age of the patients was then 24½ years. Eight of these were again followed up and reported by Mortimer *et al.* (1968). The authors included two more adults who had also been treated as coeliac children in pre-gluten days. The average age of the 10 patients was 30 years.

From a study of the literature Hardwick (1939) reported a mortality of 15% in 544 published cases. At that period the most satisfactory results were obtained by Howland (1921), who had no deaths among 30 children. He had been the protagonist of treatment by a diet in which complex carbohydrates were rigorously excluded, but fat was not reduced even though its absorption was less satisfactory than in healthy children. His diet was in effect gluten-free. In England the dietary regimen was different; fat was strictly withheld, while complex carbohydrates were not regarded with such extreme disfavour. With this method Still (1918) had a mortality of 14% and Parsons (1932) a mortality of 10%. In Hardwick's (1939) series the mortality was 30%. Since the advent of a gluten-free diet the drop in mortality is striking. Between 1951 and 1968 of 485 children with coeliac disease who attended Great Ormond Street, two died—a mortality of 0·4%.

The average age at menarche of nine women in the 1956 series was 15·0 years, ranging between 13 and 17 years. This figure was compared with an average age in the normal population of 13·4 years. In the present series the average age of menarche in 34 women was 14·0 years. This includes one mentally subnormal woman who had never been able to tolerate gluten and who began her periods at 19½ years. Otherwise the range lay between 11 and 16 years, and the average age would have been 13 years 8 months. Although the numbers are small, it appears that children treated on a gluten-free diet mature sexually at an almost normal age, and significantly earlier than those treated by older methods.

Of the 25 patients reported in 1956, eight showed evidence of persistent malabsorption and would correspond to the "relapsed" group in the present series, the proportion of relapsed patients in each group (8 out of 25; 13 out of 57)

being closely similar. Although the 1956 group reached the menarche at a later age and were probably lower in height, their relapse rate was so close to that of the children who had been given a gluten-free diet that one must conclude that when the latter are returned to a normal diet, even though they appear to tolerate gluten satisfactorily, their potentiality for relapse is the same as that of children treated by other methods. It would be incorrect to regard them as cured. Gluten intolerance is a chronic and persistent disorder. It is probable that a still later prognosis for the patients in the present series would be similar to the 10 patients reported in 1968 who had never been on a gluten-free regimen. Five of them gave a history as adults of such evidence of malabsorption as diarrhoea, megaloblastic anaemia, or tetany. Those who were not receiving folic acid supplements had a low serum folate. The serum vitamin B_{12} was normal in all. At biopsy all but one showed a flat small-intestine mucosa. Nevertheless, five of them were still in a state of comparative well-being.

Conclusions

The present investigation confirms that the mortality of coeliac disease in childhood has been reduced almost to vanishing point by the advent of the gluten-free regimen. Almost all the children achieve tolerance towards gluten during their childhood, to the extent that they remain symptom-free and can lead normal lives. It would, however, be incorrect to think of them as cured, for in later life anaemia may develop, and even without anaemia a low serum folic acid and sometimes a low serum iron may be present. Sooner or later some of them are likely to show increasing evidence of malabsorption. Pregnancy is particularly likely to convert a latent into an overt relapse.

It may well be that, once a child has been diagnosed as suffering from coeliac disease and has been shown to respond to the withdrawal of gluten, foods containing that substance should thereafter be permanently avoided. This would be the best way of maintaining good health. It would also have the advantage for the patient that frequent medical inspections stretching over years would be less necessary. During the initial years of treatment the diet would need to be strict, but later on occasional lapses to meet social requirements would be unlikely to be harmful. It must also be borne in mind that malignant lymphoma of the small bowel has been reported as a late complication of idiopathic steatorrhoea (French *et al.*, 1957; Gough *et al.*, 1962). Whether this risk would be lessened if the injury to the mucosa by gluten were permanently avoided is not at present known. On the other hand, a special diet for one child in a family adds to the mother's burden, requires the co-operation of the education authorities, and marks the child as being different from his fellows. It has been our experience that as these children approach adolescence some of them object to this distinction and revolt against restrictions for which they see no need. It is then easy to reach the unsatisfactory position where the diet is "more honour'd in the breach than the observance" (Hamlet).

There is thus a choice of policies for gluten-intolerant children. One is to advise the persistent use of a gluten-free diet. The other is to aim at restoring the child to a normal diet, knowing that the intolerance is not strictly curable and that later in life evidence of malabsorption is likely to reassert itself. It is perhaps as well that the children under review were treated according to the second policy, for had they remained persistently on a gluten-free diet it is likely that in young adult life they would have been much healthier, and the question would then have arisen whether they would have done equally well if they had been restored to a normal diet during childhood. In fact the results of this policy have been shown to be unsatisfactory and disappointing. I therefore consider the first policy to be the one of choice.

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