The management of chronic or recurrent diarrhoea in childhood

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Introduction

A generation ago, the paediatrician confronted with a child suffering from chronic or recurrent diarrhoea had few specific diagnostic alternatives to consider, and few laboratory tests with which to explore them. The treatment he could offer was largely confined to empirical alterations of the patient’s diet. The paediatrician of today has a much more formidable task. He is aware that the list of diseases which may cause diarrhoea is now extensive (Table 1) and is still growing rapidly. He knows, too, that specific and effective treatment is available for many of these diseases, so that accurate diagnosis is essential. He must have some knowledge of the advantages and limitations of the many investigatory procedures that may be relevant to diagnosis, if he is to plan his course of investigation efficiently.

The approach to the management of diarrhoea in childhood that follows is based on the author’s experience with patients of predominantly Caucasian stock, drawn from communities with good living standards, in a temperate climate. In other racial, economic or geographical settings, disease patterns may be quite different, and require some modification of priorities of special investigation that are outlined here. Discussion will be mainly confined to those diseases where diarrhoea is one of the principal presenting symptoms, and will omit reference to situations where diarrhoea is an easily explicable, late or unusual symptom, as it is in liver disease (Burke & Danks, 1966), Crohn’s disease (Rubin & Lambie, 1967), hookworm infestation, Zollinger–Ellison syndrome (Rosenlund, 1967), acrodermatitis enteropathica (Margileth, 1963) and so on.

Clinical assessment

The importance of careful clinical assessment of any patient with diarrhoea has not diminished with the increasing availability of laboratory aids to diagnosis. As Anderson (1966) has pointed out ‘... the clinician still remains the most readily available and least expensive investigatory tool’.

Because the causes of diarrhoea are so diverse (Table 1), a comprehensive clinical history is always required, but some areas of the history deserve special emphasis. Obviously, detailed enquiries should be made about bowel habits, and characteristics of the stools. Careful questioning about the age of onset of diarrhoea, fluctuation in severity with dietary or other environmental changes, and stool features such as odour, consistency and the presence of blood or mucus may provide information valuable for shaping the course of subsequent investigation.

The patient’s growth progress always deserves careful scrutiny, and any past records of physical measurements should be plotted on a percentile chart. Study of the patient’s growth pattern will often clarify the time of onset of his disease, and poor growth usually means that investigation should not be deferred. Enquiries about the patient’s temperament, and the emotional ‘climate’ of the family should never be neglected; paediatricians need no reminding of the importance of a careful family history.

On clinical examination, special attention should be given to the patient’s abdomen. Abdominal distension, surgical scars, visible peristalsis or palpable masses may influence the plan of investigation. A rectal examination is indicated if ‘spurious’ diarrhoea is suspected.

The clinician should personally inspect one or more of the patient’s stools, as a routine part of his clinical examination. Descriptions of the stools given by the mother may be unreliable, especially when the patient is the only child in the family, and the mother has no previous knowledge of normality. The significance of some stool characteristics is outlined in Table 2.

Children needing no immediate investigation

There are two causes of diarrhoea that the physician can usually diagnose with confidence on clinical grounds alone, and where special investigations can be omitted or deferred with little risk. These are firstly, ‘spurious’ diarrhoea secondary to chronic constipation, and secondly ‘chronic non-specific diarrhoea’. Each of these disorders is not uncommon, but as with many diseases of low
### Table 1. Causes of diarrhoea

<table>
<thead>
<tr>
<th>Disorders of the small intestine</th>
<th>Most useful diagnostic test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coeliac disease</td>
<td>Intestinal biopsy.</td>
</tr>
<tr>
<td>Sugar malabsorption</td>
<td>Tests of stool for pH and reducing substances</td>
</tr>
<tr>
<td>- Disaccharidase deficiency, primary or secondary</td>
<td></td>
</tr>
<tr>
<td>- Monosaccharide malabsorption, primary or secondary</td>
<td></td>
</tr>
<tr>
<td>Anatomical abnormality</td>
<td>Barium studies</td>
</tr>
<tr>
<td>- Congenital or post-surgical</td>
<td></td>
</tr>
<tr>
<td>- Malrotation, blind loop, fistula, resection and so on</td>
<td></td>
</tr>
<tr>
<td>Intestinal lymphangiectasis (Waldmann, 1966)</td>
<td>Microscopy, radiology and serum protein studies</td>
</tr>
<tr>
<td>Infestation or infection</td>
<td>Biopsy</td>
</tr>
<tr>
<td>- Giardia lamblia, tuberculosis</td>
<td>Clinical features</td>
</tr>
<tr>
<td>Kwashiorkor (Stanfield, Hutt &amp; Tunnicliffe, 1965)</td>
<td>Biopsy, serum β-lipoproteins, search for acanthocytes</td>
</tr>
<tr>
<td>a-β-Lipoproteinaemia (Salt et al., 1960; Isselbacher et al., 1964)</td>
<td>Serum electrolytes</td>
</tr>
<tr>
<td>Chloridorrhoea with alkalosis (Owen, 1964; Tucker et al., 1964; (Evanson &amp; Stanbury, 1965)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disorders of the pancreas</th>
<th>'Sweat test'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis of the pancreas</td>
<td>Haematology</td>
</tr>
<tr>
<td>Syndrome of pancreatic insufficiency and bone marrow dysfunction</td>
<td>Estimation of pancreatic enzymes</td>
</tr>
<tr>
<td>Specific deficiency of trypsinogen</td>
<td>Estimation of pancreatic enzymes</td>
</tr>
<tr>
<td>Specific deficiency of pancreatic lipase</td>
<td>Estimation of pancreatic enzymes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disorders of the large intestine</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>'Spurious diarrhoea' Constipation with overflow</td>
<td>Barium enema, rectal biopsy</td>
</tr>
<tr>
<td>Hirschsprung's disease (Nixon, 1964)</td>
<td>Barium enema</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Sigmoidoscopy</td>
</tr>
<tr>
<td>Milk-induced colitis</td>
<td>Clinical trial of milk exclusion</td>
</tr>
<tr>
<td>Enterocolitis of infancy</td>
<td>See text</td>
</tr>
<tr>
<td>Infection or infestation</td>
<td>Microscopy and culture of stools</td>
</tr>
<tr>
<td><em>Salmonella, amoebic</em> (Kagan et al., 1967)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic non-specific diarrhoea</td>
</tr>
<tr>
<td>Chronic infection, Pulmonary, renal tract</td>
</tr>
<tr>
<td>Endocrine</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
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<tr>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td>Metabolic</td>
</tr>
<tr>
<td>Renal acidosis</td>
</tr>
<tr>
<td>Ganglioneuroma</td>
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<tr>
<td>Drugs</td>
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</tbody>
</table>

### Table 2. Significance of some characteristics of the stools of patients with diarrhoea

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pale colour</td>
<td>Suggests malabsorption, liver disease</td>
</tr>
<tr>
<td>Mucus</td>
<td>Suggests infection, colitis, emotional factors</td>
</tr>
<tr>
<td>Blood-staining</td>
<td>Suggests infection or colitis</td>
</tr>
<tr>
<td>High fluid content</td>
<td>Suggests sugar intolerance, ganglioneuroma, chloridorrhoea</td>
</tr>
<tr>
<td>Oiliness ('melted butter' appearance) and very offensive odour</td>
<td>Suggests exocrine pancreatic disease, especially cystic fibrosis</td>
</tr>
<tr>
<td>Pale, bulky appearance, with metallic sheen</td>
<td>Suggests coeliac disease</td>
</tr>
<tr>
<td>Presence of vegetable matter</td>
<td>Of little diagnostic significance</td>
</tr>
</tbody>
</table>
morbidity and mortality no accurate estimates of prevalence are available.

'Spurious' diarrhoea secondary to constipation

Characteristically the patient is a child of preschool or primary school age who presents with faecal soiling. Co-existent abdominal distension may superficially suggest a diagnosis of malabsorptive disorder, but careful assessment should uncover a previous history of long-standing constipation, a normal growth pattern, and the presence of faecal masses on abdominal or rectal examination. Treatment with laxatives usually stops soiling rapidly, but must be continued for many months, and must be accompanied by sympathetic explanation to and reassurance of the parents (Coekin & Gairdner, 1960; Davidson, Kugler & Bauer, 1963; Berg & Jones, 1964).

Chronic and non-specific diarrhoea (irritable colon of childhood)

Characteristic features of this disorder are an onset at from 6 months to 1 year of age of recurrent or persistent mild diarrhoea with stools containing mucus or vegetable fragments, but unaccompanied by abdominal distension or growth retardation. A psychosomatic basis seems likely (Cohlan, 1956; Davidson & Wasserman, 1966) and the mothers of children with this syndrome perhaps tend to have obsessive types of personality. Working mothers, notably those with professional jobs, are disproportionately frequent in this group.

Investigation of children with a clinical pattern that conforms closely to that just outlined, and especially those whose growth has been adequate, is most unlikely to reveal any organic disorder. Despite this, a limited number of investigations such as microscopy and culture of the stools, and measurements of faecal fat excretion may prove useful to consolidate the reassurance that the clinician can offer the parents. Not uncommonly, such parents have previously experienced various types of advice and treatment without success, and one sometimes senses their unwillingness to be reassured unless special tests are done. If the patient is admitted to hospital for investigation, he may not pass a stool for a day or two, which pattern strongly reinforces the diagnosis!

Treatment of chronic non-specific diarrhoea with drugs is of little value, and no restriction of diet is necessary (Davidson & Wasserman, 1966). The parents should be advised that symptoms will subside within a year or two, and perhaps more quickly if stresses on the child can be relieved.

The use of special investigations when indicated

When the clinical features are sufficiently characteristic of a disease entity to allow a confident provisional diagnosis, then the investigatory procedure that will most definitively confirm that diagnosis should be carried out without delay. The use of 'screening' tests is pointless in such circumstances. For example, typical clinical features of cystic fibrosis indicate the need to estimate sweat electrolyte levels, and this need will not be diminished if results of simpler but less reliable 'screening' tests such as trypsin activity of the stools, or the Shwachman plate test (Shwachman & Gahm, 1956) prove negative. The most appropriate tests in various disorders are indicated in Table 1.

The course of investigation

When the clinician cannot feel confident that his patient suffers from one of the disorders already mentioned, or that the clinical features demand an outstanding specific test, he must decide which investigations he will use, and in what order. His course of investigation is influenced not only by various clinical features, but also by the simplicity and diagnostic sensitivity of the tests available. Some comments follow concerning the advantages and limitations of various investigatory procedures.

Miscellaneous simple tests

A number of tests, which are simple to perform, and which not infrequently provide important diagnostic information, can be recommended for virtually routine use.

Tests on stool specimens

Microscopy of stool specimens may establish the presence of parasitic infestation, if parasites or their cysts or ova are present (Kagan et al., 1967) or indicate probable pancreatic insufficiency if numerous fat globules are seen (Anderson, 1966).

Stool culture occasionally yields an organism of the Salmonella group which, especially in the first year or two of life, can cause chronic diarrhoea.

Tests for reducing substances in the stools, and for stool pH

These should be done when sugar malabsorption is suspected as a cause of diarrhoea. In childhood, when diarrhoea is due to one of the various types of sugar malabsorption, the stools are typically fluid, are of low pH, and are passed with a lot of gas (Townley, 1966). Increased levels of reducing substances shown by a simple test using 'Clinitest' tablets, and a low pH on testing with pH paper (Kerry & Anderson, 1964), indicate that the diarrhoea is due at least in part to sugar malabsorption.
Chromatography of a stool specimen to identify the offending sugar or sugars is indicated if these tests are positive (Durand, Martino & La Medica, 1962).

Haematological and other tests

Simple haematological tests including haemoglobin estimation, white cell count, and examination of a blood film are nearly always justifiable, since haematological changes occur in many of the diseases that can cause chronic diarrhoea. If results of such tests are abnormal more detailed haematological investigation may be called for.

Other investigations, such as microscopy of the urine and tuberculin testing will reveal abnormalities much less frequently than haematological tests. However, they deserve almost routine use since they are simple to perform, and since an abnormal result will often have considerable diagnostic importance.

More complex investigatory procedures

Tests of intestinal absorption

Abnormal digestion or absorption of one or more nutrients occurs in many of the diseases which cause diarrhoea, and many different types of laboratory tests have been proposed as useful indices of digestion and absorption.

Abnormal absorption of fat was one of the first biochemical disturbances to be recognized in some patients with chronic diarrhoea (Herter, 1908). Indeed, until quite recently, the terms 'steatorrhoea' (used here to mean increased faecal fat excretion) and 'malabsorption' were used almost synonymously. Now it is realized that malabsorption of other nutrients may occur in the absence of steatorrhoea, but such cases are unusual, and assessment of fat absorption is still the best index of absorption and digestion in general.

Tests of fat absorption

Faecal fat excretion: Some fat (up to 1·5 g/day) can be found in the stools of normal children who are fasting or taking a fat-free diet (Anderson, 1966).

Faecal fat output tends to rise as dietary intake of fat increases, but such is the reserve capacity of normal children to digest and absorb fat that even with liberal intakes of the order of 100 g fat/day the average daily excretion of faecal fat is 4·5 g or less. In view of the slight but definite tendency of faecal fat excretion to rise with dietary fat intake, some workers have preferred to perform 'fat balance studies', in which measurements of fat intake, as well as output, are made, and results are expressed as the percentage of intake which has been absorbed.

Normally the percentage coefficient of fat absorption should exceed 90% (Weyers & Dicie, 1957). However, results of fat balance studies expressed as a coefficient of fat absorption, make no provision for the amount of fat derived from endogenous sources, and require careful measurements of dietary fat intake during the period of stool collection.

In practice, so long as an adequate amount of fat is being ingested (40–50 g/day, or more), the absolute level of the average daily excretion of fat proves just as reliable an index of steatorrhoea as does the coefficient of fat absorption (Crowe & Blackburn, 1956; Cooke & French, 1958). This means that accurate measurements of fat intake are unnecessary.

Although faecal fat excretion is a sensitive index of intestinal absorption, its measurement involves some practical difficulties. Since the level of faecal fat may vary considerably from day to day, results of analysis of isolated specimens of stool are of no value. Steatorrhoea cannot be excluded, and rarely can be established, unless specimens collected for at least 3 days are analysed. In borderline cases, collection periods of up to 8 days may be necessary to provide a reliable average value of faecal fat excretion. Also, many laboratory technicians are reluctant to deal with faecal specimens.

Many attempts have been made to find alternative ways of assessing fat absorption that circumvent these practical disadvantages. Various tests of fat absorption, based on changes in blood level or urinary excretion of fat (Osmon, Zinn & Wharton, 1957; Kabler, Atwood & Schilling, 1959), or a fat-soluble substance (Wenger, Kirsner & Palmer, 1957; McCoord et al., 1948) that has been given by mouth, can be carried out in a matter of hours, rather than days, but unfortunately none has proved as reliable as chemical estimation of faecal fat.

Measurement of urinary iodine after oral administration of lipiodol seems the best alternative at present available (Jones & di Sant'Agnese, 1963). Tests that employ measurements of blood or stool radioactivity after the patient has ingested radio-iodinated triolein or oleic acid have also proved disappointing (Pimparkar et al., 1961a, b).

Thus, despite the shortcomings already mentioned, chemical estimation of faecal fat excretion remains the most dependable index of fat absorption, and a useful pointer to intestinal absorption in general. Practical difficulties of getting technicians to work with faecal samples are reduced if proper facilities for handling and disposing of specimens are provided (Anderson, 1966). When the patient's stools are not too fluid, and when the parents are reliable, stool collections for faecal fat determination may be satisfactorily carried out at home.
Glucose absorption

Glucose tolerance curves tend to be flat in patients with impaired small intestinal absorption, but glucose is a poor test substance because its blood level is influenced by many factors other than absorption. Xylose is a much more useful test substance.

Xylose absorption

Absorption of xylose, a pentose not normally present in blood or urine, occurs in the proximal small bowel. The rate of xylose absorption can be gauged by measurements of blood levels, or of the amount excreted in the urine.

Urinary excretion of xylose seems just as sensitive an index of absorption as do blood levels (Christian sen, Kirsner & Ablaza, 1959; Chanarin & Bennett, 1962), and does not involve as much distress to the patient. In children, a dose of xylose of 15 g/m² of body surface (Clark, 1962) or 0.5 g/kg (Jones & di Sant’Agnese, 1963) may be used. Twenty per cent or more of the dose should be excreted in the urine within 5 hr of ingestion. Careful collection of urine is essential, but this may be difficult in infants, especially in girls.

In contrast to faecal fat excretion, urinary xylose excretion is normal in patients with diarrhoea due to exocrine pancreatic deficiency (Clark, 1962). However, in some diseases of the upper intestine, notably coeliac disease, xylose excretion is very nearly as sensitive a test as is estimation of faecal fat (Hubble & Littlejohn, 1963). When a diagnosis of disease of the upper small bowel is strongly suspected, the relative rapidity and simplicity of the xylose test make it sometimes preferable to measurement of faecal fat excretion. Xylose excretion measurements are also valuable for assessing the progress of coeliac disease and other disorders of the upper small intestine.

Disaccharide absorption tests

Simple methods of demonstrating the presence and nature of unabsorbed sugar in the stools have already been outlined. When the patient has fluid stools at the time of examination, these tests are usually adequate for routine management. However, when the patient does not have diarrhoea at the time of examination, but the history suggests a possible diagnosis of disaccharide malabsorption, disaccharide tolerance tests are indicated. The patient is given a dose of 1–2 g/kg of lactose or sucrose as a 10% aqueous solution. Normal children digest and absorb amounts of disaccharide of this order rapidly and virtually completely. Normal absorption is indicated by a rise in blood glucose comparable to that seen in a glucose tolerance test, and by the virtual absence of sugar in the stools. No symptoms are produced. Children with disaccharide intolerance develop diarrhoea within a few hours of the test dose, and the stools contain large amounts of unabsorbed sugar. The expected rise in blood glucose does not occur (Townley, 1966). The unreliability of blood glucose levels as a measure of sugar absorption has been mentioned previously, and stool tests should always be done as well as blood measurements.

Radiological tests

Plain X-ray of the abdomen is rarely helpful, and should not be a routine test. Very occasionally calcification may be seen in the pancreas or peritoneum, or also rarely, appearances suggesting intestinal obstruction may be found.

Barium meal and follow-through examination is most valuable for demonstrating congenital or post-surgical anatomical abnormalities. Barium studies have high priority when the patient with diarrhoea has associated symptoms suggesting chronic or intermittent intestinal obstruction, or has a past history of intra-abdominal surgery. In other circumstances barium studies are less likely to be rewarding, and should not be done as an early routine test.

Barium enema obviously has a place when colonic disease is suspected, and when confirmation of a diagnosis of malrotation is sought.

Ideally, the clinician should be present when the radiologist is performing contrast studies. When this is not practicable, he should ensure that the radiologist is adequately informed of the nature and site of abnormality that is suspected.

Other miscellaneous radiological tests are rarely useful for the diagnosis of a cause of diarrhoea, but may provide information about complications such as pulmonary involvement in cystic fibrosis, rickets in coeliac disease, and so on.

Small intestinal biopsy

Before techniques of intraluminal biopsy of the small bowel mucosa were developed slightly more than 10 years ago, little was known about mucosal morphology in various diseases of the small intestine. Studies of fresh mucosal tissue obtained at operations had been limited (Paulley, 1954) and interpretation of pathological changes in post-mortem specimens has always been difficult due to rapid autolysis of the mucosal surface (Miller, 1921; Thaysen, 1932).

The introduction of intraluminal biopsy allowed fresh specimens of mucosa to be obtained easily and with little risk, and our knowledge of structure and function of the small intestine has grown enormously with morphological and biochemical studies of biopsy specimens.
Biopsy instruments and their use

The various types of instruments available for performing intestinal biopsy, and their application and dangers have been reviewed elsewhere (Burman, 1963; Crosby, 1963; Sheehy, 1964; Rubin & Dobbins, 1965; Anderson, 1966; Partin & Schubert, 1966), and will not be discussed in detail here.

However, it should be mentioned that although intestinal biopsy can usually be carried out more easily and rapidly in children than in adults, the risks of serious complications of the procedure are probably higher, especially when the patient is an infant or is severely malnourished (Rubins & Dobbins, 1965; Partin & Schubert, 1966; Anderson, 1966). This investigation should not be undertaken casually, and is best left to an experienced operator who is conversant with all the problems that may be encountered (Townley & Anderson, 1967).

Treatment of biopsy specimens

Several precautions are advisable, if optimal diagnostic use is to be made of biopsy samples. Specimens should be quickly but gently removed from the biopsy instrument. Specimens which tend to be curled up, should then be gently flattened out, mucosal surface uppermost, on a piece of nylon mesh. This manipulation requires a pair of fine needles, good lighting and a magnifying lens or dissecting microscope. The specimen is next immersed in cold isotonic saline, and examined immediately with a dissecting microscope. A practised observer can usually predict quite accurately from the dissecting microscope findings what the histological picture will be (Holmes, Hourihane & Booth, 1961; Townley & Anderson, 1967), and the appearance of the specimen under the dissecting microscope helps to determine the relative proportions of the sample that should be diverted for different types of study (such as histology, histochemistry, electron microscopy, enzyme assay). Pieces of the specimen can be cut off with fine sharp scissors when more than one type of study seems desirable. Proper histological assessment usually requires the study of serial sections that have been cut perpendicular to the mucosal surface. More tangentially-cut sections are difficult to interpret (Brandborg, Rubin & Quinton, 1959).

Diagnostic applications of intestinal biopsy

Morphological abnormalities of the small intestinal mucosa may be found in a number of diseases that cause chronic diarrhoea in childhood, and biochemical abnormalities are demonstrable in others (Table 3). However, intestinal biopsy is not essential for the diagnosis or treatment of many of these diseases.

Coeliac disease, the first childhood disorder recognized to be associated with abnormal morphology of the small intestinal mucosa (Sakula & Shiner, 1957), remains the most important disease in which intestinal biopsy is indicated. Characteristic mucosal changes may be found in patients with coeliac

<table>
<thead>
<tr>
<th>Disease</th>
<th>Abnormality</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Histological abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>Loss of villous pattern, with 'flat' appearance of mucosa. Surface epithelial cells dark, irregular, multilayered</td>
<td>Changes most marked in proximal small bowel. The most sensitive index of coeliac disease, but not specific. Appearances may improve with treatment</td>
</tr>
<tr>
<td>Giardiasis</td>
<td>Parasites on surface or in mucosa</td>
<td></td>
</tr>
<tr>
<td>Infective diarrhoea</td>
<td>Inflammatory reaction in mucosa</td>
<td></td>
</tr>
<tr>
<td>Alteration of villous pattern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Excess mucus in Brunner's glands or in crypts</td>
<td>Inconstant</td>
</tr>
<tr>
<td>Iron-deficiency anaemia</td>
<td>Mild abnormalities of villous pattern</td>
<td></td>
</tr>
<tr>
<td>Kwashiorkor</td>
<td>Atrophic change, with loss of villous pattern</td>
<td></td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Varying degrees of abnormality of villous pattern</td>
<td>Changes may fluctuate with severity of symptoms</td>
</tr>
<tr>
<td>Intestinal lymphangiectasis</td>
<td>Dilated lymphatics, normal surface epithelium</td>
<td>Normal appearance does not exclude diagnosis, since distribution may be patchy</td>
</tr>
<tr>
<td>α-β-Lipoproteinaemia</td>
<td>Epithelial cells loaded with fat</td>
<td></td>
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<tr>
<td>B. Biochemical abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disaccharidase deficiency</td>
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<tr>
<td>Monosaccharide malabsorption</td>
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</table>

Table 3. Causes of diarrhoea associated with small bowel mucosal abnormalities
disease who are asymptomatic, and show no abnormalities of biochemical tests of absorption (MacDonald, Dobbins & Rubin, 1965) so that biopsy provides the most sensitive test available at present for the diagnosis of coeliac disease.

Thus, intestinal biopsy should be the first major investigation when the patient has clinical features typical of coeliac disease, and facilities to perform biopsy are adequate. (Hypoprothrombinaemia should, of course, always be excluded before biopsy is done.) In other circumstances haematological, biochemical and radiological investigation should precede biopsy.

Occasionally, intestinal biopsy may be indicated to confirm a diagnosis of biochemical abnormality such as disaccharidase deficiency or glucose–galactose malabsorption, that has been suggested by results of simpler investigations.

The 'sweat test'

An abnormally high concentration of sweat sodium and chloride is the most consistently found abnormality in patients with cystic fibrosis, and measurement of sweat levels of these electrolytes is the most reliable diagnostic test for this disorder. (Shwachman, 1962; Anderson, 1966; di Sant' Agnese & Talamo, 1967).

The concentration of both sodium and chloride in sweat from normal children should be less than 50 mEq/l, but in children with cystic fibrosis levels of greater than 60 mEq/l are usually found. There is very little overlap between the two groups in childhood, but slightly more in adult life, when the upper limit of the normal range tends to be higher (Anderson & Freeman, 1960). Apart from cystic fibrosis, few disorders, of which adrenal insufficiency is the commonest, cause elevated sweat electrolyte levels, so the 'sweat test' has a high degree of specificity.

Methods and pitfalls of 'sweat testing'

Several methods of 'sweat testing' are available. Usually sweating is induced by iontophoresis of pilocarpine (Gibson & Cooke, 1959) or intradermal injection of mecholyl (Anderson & Freeman, 1958) into the skin of the volar surface of the forearm. This skin area is then thoroughly washed with distilled water, and dried. A small square of filter-paper or gauze, previously rendered salt-free, and weighed, is placed on the skin and covered with a larger square of plastic sheeting, which is sealed around the edge with adhesive tape. After about an hour, the gauze is weighed to determine the amount of absorbed sweat, which is then eluted into distilled water. The sodium concentration of the eluate may be estimated by flame photometry, and the chloride level by titration.

This procedure has been outlined in some detail to emphasize the many possible sources of error. Misleading results, especially false positive results, may occur because blood or serum oozes from the intradermal injection site; if the skin is inadequately washed; if the gauze square is not free of salt initially or is contaminated by salt from the technician's fingers or instruments during the procedure; or if the plastic square is not sealed, allowing evaporation. Results are more likely to be inaccurate when only small volumes of sweat, less than 100 μl are analysed.

Results of sweat electrolyte estimations obtained from laboratories that perform only occasional sweat tests are often unreliable. Since the diagnosis of cystic fibrosis has such important prognostic and genetic implications, the patient with suspected cystic fibrosis should be referred to a laboratory where frequent sweat tests are carried out.

When results of a 'sweat test' done in a reliable laboratory are borderline (about 50–60 mEq/l of sodium or chloride), the test should be repeated. If the second result is dubious, estimation of pancreatic enzyme levels may help to clarify the diagnosis.

Pancreatic enzyme estimations

Duodenal intubation to obtain specimens of pancreatic juice for enzyme analysis is occasionally useful. This investigation was the main diagnostic test for cystic fibrosis before the sweat abnormalities in that disorder had been recognized, and is still sometimes helpful to aid the diagnosis of cystic fibrosis when results of sweat tests are equivocal.

In recent years, a syndrome of pancreatic insufficiency and haematological abnormalities, notably neutropenia, has been described, and sometimes a blood examination will indicate a need for pancreatic enzyme studies (Shwachman et al., 1964; Bodian, Sheldon & Lightwood, 1964; Burke et al., 1967).

Isolated deficiency of a pancreatic enzyme such as lipase (Sheldon, 1964; Rey et al., 1966) or trypsinogen (Townes, 1965; Morris & Fisher, 1967) is a rare cause of diarrhoea that can only be established by assays of pancreatic juice. Amylase activity of pancreatic juice is normally absent in the early months of life.

Comments on some clinical syndromes

The following comments about some of the disorders that may cause diarrhoea concern some aspects of these disorders that are relatively new, or are problematical or are of clinical importance.

Coeliac disease

This disorder is based on a toxic effect of wheat gluten on the small intestinal mucosa (Rubin et al.,
The mechanism of toxicity is uncertain (Townley & Anderson, 1967). The extent of mucosal damage varies from patient to patient, but the upper small bowel is always more severely involved than the lower (Rubin et al., 1960).

Symptoms begin some time after cereals have been introduced to the diet, and most patients present during the first few years of life when growth is normally most rapid. The usual history is of poor weight gain, often progressing to actual weight loss, the passage of pale, bulky frequent stools, and the development of abdominal distension. A change of temperament with apathy, irritability and fractiousness is often a striking feature that is seen much more frequently than in other diseases that cause comparable degrees of malnutrition. Pallor due to iron deficiency anaemia, anorexia and muscular hypotonia are other common features.

Much less frequently in childhood, although not uncommonly in adult life, coeliac disease may present with predominant features of an isolated deficiency, such as megaloblastic anaemia, oedema due to hypoproteinaemia, refractory iron-deficiency anaemia, or rickets (Townley & Anderson, 1967). The most definitive diagnostic test is intestinal biopsy. This investigation is essential before the patient is committed to the long-term, painstaking dietary management that is the main basis of treatment.

**Treatment**

*Gluten-free diet.* Wheat and rye gluten should be completely excluded from the diet. The most important cause of sub-optimal response to treatment is incomplete restriction of gluten, and when the patient is a young child this occurs most frequently because the parents have been inadequately instructed by the physician. A number of outlines of gluten-free diets are available (Finlay & Wightman, 1956; Fletcher & McCririck, 1958; Collins & Isselbacher, 1964), but the physician should attempt to provide the patient with lists of gluten-containing and gluten-free foods relevant to his own locality.

Treatment with a gluten-free diet improves the clinical, biochemical and histological abnormalities of coeliac disease. Children with coeliac disease usually respond rapidly to treatment, showing obvious improvement within a week or two, and regaining any growth deficit within a few months.

Ideally, treatment with a gluten-free diet should be lifelong, since susceptibility to gluten can be demonstrated histologically or biochemically even in patients who remain subjectively well after resuming gluten ingestion. Also, there is mounting evidence that neoplastic disease of the small bowel (Jeffries, Weser & Sleisenger, 1964) and elsewhere, notably the oesophagus (Harris et al., 1967), occurs more commonly in patients with coeliac disease than in the general population. The development of this complication may well be influenced by the stringency of dietary treatment.

In practice, few patients will adhere strictly to a gluten-free diet after childhood, unless they are convinced of subjective benefit. However, they should be advised to restrict gluten as much as conveniently possible, and to have regular medical review, since their disease may relapse at any time, especially with an extra stress such as infection, or pregnancy.

One still sees patients who have previously been suspected of having coeliac disease, and for whom partial or complete exclusion of dietary gluten has been recommended as a 'therapeutic trial'. The diagnosis of such patients is particularly difficult, and usually requires that the patient resume a normal diet for some months to see if demonstrable historical or biochemical abnormalities develop.

Some response to a gluten-free diet is not specific for coeliac disease (Fällström, Winberg & Andersen, 1965; Hindle & Creamer, 1965; Parfitt, 1966) and therapeutic trials of a gluten-free diet have no place as a diagnostic method unless circumstances make appropriate laboratory investigation impossible.

**Other treatment.** Complications of coeliac disease such as deficiency of iron, folic acid or vitamin D or sugar intolerance, or coeliac crisis, may require other measures of treatment, but only for a short time (Townley & Anderson, 1967).

Finally, the physician who makes a diagnosis of coeliac disease should carefully assess other members of the family for clinical features of the same disorder. Although the pattern of inheritance of coeliac disease is uncertain, familial incidence of the disease is relatively high (MacDonald et al., 1965).

**Disaccharidase deficiency and disaccharide intolerance**

Dietary disaccharides are normally digested at the brush border of the epithelial cells of the small bowel mucosa and the component monosaccharides are then absorbed (Dahlgqvist, 1962). When hydrolysis of an ingested disaccharide load is incomplete, undigested sugar reaches the colon where it is fermented to a varying degree by bacteria. The sugar and its breakdown products appear in the stools with osmotically-held fluid (Townley, 1966).

Disaccharidase deficiency may occur as an inborn error of metabolism, with a congenital, persistent absence of an enzyme despite a morphologically normal mucosa, or as a secondary effect of mucosal damage.
**Sucrase–isomaltase deficiency**

Absence of the enzymes sucrase and isomaltase is the commonest genetically-determined disorder (Prader & Auricchio, 1963). Patients develop diarrhoea after sucrose is fed. Symptoms are most severe in infancy, when profuse diarrhoea with dehydration may be seen. The diagnosis may be overlooked when sucrose-containing feeds are given as treatment for infective diarrhoea, but symptoms continue. Stool tests for pH and sugar will indicate the diagnosis, which may be confirmed when necessary by biochemical studies of a small-bowel biopsy specimen.

Treatment is dietary restriction of sucrose-containing foods.

**Hypolactasia**

In many animal species, levels of intestinal lactase diminish with age. A similar tendency seems to occur in man, especially in some racial groups (Holzel, 1967). Occasionally in children, and perhaps more commonly in adults, isolated hypolactasia may cause diarrhoea. Diagnosis will be indicated by stool tests after an oral dose of lactose, and again can be confirmed, if necessary, by biochemical studies of a biopsy specimen of the small bowel mucosa. Treatment involves restriction of lactose-containing foods.

**Secondary disaccharidase deficiency**

In diseases such as coeliac disease (Townley, Khaw & Shwachman, 1965) or infective enteritis (Burke, Kerry & Anderson, 1965) associated with damage to the small bowel mucosa, the capacity of the mucosa to hydrolyse all disaccharides is impaired. However, lactose is the disaccharide which in practice most commonly causes symptoms of intolerance and is responsible for abnormal results of stool tests. Temporary exclusion of lactose from the diet is sufficient symptomatic treatment. More rarely dietary restriction of sucrose may also be required. (Sunshine & Kretchmer, 1964).

**Infestation with giardia lamblia**

Giardiasis is the commonest type of parasitic infestation that causes diarrhoea in temperate climates. Clinical features resemble those of mild coeliac disease, and the diagnosis is usually made by identification of the parasite or its cysts on microscopy of the stools. Treatment with mepacrine is usually effective (Anderson et al., 1961).

**Cystic fibrosis**

Cystic fibrosis is one of the commonest organic causes of chronic diarrhoea in children of European extraction, with an incidence of about 1 in 2000 (Steinberg & Brown, 1960; Danks, Allan & Ander-
**Ulcerative colitis**

This is a fairly uncommon cause of diarrhoea in childhood, especially during the first decade. Diarrhoea, sometimes with blood or mucus in the stools, and sometimes associated with abdominal pain is the predominant symptom. Barium enema and sigmoidoscopy are the most valuable diagnostic aids. Treatment does not differ in principle from that used for adults with ulcerative colitis (Davidson, Bloom & Kugler, 1965).

**Milk-induced colitis**

A few children have chronic diarrhoea that is not attributable to lactose intolerance, but which subsides when milk is excluded from the diet. Usually the patient is a young baby whose stools may contain mucus or blood. Histological features of colitis may be seen in a suction biopsy specimen. Milk tolerance may return to normal after a few months or years (Gryboski, 1967). In the author’s experience, this condition is rare, but a trial of treatment by milk exclusion seems justifiable in any patient with intractable unexplained diarrhoea.

**Enterocolitis in early infancy**

This term is used to describe a small group of infants who, soon after birth, develop diarrhoea for which no cause already mentioned can be found. Avery et al. (1968) recently described a number of patients of this type, and suggested that various secondary factors such as altered motility, mucosal damage, infection, vitamin and electrolyte deficiencies may combine to cause persistent diarrhoea. Treatment is largely supportive. Avery et al. (1968) suggests a place for steroids and colostomy in some cases, but these measures need further evaluation.

It seems appropriate that reference to this group of children, in whom the exact cause of diarrhoea remains unexplained, should conclude the discussion. Our knowledge of the causes and mechanisms of diarrhoea is still far from complete, and doubtless there are many more bases for diarrhoea that are yet to be determined.

**References**


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The management of chronic or recurrent diarrhoea in childhood.

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