Papers and Originals

DIAGNOSIS AND MANAGEMENT OF COELIAC DISEASE IN CHILDHOOD

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Coeliac disease does not occur commonly in childhood. Carter, Sheldon, and Walker (1958–9) calculate its incidence at between 1 in 2,000 and 1 in 6,000 of the population. This incidence may be compared with that of the other common cause of steatorrhoea in children, fibrocystic disease of the pancreas, which Carter (1962) states affects 1 in 2,000 children.

Since coeliac disease has to be considered in the differential diagnosis of chronic diarrhoea, of wasting disorders, and of growth failure in children, its diagnosis is a common subject of debate in children's hospitals. Its diagnosis rests on the clinical picture, on the proof of steatorrhoea and malabsorption, on the evidence provided by radiography of the small intestine and mucosal biopsy, on the response to a gluten-free diet, and, if mucosal biopsy has not been obtained, on the relapse occurring when gluten is reintroduced into the diet. These diagnostic procedures are laborious and lengthy and require much expert knowledge in their performance and interpretation. Not infrequently these diagnostic inquiries, other than mucosal biopsy, may give equivocal answers.

The classical picture of the infant who presents with a wasting disorder some months after gluten has been introduced into the diet, with loss of subcutaneous fat, with vomiting, with the passage of "pale, bulky, and offensive stools" (Gee, 1888), and with a change in disposition and behaviour, can provide a diagnosis which to the experienced clinician hardly requires further investigation. Less severe forms of the disease, presenting in later childhood, are the common diagnostic problems of to-day. These demand the fullest available range of diagnostic investigations. The first requirement is to establish the presence of malabsorption.

Steatorrhoea

Reduced absorption of fat with steatorrhoea has been regarded as a *sine qua non* for the diagnosis of coeliac disease. The daily output of faecal fat is generally measured by the method of van der Kamer and his colleagues (1949). In infants the intake of fat may also be easily measured, but in older children a normal ward diet containing 30 to 60 g. of fat provides an adequate intake. The collection of faeces must be continued over a minimum period of five days, and for longer periods if the results are equivocal. Steatorrhoea in children over the age of 18 months was defined by Cameron and his associates (1962) as a mean faecal-fat excretion above 4 g. a day or an absorption of less than 90% of the dietary intake, while in those under 18 months an absorption of less than 85% was considered abnormal. These authors reported that of eight new cases of coeliac disease three presented without steatorrhoea. One child aged 2 years 4 months had a mean daily fat excretion of 2.3 g.; the second, aged 3 years 2 months, an excretion of 3.4 g.; and the third, aged 8 years 10 months, an excretion of 1.7 g. It is apparent that while steatorrhoea is an important diagnostic criterion of coeliac disease the failure to establish its presence cannot be regarded as excluding the diagnosis.

Because of the exacting ward and laboratory work involved in these estimates of fat excretion, several workers (Silverman and Shirkey, 1955; Delory *et al.*, 1956; O'Brien *et al.*, 1959) have introduced a "lipiodol"-absorption test as a simple assessment of steatorrhoea. Jones and di Sant' Agnese (1963) have published an improved method which they claim correlates well with defective fat absorption as measured by chemical methods of estimating fat excretion. The principle underlying the test is that during the process of transport of the fat across the small intestine the iodine is split off and excreted in the urine. The degree of recovery of iodine in the urine reflects the percentage absorption of lipiodol. This may well be a useful screening method for the presence of steatorrhoea, though it would be too much to hope that it would detect malabsorption in those patients, admittedly not the majority, in whom an increased excretion of fat is not determined by chemical methods.

Xylose-excretion Test

Obviously another test for malabsorption is required in addition to methods used to demonstrate steatorrhoea. We have used the absorption of D-xylose (Hubble and Littlejohn, 1963) in the diagnosis of coeliac disease and found it to be satisfactory. An oral dose of 5 g. of xylose is given and the urine collected for a five-hour period, and the output of xylose measured. Values of 25% of the administered dose and above indicate normal absorption in the upper part of the small intestine, while values below 15% are indicative of malabsorption. There is an equivocal range between 15% and 25% in which absorption may or may not be normal. However, in only 5 out of 35 patients with coeliac disease examined did the results fall within the equivocal range.

This test differentiates between coeliac disease and fibrocystic disease of the pancreas (Clark, 1962); and a positive result indicates malabsorption in the upper part of the small intestine, of which the commonest cause in children is coeliac disease. A positive result does not prove coeliac disease, and other rarer diagnoses may have to be considered, such as giardiasis, sensitivity to cow's milk, protein-losing enteropathy, and abetalipoproteinaemia (Anderson *et al.*, 1961; *Brit. med. J.*, 1962).

Radiography of Small Intestine

Radiography of the small intestine using a mucus-resistant barium-sulphate suspension is a valuable investigation in the diagnosis of coeliac disease (Astley and Gerrard, 1954). The most important sign is dilatation of the small intestine, and Cameron *et al.* (1962) found this to be present in 26 out of 31 cases of active coeliac disease in which this investigation was made. However, dilatation of the small intestine was also reported in 6 out of 14 patients suspected of coeliac disease who were submitted to mucosal biopsy, and in whom the final diagnosis was not coeliac disease.

Radiography of the small intestine, like the measurement of fat excretion in the faeces and of xylose in the urine,

is a useful aid in the diagnosis of coeliac disease, but like these tests it provides no absolute answers.

Biopsy of Mucosa of Small Intestine

The characteristic coeliac changes in the mucosa of the small intestine are flattening of the villi and increased cellularity. These changes are always present in coeliac disease in children who are taking gluten in their diet (Cameron *et al.*, 1962). Whether the complete changes are specific in childhood for coeliac disease, as these authors stated, must now be regarded as debatable. Certainly these changes are also characteristic of sprue. And they may be seen in lesser degree, as these authors agreed, in giardiasis, in anaemia, and in surgical specimens excised for jejunal atresia. They regarded these less severe changes as evidence of non-specific duodeno-jejunitis. Whether the complete coeliac change with flattened villi may occasionally be found in children with other disorders remains to be established. The coeliac change in the mucosa is undoubtedly the most specific of all the diagnostic criteria that can be sought for in coeliac disease in children.

Cameron and his colleagues in discussing the technique of the biopsy reported that their failure rate with the child's Rubin or Shiner intestinal biopsy tube was higher than with the Crosby capsule, and the screening time required for the Shiner tube was longer than for the Crosby capsule (17 minutes as against 8 minutes). For these two reasons they preferred the Crosby capsule, though they regarded the capsule as too large to pass through the pylorus of infants under the age of 18 months. They encountered no complications in more than 70 biopsies in children. Since their paper was published a fatal case of peritonitis in a child of 18 months has been reported (Shackleton and Haas, 1962) after the use of the Crosby capsule. Another case of peritonitis after the use of the Crosby capsule in a woman aged 22 has been reported (Struthers *et al.*, 1963). Crosby (1963) pointed out that the instructions issued with the capsule stated that in order to obtain a superficial specimen of mucosa the pull on the syringe should be quick and strong, and if a slow gradual pull was used a specimen of greater depth would be obtained.

More than 80 further biopsies have been performed in the Birmingham Children's Hospital since the first account was published, and in three patients complications have occurred. In one case the capsule remained attached to the intestine for more than 24 hours (patient of Dr. O. H. Wolff) and in another the child had a pyrexial reaction, abdominal pain, and what appeared to be a localized ileus of the small intestine. The third child was suffering from a severe malabsorption syndrome with hypocalcaemia and tetany and developed peritonitis after the biopsy. This settled without laparotomy, but for two or three days the patient's condition gave rise to anxiety concerning diagnosis and therapy.

Biopsy of the small intestine, like hepatic and renal biopsy, cannot be undertaken without some hazard. Experience is obviously required in those making small-intestinal biopsies, together with close observation of the patient for 48 hours after the operation. The more severe and the more prolonged the coeliac disease the thinner will be the intestinal wall and the greater the danger of perforation. If upper-abdominal pain occurs after biopsy then the patient should be treated for a suspected perforation. Dr. Astley has recently used the new capsule described by Read *et al.* (1962) and finds it an improved model in at least two respects. However, in our experience this new capsule does not make a smaller bite than the earlier model. A similar model, with a smaller aperture, may provide a safer instrument for use in children. The slightly increased hazard of any type of Crosby capsule has to be weighed against the higher failure rate (in our hands) and the occasional specimen inadequate for examination when the Shiner or Rubin tube is used.

We still regard the change in the intestinal mucosa as the best criterion for the diagnosis of coeliac disease. The response to a gluten-free diet will provide a presumptive diagnostic answer, and relapse on a gluten-containing diet will dispose of the dilemma of *post hoc* or *propter hoc*. These procedures, however, require much time and expert observation. In our own clinic (and occasionally as we know from patients coming from expert colleagues) there are patients in whom a biopsy has not been made and in whom the diagnosis of coeliac disease was eventually discarded, and others in whom the diagnosis of coeliac disease was ultimately made after a long period of uncertainty. Any disease which carries a lifelong therapy—diabetes, pernicious anaemia, hypothyroidism—demands of the physician certainty, not presumption, in diagnosis.

Essential Diagnostic Procedures

Since any one investigation, other than that of the mucosal biopsy, may give an uncertain result, a small group of procedures must be performed to establish the diagnosis of coeliac disease in children. To prove the steatorrhoea, the excretion of fat in the stools must be measured; to establish malabsorption in the upper part of the small intestine the D-xylose-excretion test should be done; and the demonstration of dilatation of the small intestine by radiography gives useful information, readily obtained. Failing a biopsy, remission on a gluten-free diet and relapse on a gluten-containing diet provide the necessary therapeutic confirmation of the diagnosis.

Management of Coeliac Disease in Childhood

The essential part of the management of coeliac disease is the provision of a diet free from gluten, and therefore the avoidance of wheat and rye flour. Gluten-free flour can be easily obtained (and it may now be prescribed by doctors on E.C. 10), but mothers who live in cities usually prefer to buy gluten-free bread and biscuits. Children offer no objection to the diet, and when they break it it is either because of the attraction of gluten-containing foods or their dislike for rules of behaviour which separate them from their siblings and friends. Some parents find the continuing maintenance of these dietetic prohibitions more difficult than do others; they require, and deserve, the continued encouragement and support of doctors, dietitians, and health visitors.

Once the diagnosis has been made, and the treatment understood, the chief duty of the doctor, whether in the clinic or the consulting-room, is to assess the child's nutritional progress. In practice this means the measurement of height and weight and the observation of sexual development. So far as the value of the observations is concerned, one may say, in exaggeration, that what is not recorded has not been observed and what is not charted has not been measured. Measurements frequently recorded—longitudinal records to study height and weight velocities—are required. An increase or decrease in these velocities is thus easily determined and can be correlated with a relevant situation—enhanced appetite, adolescent growth spurt, diarrhoea, illness, emotional disturbance, breaking

the diet, and so forth. The best charts available for British children are those prepared by Tanner (1958), to be obtained from the Institute of Child Health, Great Ormond Street, London W.C.1.

Adherence to a gluten-free diet produces a full clinical remission within one to two years, and with the return of satisfactory nutrition the absorption tests return to normal. If the gluten-free diet is strictly followed small-intestinal radiography and the mucosal change as revealed by biopsy will also become normal (Anderson, 1960 ; Cameron *et al.*, 1962). A full clinical remission can be maintained in some children when they are restored to a gluten-containing diet, after varying periods on a gluten-free diet (Sheldon, 1959). These children, despite the fact that they are in good nutritional health and their absorption tests are normal or nearly normal, are in fact still suffering from coeliac disease, as may be shown by some dilatation of the small intestine and by the abnormal mucosal appearances on biopsy (Cameron *et al.*, 1962). The recognition that coeliac disease is cured only as long as gluten is removed from the diet poses problems in the management of these children. The problems can be stated in the following questions. What are the clinical criteria which justify the reintroduction of a gluten-containing diet ? At what age may this be successfully attempted and after what period on a gluten-free diet ? What are the personal and social conditions which make the reversion to a normal diet justifiable ? What are the clinical appearances which require a gluten-free diet to be resumed ?

The histories of 41 children suffering from coeliac disease have been analysed in order to attempt answers to these questions. They are divided into the following groups: (1) Those who have made satisfactory clinical progress on a gluten-containing diet—*eleven children.* (2) Those who have been tried on a gluten-containing diet but who have been returned to a gluten-free diet because their progress was judged to be unsatisfactory—*nine children.* (3) Those whose dietetic control was thought to be inadequate and who were therefore not transferred to a gluten-containing diet—*ten children.* (4) Those whose period on a gluten-free diet had been less than four years—*eleven children.*

Group 1. Eleven Children Transferred to a Gluten-containing Diet Making Satisfactory Progress

The average period during which these 11 children had been maintained on a gluten-free diet before being transferred to a gluten-containing diet was five and a half years, with a range of one to eight and a half years. Only one of these children (Case 34) had been maintained on a gluten-free diet for less than four years. The mean age at transferral to a gluten-containing diet was 11 years, with a range of six and a half to sixteen and a half years. Three of these children (Cases 2, 8, and 44) were under the age of 10 years at the time of transfer to a gluten-containing diet. The average period of observation subsequent to the institution of a gluten-containing diet was two and three-quarters years, range one and a half to seven years.

The history of one of these children illustrates several problems in the management of coeliac disease.

Case 34.—A girl, now aged 13½ years, was diagnosed as suffering from coeliac disease at the age of 13 months. Although a gluten-free diet was prescribed after her three admissions at the ages of 13 months, 18 months, and 5 years 9 months it was never maintained for more than six months (5 years 9 months to 6 years 3 months). In-patient investigations on the third (5 years 9 months), the fourth (8 years 8 months), and the fifth (10 years 5 months) admissions showed a normal fat absorption on each occasion and all other diagnostic criteria were negative (except for the mucosal biopsy). Despite the normal results to investigations there was a story of recurring poor health with intermittent diarrhoea. At 10 years of age, when she had been on a normal diet for three years nine months, her weight was on the 10 percentile and her height on the 25 percentile. The biopsy report at this time showed moderately severe changes of coeliac disease with no villous projections, but the crypts and the brush border were fairly well preserved. She was allowed to continue on a normal diet from this time and her health has steadily improved in the last three years. Both her weight and her height have climbed to the 75 percentile. The menarche occurred at the age of 12 years 4 months. Attacks of diarrhoea now happen very rarely.

Comment.—This patient's story illustrates several aspects of the management of coeliac disease. Firstly, that the abnormal mucosa may be the only positive finding in the full range of investigations. Secondly, that coeliac disease may be active despite the fact that absorption tests, including fat, are within normal limits. Thirdly, that there comes a time in the life of most patients when their nutrition greatly improves despite the taking of a normal diet, and this happens usually between 9 and 14 years of age. There can be little doubt as one studies this girl's growth charts and her in-patient and out-patient records that her health and development from infancy to the age of 10 years would have been improved by the taking of a gluten-free diet, but from the age of 10 years onwards a gluten-free diet could have made little difference to her nutrition.

Eight of these 11 children were submitted to intestinal biopsy while they were in full clinical remission on a gluten-containing diet, and in these eight children the biopsies showed the changes of coeliac disease, sometimes of a severe degree. In none of our patients has the intestinal mucosa been normal when gluten was being taken in the diet. Nine of these 11 children had a barium meal and follow-through while on a normal diet and in only two of them was there no dilatation of the small intestine reported.

By contrast with the structural abnormality of the small intestine, the absorption tests in these children while taking a normal diet were usually normal. Only two of them showed a slight excess of fat in the faeces, and in one of them the xylose-absorption test was in the equivocal range (18% excretion).

The dissociation between the abnormality of the small intestine demonstrated both by barium meal and by biopsy and the predominantly normal absorption tests gives laboratory confirmation of the good nutritional state of these children. Why the damaged mucosa does not, in the majority of patients and in the second decade of life, continue to interfere seriously with absorption remains one of the many unsolved problems of coeliac disease.

The nutrition of these 11 children has continued to be good on a gluten-containing diet. Four of them lost some weight at the change-over, but six months later their weight had regained the channel in which they had been travelling. In two of them height velocity fell away in the first six months but was regained in one year. In the five girls over the age of 12 years the average age of the menarche was 12 years 9 months. The sexual maturation of the three boys over the age of 14 years was well within average limits.

Group 2. Nine Children Transferred to a Gluten-containing Diet Whose Subsequent Progress was Unsatisfactory

The average age of these nine children at transference to a gluten-containing diet was 8 years, with a range from 5 to 10½ years. The average period on a gluten-free diet before the change-over was four and three-quarters years,

with a range from 19 months to eight years. The period on a gluten-containing diet before transfer back to a gluten-free diet averaged two years, with a spread from six months to three years. The further period of observation on a gluten-free diet averaged two and a half years.

There is therefore little difference between groups 1 and 2 in regard to the period on a gluten-free diet (average five and a half and four and three-quarters years respectively), but there is a considerable difference between the ages at transfer (group 1, average 11 years; group 2, average 8 years).

The reasons for the return of these children to a gluten-free diet are summarized in the following brief case histories.

Case 1.—A gluten-containing diet was resumed in this boy at the age of 7½ years and continued for one year. He became irritable and anorexic for a few months, but these symptoms later corrected themselves. During the year his weight fell from the 75 percentile to the 50 percentile and his height from the 50 to the 40 percentile. Investigation after one year showed that the mucosa which had been normal in two biopsy specimens (1960, 1961) during the gluten-free period showed moderate coeliac changes on a gluten-containing diet.

Case 4.—At the age of 10½ years this boy was given a normal diet, after which his height remained stationary for nine months and his weight advanced as expected for three months but remained stationary for the next six months. During this period his absorption tests became abnormal, and the intestinal mucosa which had been normal showed severe coeliac change.

Case 15.—After five and a half years on a gluten-free diet, this boy was given a normal diet at the age of 7 years 3 months for nine months. His height velocity declined from the 75 to the 50 percentile and his weight from the 90 to the 75 percentile.

Case 16.—This boy was on a gluten-free diet from the age of 3 to 7 years. In 1958 he was investigated in another clinic, where he was thought not to be suffering from coeliac disease. He was reinvestigated at the Birmingham Children's Hospital in 1961, when a biopsy showed a grossly abnormal mucosa, and radiography demonstrated dilatation of the small intestine. There was mild steatorrhoea, but the response to the xylose test was normal. On a gluten-free diet for the last year his height has climbed from the 3 to the 10 percentile. His father's height is 61½ in. (156 cm.) and his mother's 60 in. (152 cm.).

Case 19.—In this boy, now aged 14½ years, coeliac disease was diagnosed at the age of 2 years. He continued on a gluten-free diet until he was 10½ years. His height was on the 10 percentile, and his weight on the 3 percentile. On a gluten-containing diet for one year his weight remained stationary and his height fell away 1 in. (2.5 cm.) below the 10 percentile. On a gluten-free diet (three years) his height has advanced to the 25 percentile and his weight to the 10 percentile (including the period of the adolescent growth spurt).

Case 20.—This girl, now aged 12½ years, was diagnosed as suffering from coeliac disease at the age of 3 years. There have been two periods on a normal diet from the age of 5 years 2 months to 5 years 10 months and from 8 years 4 months to 9 years 4 months. On each occasion there was actual weight loss, and the height velocity fell below the 10 percentile, in which her linear growth had been travelling.

Case 26.—This boy, now aged 13¼ years, was diagnosed as suffering from coeliac disease at the age of 4½ years. During six months on a gluten-containing diet at the age of 9 years he lost weight and gained no height. Judging by the clinical records and the evidence from two periods of in-patient investigation (including two biopsies) it has required two years of a gluten-free diet to restore a normal state. His weight and height are now on the 50 percentile.

Case 29.—This girl of 13½ years was diagnosed as having coeliac disease at the age of 8 years. After 20 months on a gluten-free diet the absorption tests were slightly abnormal, the small intestine was dilated, and the intestinal mucosa was grossly abnormal. She returned to a gluten-containing diet for 15 months, when her height gain was 1½ in. (3.8 cm.) (expected height gain 2½ in.; 6.4 cm.) and she had gained no weight (expected weight gain 12½ lb.; 5,670 g.). In the subsequent three years on a gluten-free diet her height has advanced from the 25 to the 75 percentile and her weight from the 50 to the 90 percentile. The menarche was in June, 1962, and the acceleration of height and weight is to some extent associated with the adolescent growth spurt.

If the indications for allowing a gluten-containing diet are doubtful, there can be little controversy concerning the need to return to a gluten-free diet. Weight and height retardation which is not corrected after a few months on a gluten-containing diet provides the essential clinical criterion. In these eight patients the clinical relapse was confirmed by abnormal absorption tests. Satisfactory progress in all patients followed the resumption of a gluten-free diet.

Group 3. Ten Children with Inadequate Dietetic Control Who Have Therefore not been Transferred to a Gluten-containing Diet

These 10 children have been observed for an average of eight and a half years, with a range of five to eleven and a half years. They have not adhered with continuous strictness to their diet and their attendance at the follow-up clinic has usually been irregular. During the periods when they have been persuaded to a closer attention to a gluten-free diet their height and weight have showed a notable advance. In general it can be assumed that their dieting has never been sufficiently strict to allow healing of the intestinal mucosa, though the recurring persuasion and encouragement at the clinic have in most cases ensured reasonable nutrition.

The following description of a boy now aged 16 years is characteristic of the group.

Case 13.—He was diagnosed as suffering from coeliac disease at the age of 7 years. From then until he was aged 12 years 8 months he and his parents were irresponsible about his diet. His height in 1959 was on the 3 percentile and his weight on the 10 percentile. The absorption tests done in 1959, 1960, and 1961 (aged 13, 14, and 15 years) gave normal results, but the barium-meal examination both in 1959 and in 1961 showed dilatation of the small intestine and the biopsy showed severe damage to the intestinal mucosa. At the age of 15½ years pubertal changes began with the growth of pubic hair, but it seems unlikely that his sexual development will be complete before the age of 17 to 18 years.

By insisting on the need for a gluten-free diet in such children we may hope to diminish the degree of their malnutrition. Some restriction of gluten intake is preferable to the ingestion of the normal gluten load.

Group 4. Eleven Children Who Have Been on a Gluten-free Diet for Less Than 4 Years

These 11 children fall into two classes. (*a*) Five children who were treated inadequately for some years from the time of diagnosis and whose period on a strict gluten-free diet has been less than four years. Their average age is 8 years, with a range from 4½ to 13 years. The average period on a strict gluten-free diet is two years, during which time their progress has been satisfactory. (*b*) Six children in whom the average age of diagnosis was 1 year 10 months, and the average period on a gluten-free diet has been two years. In five of these six children progress has been completely satisfactory; in one of the six there is uncertainty whether the diet is strictly gluten-free.

Age of Transfer to a Gluten-free Diet

The only important difference between the children who have been successfully transferred to a gluten-containing diet and those children in whom the change-over was unsuccessful is the age at which the attempt was made. Of the 11 children in the successful group only three were under the age of 10 years at the time of transfer; of the unsuccessful group six of the eight children were under the age of 10 years when the attempt was made. However, when the clinical, chemical, radiographical, and histological findings are compared in the two groups, there are no other reliable criteria on which judgment could be founded regarding the probable results of the change to a normal diet.

Sheldon (1959), having treated 95 children suffering from coeliac disease with gluten-free diets for periods of one to three years, found that 44 of them continued to grow satisfactorily when they were given normal diets, while 23 relapsed. The other 28 children remained "persistently more than one standard deviation below the average height appropriate to their age," whether on a gluten-free or on a gluten-containing diet. These children Sheldon regarded as inheriting small stature. It is apparent that there is one major difference between his cases and ours in that he makes no mention of any children in his group who were considered to be erring in dietetic control, while in our patients approximately one-quarter of them were not strict in their diets. Both series, however, demonstrate that in a number of patients after a varying number of years it is possible to restore them to a gluten-containing diet and to maintain them in good nutrition, though no principle develops in either series which proffers a certain signpost to a successful change-over. Only the Hunterian advice emerges of "Why not try the experiment?" The evidence given here that even those children who maintain perfect nutrition on gluten-containing diets are nevertheless still suffering from coeliac disease, despite an adequate absorption of nutrients, must raise in some minds the contrary question of "Why try the experiment?"

"Why Try the Experiment?"

The paediatrician regards it as his duty to send his patients forward into adult life with their harmful dispositions, whether of psyche or soma, recognized and controlled so far as may be. There is no known way of eliminating the toxic reaction to gluten which develops in susceptible individuals, other than the withholding of wheat and rye flour from the diet. Yet in many patients, after a period of treatment, the taking of gluten continues to damage the mucosa but does not interfere with health. Are such patients to endure the personal and social discomforts of a gluten-free diet simply to preserve the health of the mucosa of the small intestine? This is a question only to be answered in the context of the individual patient, and the physician must be sure that he does not answer it according to his own prejudices—as a puritan who believes in the virtues of self-denial, as an ascetic who takes pleasure in mortifying other people's flesh, as a perfectionist who pursues the way of complete rectitude for himself and his patients—or, alternatively, as an easy-going epicure who prefers to give advice agreeable to his patients. Auden begged for a doctor who should be

> "An endomorph with gentle hands
> Who will not make absurd demands
> That I abandon all my vices."

Bacon was exercised with this dilemma when he wrote: "Physicians are some of them so pleasing, and conformable to the Humor of the Patient, as they presse not the true Cure of the Disease; And some other are so Regular, in proceeding according to Art, for the Disease, as they respect not sufficiently the Condition of the Patient. Take one of a Middle Temper."

Our coeliac patients have already accepted from their nursery days upwards the rule that the confectionery delights of the table are not for them. They have taken to gluten-free bread, biscuits, and cake as easily as the infant takes to cod-liver oil. Many of them have learnt at home and at school to look on without envy while their relations and friends swallow with gusto Norfolk dumplings, Yorkshire pudding, Bakewell tart, and Dundee cake. Are their doctors now to encourage them to acquire tastes which may be harmful to them? On the other hand, for these children community life—in school, in canteens, at parties, and on holiday—must provide social difficulties that any normal individual would prefer to avoid. Life in the Services on a gluten-free diet is impossible. For some children and for some parents the hardships engendered by a gluten-free regime will be greater than for others.

Parents and children should be given the facts and should be encouraged to make their own choice. The experience of the last four years recorded here inclines me to say that it is better to postpone this discussion until after the child is 10 years of age, and if the doctor's advice is then asked he should usually give an opinion that a gluten-containing diet should not be tried till after puberty is fully established. We reasonably assume, although this cannot be regarded as a proved fact, that some restriction of gluten is better than no restriction at all; so that some temporary relaxation of diet for social reasons may certainly be permitted in adolescence.

There are two further considerations which influence parents and patients greatly. The first, that if the taking of a normal diet precipitates a relapse, and this possibility cannot be forecast, then a return to a gluten-free diet will be necessary. The second, that when taking a gluten-free diet the child ceases to be a patient, but that, when a normal diet is taken, regular, and indeed lifelong, medical supervision will be required.

Summary

The four important investigations in establishing the diagnosis of coeliac disease are (*a*) the estimation of fat in the stools; (*b*) a test of absorption in the upper part of the small intestine, and of the available tests the D-xylose excretion test is the most useful; (*c*) the radiography of the small intestine; and (*d*) the biopsy of the mucosa of the small intestine.

The method of small-intestinal biopsy and its difficulties are discussed and it is concluded that the coeliac change in the mucosa provides certain proof of coeliac disease. So far as our present knowledge goes, gross flattening of the villi is not caused by any other disease in children occurring in this country. The diagnostic alternative where a biopsy is not available is remission on a gluten-free diet and relapse on a gluten-containing diet.

To illustrate the management of coeliac disease the histories of 41 children are reviewed: 11 maintained satisfactory progress on a gluten-containing diet, 9 relapsed when resuming a gluten-containing diet, 10 were not sufficiently strict in their diets to justify the consideration of a normal diet, and 11 had been taking a gluten-free diet for less than four years. No criteria have been established for deciding in which children the transfer to a gluten-containing diet can successfully be made. Lacking these

criteria, it is advised that the gluten-free diet should as a rule be maintained till after puberty, although temporary relaxation of the diet may be allowed to adolescents for personal and social reasons.

I am grateful to my colleagues Dr. O. H. Wolff and Dr. B. D. Bower, who have allowed me to include some of their patients in this report. Dr. J. M. French and the late Mr. Harold Salt were responsible for the estimates of fat, and Miss S. Littlejohn for the D-xylose excretion tests. Dr. R. Astley provided the radiological opinions and also assisted the registrars, Dr. M. Hallowell, Dr. Colin Miller, Dr. A. C. K. Antrobus, and Dr. R. Glass with the biopsies. Dr. A. H. Cameron reported on the biopsy specimens of small-intestine mucosa. Sister D. Horler did much accurate ward work in the collection of urine and faeces.

REFERENCES

Anderson, C. M. (1960). *Arch. Dis. Childh.*, **35**, 419.
—— Townley, R. R. W., Freeman, M., and Johansen, P. (1961). *Med. J. Aust.*, **2**, 617.
Astley, R., and Gerrard, J. W. (1954). *Brit. J. Radiol.*, **27**, 484.
Brit. med. J., 1962, **2**, 1241.
Cameron, A. H., Astley, R., Hallowell, M., Rawson, A. B., Miller, C. G., French, J. M., and Hubble, D. V. (1962). *Quart. J. Med.*, **31**, 125.
Carter, C., Sheldon, W., and Walker, C. (1958–9). *Ann. hum. Genet.*, **23**, 266.
Carter, G. O. (1962). *Human Heredity*. Penguin Books, Harmondsworth, Middlesex.
Clark, P. A. (1962). *Gut*, **3**, 333.
Crosby, W. H. (1963). *Lancet*, **1**, 500.
Delory, G. E., Israels, S., and Jonasson, H. (1956). *J. Dis. Child.*, **92**, 24.
Gee, S. J. (1888). *St. Bart's Hosp. Rep.*, **24**, 17.
Hubble, D., and Littlejohn, S. (1963). *Arch Dis. Childh.* In press.
Jones, W. O., and di Sant'Agnese, P. A. (1963). *J. Pediat.*, **62**, 44.
O'Brien, D., Walker, D. M., and Ibbott, F. A. (1959). *Paediatrics*, **23**, 422.
Read, A. E., Gough, K. R., Bones, J. A., and McCarthy, C. F. (1962). *Lancet*, **1**, 894.
Shackleton, J., and Haas, L. (1962). Ibid., **2**, 989.
Sheldon, W. (1959). *Pediatrics*, **23**, 132.
Silverman, F. N., and Shirkey, H. C. (1955). Ibid., **15**, 143.
Struthers, J. E., Attwood, W. L., and Kern, F. (1963). *Lancet*, **1**, 447.
Tanner, J. M. (1958). In *Modern Trends in Paediatrics*, edited by A. Holzel and J. P. Tizzard, p. 325. Butterworth, London.
van de Kamer, J. H., Huinink, H. ten B., and Weyers, H. A. (1949). *J. biol. Chem.*, **177**, 347.

IMMUNOLOGICAL STUDIES IN THE POST-CARDIOTOMY SYNDROME

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The post-cardiotomy syndrome (P.C.S.) is an uncommon complication of heart surgery occurring after a latent period and recognized by fever, pleuropericarditis, raised erythrocyte sedimentation rate, and spontaneous resolution. Arthralgia and a tendency to relapse are less common features. Corticosteroid rapidly suppresses the disorder, and when used prophylactically prevents its appearance (Dresdale *et al.*, 1956). Mild symptoms are readily overlooked, especially when the onset is delayed for several weeks or months after operation.

The P.C.S. was first recognized as a complication of mitral valvotomy and was attributed to reactivation of rheumatic fever (Soloff *et al.*, 1953). However, its appearance after operation for congenital heart disease denied this aetiology (Ito *et al.*, 1958). It was also thought to be due to blood (or some foreign substance such as penicillin) in the pericardium, a view which was supported by reports of the P.C.S. as a complication of stab wounds of the heart (Segal and Tabatznik, 1960) and after implantation of a pacemaker (Dressler, 1962). However, it is now generally thought that a less direct process concerning hypersensitivity to antigenic material liberated by trauma is the more likely cause. Kaplan (1960) demonstrated a reaction between homologous heart tissue and factors in the serum of patients who had undergone mitral valvotomy. This suggested that trauma resulted in the production of autoantibodies, but his findings were not related to the P.C.S. Further support for this approach came from the work of Ehrenfeld *et al.* (1961), who found heart antibody-like factors in the serum of patients with different heart diseases, including one who had had mitral valvotomy and whose post-operative course was uneventful.

In this report we present the results of immunological tests on patients undergoing mitral-valve surgery, and we relate these to the subsequent clinical course. Our results strongly indicate the presence of a disturbed immunological mechanism in patients who develop the P.C.S.

Investigation

The Patients.—All of the patients studied, except one, had mitral valvotomy performed by the transventricular route (by Mr. Vernon Thompson or by Mr. Geoffrey Flavell). They were assessed pre- and post-operatively by us and with one exception have remained under close out-patient observation. Specimens of serum were taken from the patients pre-operatively, on or about the 10th and 30th post-operative day, and more frequently if the post-operative course was complicated. Tests were also made on blood from 12 patients after thoracotomy for non-cardiac surgery, from six patients after laparotomy, and on the sera from 35 healthy blood donors as controls.

The Test

We decided to use only the tanned-red-cell haemagglutination test in the present study. Fresh sheep cells were tanned by the method of Boyden (1951). Tissue extract was prepared by grinding fresh human auricular appendage (obtained at mitral valvotomy) with abrasive ("aloxite") in a solution of phosphate-buffered saline at *p*H 7.2. This was centrifuged and the supernatant fluid was diluted to approximately 1 in 20. The diluted tissue extract was then added to an equal volume of a 2% suspension of tanned red cells and allowed to stand at room temperature for 45 minutes. The sensitized cells were then washed three times with saline containing 1% guinea-pig serum at *p*H 6.4. The patient's serum and the guinea-pig serum were treated by heating to 56° C. for 30 minutes in order to remove complement, and by absorbing with fresh sheep red cells to remove non-specific agglutinating factors. The patient's serum was serially diluted with buffered saline and 1% guinea-pig serum, an equal volume of 2% sensitized red cells being then added to each dilution. Control tests were carried out by adding sensitized cells to saline without patient's serum and by adding tanned but not sensitized cells to patient's serum.