Current Practice

Malabsorption

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The concept of the malabsorption syndrome has widened enormously in the last 10 years with the introduction of such techniques as intestinal biopsy and the delineation of biochemical defects such as disaccharidase deficiency, which may occur as an isolated phenomenon. Furthermore, it is now realized that malabsorption of any nutrient may give rise to a nutritional defect in the absence of bowel symptoms, and indeed steatorrhoea may not even be present. Small bowel function should therefore be investigated in any patient with unexplained diarrhoea or a nutritional disturbance which is not solely accounted for by deficient dietary intake. One classification of the causes of malabsorption is given in Table I.

TABLE I.—Classification of Malabsorption States

DISORDERS OF DIGESTION	
Pancreatic Deficiency—cystic fibrosis, inflammation, carcinoma, etc.	
Bile Salt Deficiency—liver disease, biliary disease, ileal resection.	
*Inadequate Mixing—gastric surgery.	
DISORDERS OF ABSORPTION	
Loss of Absorptive Surface.	
(a) Surgical—resection, by-pass.	
(b) Mucosal damage—coeliac disease, tropical sprue, radiation drugs, etc.	
(c) Infection—Whipple's disease, enteritis, hepatitis, tuberculosis.	
(d) Inflammation—Crohn's disease.	
(e) Infestation—hookworm, giardiasis, strongyloidiasis, etc.	
(f) Infiltration—amyloid, lymphoma.	
*Stagnant Loop Syndrome	
Blind loops, strictures, fistulae, diverticula, scleroderma.	
Lymphatic Obstruction	
Vascular	
Mesenteric insufficiency, cardiac failure, constrictive pericarditis.	
Endocrine	
Hypoparathyroidism, diabetes mellitus, Addison's disease.	
Zollinger-Ellison syndrome, thyrotoxicosis, carcinoid syndrome	
systemic mastocytosis.	
Miscellaneous	
(a) Drugs—neomycin, PAS, phenindione, etc.	
(b) Hypogammaglobulinaemia.	
(c) Pneumatosis cystoides.	
(d) Acrodermatitis enteropathia.	
(e) Allergic gastroenteropathy.	
ISOLATED BIOCHEMICAL ABNORMALITY	
Disaccharidase deficiency.	
Monosaccharide malabsorption	
Abetalipoproteinaemia.	
Cystinuria.	
Hartnup disease.	
Pernicious anaemia.	

* These conditions have been dealt with in other articles in this series.

Clinical Presentation

Either gastrointestinal or nutritional features may dominate the clinical presentation of patients with malabsorption.

Gastrointestinal Symptoms

Diarrhoea.—This is the commonest symptom. The stool may have no diagnostic features apart from being loose. Fatty stools are classically described as being pale, greasy, bulky, unformed, and difficult to flush away. The offensive odour is due to bacterial degradation of unabsorbed fatty acids, carbo-

hydrate, and protein. Frothy, acid, and liquid stools result from the fermentation of unabsorbed carbohydrate. Severe exacerbations of any malabsorption state can cause watery diarrhoea. Some patients will deny that the stools are abnormal, and they may even be constipated, but careful questioning may reveal some of the characteristics of steatorrhoea. Blood is not present in the stool unless the primary disease is inflammatory or neoplastic, or rarely when vitamin K deficiency has developed.

Other Symptoms.—Complaints of distension, bloating, flatulence, borborygmi, abdominal cramps, and excessive bowel activity are frequent. These symptoms may follow ingestion of specific dietary constituents (for example, milk), but a history of food intolerance may be misleading and should be interpreted with caution. Severe pain is unusual; its presence should suggest chronic pancreatitis, inflammatory bowel disease, or mesenteric vascular insufficiency, although occasionally acute episodes of painful distension can accompany primary malabsorption states. Vomiting is rare, except in children with coeliac disease.

Fever.—This is an unusual symptom of coeliac disease but may occur in such conditions as parasitic infestation, inflammatory bowel disease, Whipple's disease, and hypogammaglobulinaemia.

Nutritional Symptoms

These are protean and are listed in Table II. The most common manifestations of nutritional deficiencies are weight loss, anaemia, sore mouth, bone disease, and oedema. A florid picture is uncommon but subclinical biochemical abnormalities occur frequently.

Weight Loss.—This symptom is associated with anorexia; the patients do not have a normal or increased appetite as suggested in textbooks. Weight loss is a result of this anorexia, and is rarely solely due to malabsorption except in pancreatic insufficiency where gross steatorrhoea (over 40 g. per day) may occur, as loss of weight requires a phenomenal loss of calories in the stool. Anorexia is due to several factors and cannot be explained only on the basis of folate deficiency.

Anaemia.—There is often a mixed picture with changes of iron deficiency and megaloblastic anaemia present. These patients may be diagnosed as having pernicious anaemia and may fail to respond to vitamin-B₁₂ therapy, or they may present with an atypical megaloblastic anaemia with free acid on gastric aspiration. Unexplained megaloblastic or iron deficiency anaemia should call for investigation of the gastrointestinal tract.

Bone Disease.—Bone pain, tenderness, and deformity may occur without gross bowel symptoms and may be misdiagnosed as arthritis or rheumatism. The symptoms usually affect the proximal limb bones, especially the hips, and are often asso-

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ciated with a proximal myopathy. Pressure over the fingers may be painful.

TABLE II.—Nutritional Disturbances From Malabsorption

Clinical Feature	Deficiency	Comment
Weight loss	Calorie	Common. Anorexia important
Weakness	(a) Protein—muscle wasting (b) Electrolyte—K, Na, Mg Multiple	Common
Short stature	Multiple	Long-standing malabsorption Not uncommon
Amenorrhoea } Infertility } Oedema } Anaemia }	Secondary hypopituitarism Hypoproteinaemia (a) Mixed—folate, iron (vit. B ₁₂) (b) Megaloblastic—folate, vit. B ₁₂ (c) Hypochromic—iron (d) Other—vit. B ₆ , ?vit. E	Rarely symptomatic Common
Glossitis } Cheilosis } Stomatitis } Bone disease }	Vit. B complex, vit. B ₁₂ , folate, iron	Common
Tetany } Muscle cramps }	Vit. D, calcium	Florid: uncommon Biochemical: common May be precipitated by blood transfusion or I.V. infusion
Bleeding } Bruising } Purpura }	Calcium, magnesium and sodium	Rarely symptomatic
Skin	Vit. K affecting Prothrombin, Factor VII, Christmas and Stuart factors	Common. Protean types. Rarely diagnostic
Neuropsychiatric } peripheral neuropathy } emotional depression, etc. }	Vit. B complex, vit. B ₁₂ , vit. E unknown factors	Common. Rarely diagnostic

N.B.—Deficiencies of vitamins A and C are rarely manifest clinically.

Past History

Childhood Illnesses.—Subjects with adult coeliac disease may admit to having been anaemic or sickly in childhood, when they may have been unable to play games or may have suffered other disability.

Previous Surgery.—Abdominal operations may have resulted in resection of specialized or extensive areas of small intestine or formation of blind-loops, bypasses, and strictures. Previous gastric surgery usually results in mild malabsorption, which is often of no clinical significance, although deficiencies of iron, calcium, and vitamin B₁₂ may develop. A severe malabsorption syndrome developing in a patient who has had a gastrectomy indicates the presence of a second lesion, such as pancreatic insufficiency or a stagnant loop.

Residence in the Tropics.—Tropical sprue may first present many years after leaving an endemic area. Malabsorption first developing in the tropics should suggest sprue or parasitic infestation. However, malabsorption syndromes usually associated with temperate climates can also occur in tropical areas.

Family History.—This is rarely of help except in some cases of coeliac disease and disaccharidase deficiency.

Examination

In many subjects physical signs are absent or minimal, but when present they may again be divided into gastrointestinal and nutritional.

Patients with severe malabsorption appear grotesque. There is gross abdominal distension, and dilated loops of bowel may be seen through a thin abdominal wall. The percussion note may be hyper-resonant owing to gas, or dull owing to fluid in the loops of bowel, but shifting dullness does not occur. The face is thin, resulting in a haggard, anxious expression, and wasting of both muscle and fat in the limbs contrasts with the abdominal distension. Mottled brown pigmentation, especially of the forehead and temples, may be seen, and finger clubbing sometimes occurs. Other nutritional features are given in Table II.

The stool should always be inspected. It may strongly suggest malabsorption. A constipated stool in the presence of a nutritional defect does not exclude malabsorption, but the presence of pus, blood, or mucus makes the diagnosis unlikely. Oily material which solidifies on cooling suggests pancreatic steatorrhoea. Microscopy may reveal fat, muscle fibres, or parasites.

Investigation

The purpose of the investigation is threefold.

- (1) To demonstrate the presence of malabsorption.
- (2) To evaluate the effect of malabsorption on the nutrition of the patient.
- (3) To determine the cause.

Demonstration of Malabsorption

Specific tests of absorption often involve the collection of excreta—which is unpleasant and subject to error. They are often empirical, since they involve ingestion of an abnormally large amount of a substance which is not a normal dietary constituent, and which is given in the fasting state and not as part of a meal. The commonly used tests are xylose tolerance, lactose tolerance, vitamin-B₁₂ absorption, and faecal fat excretion.

Xylose Tolerance.—After an oral dose of 25 g. of D-xylose, more than 4.2 g. should appear in the urine in five hours, and the blood xylose level at one and a half hours should be more than 32.5 mg./100 ml. This test was introduced at a time when xylose was thought to be absorbed by diffusion, to be metabolically inert, and to be excreted quantitatively in the urine by glomerular filtration without renal tubular reabsorption. Though these assumptions have been shown to be incorrect the test has proved useful in clinical practice. Xylose is relatively poorly absorbed from the jejunum and cannot be absorbed by the ileum. In the normal subject there is little reserve capacity for absorption, and so any condition which impairs absorption will readily be shown up. For this reason a 25 g. dose of the sugar should be used rather than a 5 g. dose, since larger doses will stress the bowel and reveal borderline cases of malabsorption. Unfortunately, falsely low values are often found and usually represent incomplete urine collection or voiding, but also occur in patients with renal failure, myxoedema, and skin diseases, in older subjects, and after food or delayed gastric emptying. In such patients it is therefore essential to estimate the blood xylose level during the test, and this is proving more reliable than the urinary value. Xylose absorption is a useful guide to jejunal function, though it does not correlate with the degree of steatorrhoea or the serum carotene level.

Glucose Tolerance.—Blood levels of glucose depend on many factors besides absorption, and so this test is losing favour. However, it is useful in pancreatic steatorrhoea, because a diabetic curve is often found.

Disaccharide Tolerance.—Ingestion of 50 g. disaccharide, which is usually lactose or sucrose, should result in a maximum rise of blood glucose of over 20 mg./100 ml. In primary lactase deficiency a flat curve is found, but the curve following ingestion of 25 g. glucose and 25 g. galactose is normal. Lactase deficiency secondary to mucosal damage may show impaired absorption of the monosaccharides. Unfortunately, when venous blood is used, 20% of lactose tests have been found to be flat in normal subjects with normal intestinal lactase concentrations. Disaccharidase deficiency can often be diagnosed by the production of symptoms such as abdominal pain, borborygmi, and diarrhoea by the sugar load.

Stool pH.—Unabsorbed carbohydrate is fermented to short-chain organic acids in the colon and these should lower the faecal pH. This is the case in children, but in adults the colon compensates and pH measurements are unreliable.

Vitamin B₁₂ absorption.—Malabsorption of the vitamin in the presence of intrinsic factor denotes an intestinal lesion. Malabsorption which is corrected by the administration of antibiotics denotes an abnormal small intestinal flora. If antibiotics and intrinsic factor fail to correct the malabsorption, a lesion of the ileum is probable.

Various methods are available, but the most widely used is the urinary excretion (Schilling) test. A physiological amount of vitamin labelled with radioactive cobalt is ingested, after which a large flushing dose of unlabelled vitamin is given parenterally to drive labelled vitamin out of the tissues, thus enhancing renal excretion. The test is therefore dependent on mobilization, displacement, and excretion as well as absorption of the vitamin. Renal failure, food ingestion, and errors in urine collection lead to false results, but increasing age has little effect on excretion. Timing of the flushing injection can influence excretion, but failure to administer the injection is a more common error. The main objections to the test are poor reproducibility in some patients with gastrointestinal lesions, and the administration of the large dose of vitamin which could interfere with subsequent haematological investigation. Normally, 0.5–1.0 μ g. of labelled vitamin is given, of which more than 10–13% should be excreted in 24 hours.

Faecal Fat.—Pooled three-day or five-day samples of faeces have to be analysed, as there is tremendous daily variation in fat excretion owing to variable colonic emptying. Analysis of serial pooled samples may also show variation in disease and so a single analysis may be insufficient for accurate assessment. Normal values are less than 6 g. per day, of which approximately 2 g. comes from endogenous sources. These values are not affected quantitatively or qualitatively by varying the dietary intake of fat in a normal bowel because of its large reserve capacity. When the reserve is compromised by disease or resection of the small intestine, increasing the load of dietary fat can produce steatorrhoea. It is therefore important to place an adequate stress on the bowel, and this may be done by giving a 100-g. fat diet and starting stool collections after a 48-hour equilibration period. Provided that the diet is completely eaten tests may be repeated and the results compared so that progress can be assessed. Fat excretion using a standard ward diet is an adequate test if an abnormal value is obtained. However, the fat content of such a diet may vary from 50–150 g. per day depending on such factors as ingredients, cooking, appetite, and the personal tastes of the patients, so that variable results will be obtained in patients with borderline malabsorption.

Other Tests of Fat Absorption.—In order to dispense with stool collections tests measuring the uptake of marked fat into the bloodstream have been introduced. The best known are the vitamin A absorption and I^{131} -radiotriolein tests, which provide a rough correlation with malabsorption, but results overlap the normal range enough to make them unreliable. Furthermore, there are several theoretical and technical objections to the radiotriolein test as a measure of fat absorption.

Evaluation of Nutritional Defect

Haematological Investigations.—Preliminary investigation will show an iron deficiency or a dimorphic anaemia. A blood film should be carefully scrutinized for macrocytes and hypersegmented polymorphs. The presence of Howell-Jolly bodies is a clue to the presence of splenic atrophy associated with coeliac disease. If malabsorption is now suspected, the serum B_{12} and folate should be estimated and a sternal marrow puncture performed. Iron deficiency is indicated by depleted marrow stores, low serum iron, and high iron binding capacity. Folate stores—which are not reflected by the serum level—have to be measured by urinary formiminoglutamic acid or red cell folate levels.

Metabolic Bone Disease.—Abnormal levels of serum calcium with normal or subnormal serum phosphorus values and a raised serum alkaline phosphatase indicate bone disease. Confirmatory tests will be necessary.

Serum Albumin.—This measurement reflects the balance between breakdown and synthesis, both of which may be abnormal.

Prothrombin Time.—This is rarely prolonged, but should always be assessed prior to biopsy.

Determination of Cause

Once malabsorption has been shown to be present and its effects on nutrition have been assessed, the cause should become evident from the clinical features and the pattern of the abnormal absorption tests and deficiencies described above—for example, gross steatorrhoea with a normal haemoglobin and xylose tolerance suggests pancreatic insufficiency; radiography and biopsy of the small intestine will give further information.

Radiography.—An adequate barium meal and follow-through is essential. Malabsorption due to structural lesions of the bowel, such as diverticula, Crohn's disease, strictures, and fistula can be diagnosed. Characteristic alterations in motility indicate scleroderma. Coarse gastric rugal folds suggest Menetrier's disease or the Zollinger-Ellison syndrome. A "malabsorption pattern" may be demonstrated. This includes intestinal hurry, flocculation and segmentation of barium, dilatation of bowel loops, thickening of the mucosal pattern, and segmentation in a loop with a smooth mucosal pattern (Moulage sign). This appearance suggests malabsorption but does not diagnose the underlying disease. A mild malabsorption pattern may occur in "functional bowel disorders." Conversely, malabsorption can occur without any radiological signs, especially if the gastrointestinal symptoms are minimal. Barium enema may be needed to demonstrate Crohn's disease or a colonic fistula.

Small Intestinal Biopsy.—Biopsy has revolutionized the concept of small intestinal disease by producing fresh tissue for microscopy, culture, and biochemical analysis. Complications are rare in adults, but nevertheless it is desirable to perform the procedure in hospital where the patient can be observed afterwards. Artifacts from incorrect orientation and sectioning of the specimen can lead to misdiagnosis. The specimen should first be examined with a hand lens or preferably a dissecting microscope. Normal villi are shaped like fingers, tongues, or narrow leaves, but contrary to popular opinion finger-shaped forms rarely predominate in the upper jejunum. Histological examination, besides assessing the shape of the villi, reveals abnormalities in the epithelial cells and infiltration of the lamina propria. Although the small intestine can respond to injurious stimuli only in a limited way, certain appearances are quite specific, and Whipple's disease, intestinal lymphangiectasia, abetalipoproteinaemia, amyloid, lymphoma, and the nodular form of hypogammaglobulinaemia can be diagnosed. *Giardia lamblia* and certain worms may also be found in the specimen. Since the distribution of some lesions is not uniform a negative biopsy does not exclude the diagnosis. Biopsy is mandatory in all cases of obscure nutritional deficiency even in the absence of steatorrhoea.

(In next week's article clinical syndromes of malabsorption and their treatment will be described.)

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