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SOME PROBLEMS IN NUTRITION

Chairman: PROFESSOR S. J. COWELL, *University College Hospital Medical School, University Street, London, W.C.1*

The Gluten-free Management of Coeliac Disease

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Coeliac disease had for 50 years been one of the most baffling diagnostic and therapeutic problems in clinical paediatrics when, about 4 years ago the Dutch workers (Dicke, 1950*a*,*b*; Weijers, 1950) showed that it was an intoxication with the protein fractions of wheat and rye flour.

Coeliac disease had never been accurately defined and there was always some doubt as to whether it was a single disease, but it can be clearly described. It may first show itself at any time between later infancy and middle childhood, but in three-quarters of the cases the disease begins during the 2nd year of life. A happy toddler who has hitherto gained weight steadily throughout a normal infancy gradually over the course of a few weeks goes off his food, ceases to gain weight, perhaps vomits occasionally, and the stools are noticed by an observant mother to become progressively paler, bulkier, softer and more offensive; in most cases the child loses his happy disposition and becomes difficult, cantankerous, and impossible to feed or to amuse. If a regular chart is kept the weight will be found to oscillate widely from day to day, indicating a marked degree of hydrolability, so that any transient gain is soon balanced by a loss; the child becomes thin, the abdomen gassy and protuberant, the limbs and buttocks wasted and in the course of months even the face becomes thin, pinched, and sallow. Anaemia may develop, and sometimes there are attacks of abdominal pain, but these are by no means the rule. Untreated, or inadequately treated, the individual will maunder dismally on through childhood stunted, wasted, and inflated with gas; violent crises of dehydration may occur and in one of these the child may die; but if he survives, the symptoms will in the course of many months or years gradually become less severe, the appetite will slowly improve and he may emerge from the disease into later childhood a malnourished dwarf, subject still to an occasional return of symptoms.

Historical account

Coeliac disease was first described, in much these terms, by Gee (1888) and by

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Gibbons (1889–90). While offering no theories about aetiology Gee gave his opinion that the cure would be found in dietetic management and that a restriction in the intake of farinaceous food was essential. Fat he regarded as harmless and indeed advocated the feeding of fresh butter and cream. Gibbons recorded the history of a child who was fed for the whole of one season exclusively on best Dutch mussels, with a total disappearance of all the symptoms. With the close of the mussel season symptoms returned. Unfortunately the following year the child could not be persuaded to eat a single mussel.

Following the initial description of the disease, papers were published in Europe and in America in the first two decades of the century dealing mainly with the complications of severe coeliac disease, such as dwarfism and rickets, and also with the results of stool analysis, which showed impaired absorption of carbohydrates and of fat (Heubner, 1909; Herter, 1908).

Sir Frederick Still (1918*a–c*) was over-impressed with the importance of fat and thought that there was a specific intolerance to cow's milk, which he attributed to its fat content. It is interesting that Still agreed with Gee, erroneously as we now know, that cow's milk was injurious, but he incriminated the fat of cow's milk which Gee had specifically exonerated, and had indeed advised feeding as cream. Still agreed that there was, as he put it 'some difficulty in dealing with starches, though much less than with fats' and noted correctly that rice, lentil flour, and potato were harmless, and that bread was the worst form of carbohydrate.

From the time of the first world war onwards this excessive emphasis came to be placed upon the fat content of the stools in coeliac disease, and a quarter of a century was to elapse before attention was again securely focused upon the specific intolerance to certain carbohydrate-containing foods and upon the harmlessness of fats, both of which had been well recognized by Gee and by Gibbons.

Sir Leonard Parsons (1932) gave the full weight of his authority to the view that the outstanding feature of the disease was an inability properly to absorb fat and described the wasting as 'chiefly due to the absence of stored fat'. He advocated a diet which proceeded by stages, and in which starch-containing foods were added last. The children were to be fed upon protein milk till the stools were firm and the appetite good, after which other protein-containing foods were added, and lastly carbohydrates. But throughout the period of the diet he advocated a low fat intake.

Many variations upon this kind of diet have been tried under a variety of names in the past 20 years. Their common defects have been three-fold.

(1) They were not clearly based upon any principle and therefore were difficult to design, operate and control, especially at home.

(2) Partly because of this difficulty, they were seldom continued for long enough.

(3) So much was excluded from the diet that it was difficult to avoid starvation. The exclusion of high-caloric fat was particularly harmful in this respect.

After the war attention came to be focused upon the use of a completely starch-free diet and in 1947 Dorothy Andersen (1947) recommended a high-protein diet in which carbohydrates were given solely as sugar and from which all polysaccharides

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were excluded for a year or more. She too, however, advised a restriction of fat intake.

Observations at The Hospital for Sick Children, Great Ormond Street

From this point onwards I can take up the story in terms of clinical material with which I am familiar, for after the war Dr Sheldon (1948) began to collect a series of cases at Great Ormond Street and to treat them systematically on a strictly starch-free diet. He showed by balance studies (Sheldon, 1949) that the fat absorption rose to normal figures on the total exclusion of starch, and thereafter gave a diet of normal fat content. On this régime the children lost their symptoms within weeks and rapidly regained normal health and dimensions.

The assessment of progress and of the normality of growth, once the major symptoms of the disease have been relieved, is one of great difficulty: for each child has his own norm and it is irrelevant to judge one individual's growth by comparison with a pseudolongitudinal weight chart which has in fact been built up by the juxtaposition of a series of cross-sectional studies of a large population. We have in fact used such a chart as a guide, but as no more than that. The ideal growth curve of a child recovering from coeliac disease begins with a recovery phase in which tissues are being rebuilt and the growth lag made good: in this phase the rate of gain in weight and height is abnormally high: when the child's individual optimum is reached the curve flattens out towards a normal rate of gain, but does not fall below this gradient.

On the starch-free (and incidentally gluten-free) diet this ideal curve was attained while the children were under our own dietetic control in hospital, where they gained weight rapidly at gradients between 20 and 100 lb. a year; but in few cases was this curve continued after discharge. In most cases a flattening in the gradient, before the optimum had been reached, coincided with discharge from hospital. Despite this growth failure, however, the children nearly all remained free from major symptoms, in what passed for normal health, and grew slowly, while their parents were attempting with variable energy and success to maintain a starch-free diet at home.

We suspected that this growth failure was attributable to the great difficulty, both technical and economic, of giving at home a diet from which both the staple foods, bread and potatoes, were entirely excluded; but there seemed little to do about it short of admitting apparently well children to hospital and keeping them there indefinitely. Whenever one of these children became ill and was readmitted, the ideal curve was resumed once more upon the reinstitution of a strict starch-free diet.

This was the position when, in 1950, Dicke (1950*a*,*b*) and other workers (Weijers, 1950) in Holland reported that pure wheat starch, from which all protein had been excluded could be added with impunity to the polysaccharide-free diet, but that the symptoms of the disease recurred if gluten, the protein component of wheat flour, or of rye flour, was added. This clinical observation ran parallel with the effects upon fat absorption.

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The promise which starch-containing, gluten-free diets offered of easier dietary maintenance at home, and our success with the diet in clinical trials, led us (Sheldon & Lawson, 1952) towards the end of 1951 to review all cases treated with starch-free diets since 1947. Of sixty-four children one only had died of the disease, one had been killed in a motor accident and we had lost track of three. Fifteen of the children, whose nutritional status was clearly unsatisfactory, were put on to a gluten-free diet, and all showed a consequent steepening in the weight gradient above normal rates of gain.

Since this time all cases have been put on to a diet that is entirely normal except for the exclusion of wheat and rye gluten, from an early stage of treatment. Ideal growth curves are obtained, and these continue after discharge from hospital.

The tendency of coeliac disease spontaneously to become less severe as the months and years pass has led many observers to claim a greater success for their therapeutic methods than was deserved. At the same time there was no clear criterion of full success in treatment. Parents who have experienced the miserable months and years of coeliac disease in its most active phase may well accept as normal an improved state of health and growth which is in fact suboptimal. It is our view that the rate of growth is the most sensitive of all methods of judging success and offers a criterion which is simple in application except that it requires regular follow up over long periods.

This, briefly, is the history of the management of coeliac disease up to the discovery in Holland (Dicke, 1950*a*,*b*; Weijers, 1950) of the specific noxious agent in coeliac disease, and of the vindication of their work in the management of a long series of cases in England (Sheldon & Lawson, 1952).

We are left with a knowledge of how we may successfully treat the disease, but with many unanswered problems about its nature.

Problems of diagnosis and treatment

I would like to deal shortly with some of the problems of diagnosis and management, and with some of the problems still unanswered in the natural history of the disorder.

Diagnosis. In the past diagnosis was by exclusion in a child suffering from the symptoms I have described. Various laboratory methods such as stool analysis and glucose-tolerance curves have been used: but these give unequivocal answers only in cases so severe that the diagnosis is easy. And it is my experience that they have never helped in making a diagnosis that was in serious clinical doubt. The uniformity of response to the gluten-free diet justifies the use of this diet as a therapeutic test in doubtful cases. If there should be found similar cases which do not respond to the diet (and in a series of 120 cases we have as yet found none), they should be studied separately as a different disease. This therapeutic test should not however be embarked upon lightly for it takes many months. Mere response to the diet is not of course enough; the proof is only made when after several months of satisfactory progress a relapse is initiated by reintroducing gluten into the diet.

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Gluten hangover. When gluten is withdrawn from the diet, there is not an immediate clinical improvement and the child may remain difficult to feed for about a fortnight and sometimes for as long as 6 weeks. During this time the child will be on a largely fluid diet, the caloric value of which is made up by additional glucose. But this is a waiting period, during which previously ingested gluten is still exerting a toxic effect and, however much food is forced into the child, he will not gain weight. This waiting period—I have called it the gluten hangover—is, I think, responsible for most of the reported clinical failures on the gluten-free diet. There is laboratory confirmation of this phenomenon. Professor Frazer and his team at Birmingham (Anderson, Frazer, French, Gerrard, Sammons & Smellie, 1952) have shown that the fat absorption rises to normal on gluten exclusion, but that it takes from 4 to 6 weeks to gain its highest value: and that if gluten is then administered the fat absorption falls again within a few days and takes a further 4 to 6 weeks to reach normal when the diet is reinstated. Our own unpublished studies confirm these laboratory findings.

Assessment of progress. Our studies have shown us that the height and weight curves are a more precise indication of whether or not optimal results have been achieved than are either the clinical history or clinical examination. Many children who had previously been treated with the starch-free diet and who were reviewed when the gluten-free diet was begun were in a state of health with which parents and school authorities were well satisfied. Study of their weight charts, however, suggested that they might be doing better, and on a gluten-free diet they showed an immediate spurt in weight and height gain and experienced better health and happiness than they had ever known.

It is not yet known how long children must remain on the diet. The present policy is that they should remain on the diet for 2 years, after which their growth is carefully followed over a further year to see that progress is satisfactory. It seems likely that in some cases the diet will have to be re-introduced. It is certain that each child must be considered individually in this respect.

There is no doubt that in some cases the disorder continues into the sprue of adult life. I know of one woman who is being treated for sprue at a London hospital, who in childhood had formed one of the series of cases of coeliac disease reported by Still (1918*a–c*).

The neatest collection of weight charts would no doubt be assembled if the diet was maintained throughout childhood in all cases. But there are many children, and probably a large majority, for whom this would be unnecessary: and it must be remembered that although the diet is not technically or economically difficult to give, it nevertheless interferes deeply with the growing child's life at home and social activities, as no meal may at any time be taken that has not been prepared by one fully trained in the technique of gluten exclusion.

The diet

During the early days and weeks of treatment the successful administration of a harmless, acceptable diet in quantities which he will accept to an unco-operative

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miserable child, who has not enjoyed a meal for many months, takes precedence over the achievement of body building. A fully adequate caloric intake cannot be achieved in a day or two. There will be in most cases an initial period of up to a month in which a nurse, and preferably one nurse only, will have to spend much of her time persuading the child to feed. After a week or two, sometimes within a few days, the child's whole attitude to life changes perceptibly for the better, the appetite begins to return and the stools become normal.

At this stage one might hope to give a 40 Cal./lb. diet in the form of 1 : 8 Prosol (Trufood Ltd.)* with added sugar, giving 3·5 g protein/lb. body-weight. When this amount is accepted the quantity is gradually increased and there are added one at a time ripe banana, egg custard, lean chicken and meat. Gradually a diet of normal constitution with a normal fat and high protein content, but with the absolute exclusion of all material containing wheat or rye flour, is achieved.

There is no difficulty in giving this diet in hospital, where the services of a dietitian are available, but its maintenance at home is dependent upon careful and repeated indoctrination of the parents, and we have found it necessary to have a dietitian as a member of the out-patient follow-up team to repeat, extend and perhaps explain our advice.

Flour is replaced by pure wheat starch and by cornflour. This presents no real difficulty except that additional eggs and fat have to be used in cooking, for otherwise the loaf or cake, deprived of its glutinous content, will not hold together.

The main practical problems arise from the difficulty of excluding certainly all the manufactured products that may contain small quantities of wheat or rye flour. We have not carried out any precise experiments to define the threshold toxic dose of gluten, but it is within our experience that this is small, for relapses have been induced by the addition to the diet of one or two slices of toast a day, of a probable gluten content of 1–2 g.

Two social difficulties have also proved intractable at times. One is that of ensuring a gluten-free lunch for a child who normally takes it at school; and the other that of persuading a child to eat happily a diet which differs from that of other members of the family.

Mechanism of the disorder

Wheat gluten. Of the mechanisms of the disorder we have as yet little knowledge. We know only that wheat gluten is the proximate cause of the disease in susceptible children. I would point out that gluten is not a pure substance. Its definition is a commercial one. It is the sticky mass left behind when flour is extracted with water, after all the starch has been taken off in suspension and all the soluble proteins and other soluble substances have been dissolved away. It is about 90% protein and it seems reasonable to assume that the toxic substance is a protein. It can be further divided into two fractions by alcohol extraction, and of the two fractions thus defined, gliadin and glutenin, it seems that both have some toxic

* Prosol is a dried skim milk with added protein. When reconstituted with eight parts of water it has the composition: protein 7·75, fat 0·125 and carbohydrate 3·4%.

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action, but that gliadin is probably more effective weight for weight than glutenin.

One fact seems clear. We cannot explain coeliac disease as a simple one of malabsorption. When gluten is reintroduced into the diet all the symptoms of the disease recur much more quickly than any mere starvation could have its effect. Then in the later stages of the disease children are symptom free, have good appetites and normal stools, while failing to grow in height and weight. There must be some specific interference with intermediate metabolism.

Fat. The earliest observers, their powers of direct observation not yet clogged with an excess of laboratory examinations, did not observe that fat did any harm, and more precise laboratory studies themselves have shown that the defect of fat absorption is a slight one only, and that when the disease is in full activity from three-quarters to four-fifths of the ingested fat is normally absorbed.

Mothers themselves do not describe the stools as fatty until the idea has been suggested by a physician, but rather as bulky, porridgy or like scrambled egg. When I saw the mothers of sixty children with coeliac disease and retook the initial histories, the words 'fatty' or 'oily' were used spontaneously by only one mother. There is no doubt that dogged insistence on the restriction of fat on insufficient evidence of necessity has been responsible for much of the enforced starvation to which these children have in the past been subjected.

SUMMARY

Coeliac disease was accurately described 60 years ago when it was correctly observed that certain starch-containing foods were the most harmful and that strict dietetic management was a prerequisite to success in treatment.

For the intervening half century physicians, with a few exceptions (*e.g.* Haas, 1938; Haas & Haas, 1950; Howland, 1921), have been misled by the results of stool analysis into the belief that failure of fat absorption played a major part in the natural history of the disease. This led them to contribute to the child's starvation by the exclusion from the diet of a high caloric food which could be effectively absorbed.

The starch-free diet, of normal fat content, achieved success under the strict dietetic control which is possible in a special unit in a fully equipped hospital, but this success was not fully maintained after discharge of the children to their homes. The failure is accounted for by the economic and technical difficulty of giving consistently at home a diet from which bread and potatoes are wholly excluded.

The discovery in Holland in 1950 of the aetiological role of wheat gluten suggested that the success of the starch-free diet might have been due to the incidental exclusion of gluten.

The relative simplicity of the gluten-free diet gave us high hopes that by this means the success already achieved in hospital might be sustained after discharge.

The diet has been applied with full success to Dr. Sheldon's original series of sixty-four cases, which has since expanded into the 120 who are now the subjects of a prolonged follow-up study. We have fully confirmed in this series, by clinical

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means, the findings made by short-term clinical and laboratory tests on a small series of cases in Holland.

As physicians we may be satisfied that at last normal health and growth may be regained and maintained by children suffering from this disorder, but as natural historians we are left with many unsolved problems, some of which I have outlined here.

I wish to express my thanks to Dr. Wilfred Sheldon for allowing me to report on joint work on his cases.

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Statistical Aspects of Dietary Surveys

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Dietary surveys are widespread and numerous, and have indeed become a regular part of the policy-making apparatus of national and international governing bodies. They are very laborious and expensive. There are great variations in methods of investigation and interpretation, and in the scale of operations considered necessary. Qualitative discussions of the faults and merits of the differing techniques are available in several reviews (e.g. Bigwood, 1939; (U.S.A.) National Research Council, 1949; Norris, 1949; Leitch & Aitken, 1949–50). There are also quite a number of papers containing quantitative comparisons of some particular aspects of technique, or data that allow such comparisons to be made. But there seems to have been no attempt to collect these scattered quantitative findings and to use them for a balanced statistical appraisal of the relative costs, advantages and errors of different methods of conducting dietary surveys. This paper is a tentative first approach to such an operational analysis.

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