Current Practice

MEDICINE IN THE TROPICS

Malabsorption

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Malabsorption implies a defect in the absorption of one or more nutritive substances, due to an abnormality either in the intestine or in one of the digestive organs. Impaired absorption of several substances, such as fat, protein, fat-soluble vitamins, vitamin B_{12}, folic acid, and iron, is often present (Table I). Selective malabsorption of a single substance may, however, occur, as in vitamin-B_{12} malabsorption in pernicious anaemia or disaccharide malabsorption in disaccharidase deficiency. Malabsorption syndromes are present throughout the world. The main causes tend to be different numerically in tropical zones compared with temperate zones. As work in the field increases, however, it becomes abundantly obvious that the geographical distribution of aetiological factors is not as clear-cut as was formerly supposed.

TABLE I.—*The Results of Defective Absorption of Various Dietary Substances*

	Fat	Steatorrhoea, weight loss
	Carbohydrate	Flatulent dyspepsia, abdominal distension
	Protein	Wasting, oedema
Water-Soluble Vitamins	Folic acid	Macrocytic, megaloblastic anaemia, glossitis
	Vitamin B_{12}	Macrocytic, megaloblastic anaemia, glossitis, neuropathy
	Vitamin-B complex	Cheilosis, angular stomatitis, dermatitis polyneuritis
	Vitamin C	Bleeding tendency
Fat-Soluble Vitamins	Vitamin A	Follicular hyperkeratosis, xerophthalmia
	Vitamin D & calcium	Skeletal changes, tetany
	Vitamin K	Purpura, haemorrhages
	Iron	Hypochromia
	Sodium	Muscular weakness, cramps
	Potassium	Flaccidity, arrhythmias
	Magnesium	Muscular weakness
	Water	Nocturnal diuresis

Until very recently the malabsorption syndrome was thought to be rare throughout tropical Africa. Malabsorption in the tropics was formerly equated with tropical sprue. Many cases present with the florid symptoms outlined below. Many less severe cases exist, however, and present in less dramatic ways. As most of the signs and symptoms of malabsorption are a result of *malnutrition,* this is the main differential diagnosis. Severe malnutrition causes damage to the absorptive areas of the small intestine, and the two conditions may be coexistent. Any condition producing diarrhoea and severe small-intestinal hurry will be accompanied by some degree of malabsorption. Such conditions are common in tropical regions and often have a bacterial or virus origin.

Clinical Presentation

A detailed dietary history must always be obtained, especially to exclude malnutrition, as the clinical signs in the two conditions are often very similar. This may be very difficult in indigenous populations owing to language difficulties. In the severe case steatorrhoea (Gk. *stear* fat, *rhoia* flux) is usually, but not always, present. Diarrhoea is usual, with voluminous, pale, frothy, foul-smelling stools which have a porridge-like consistency. They tend to float, and are often not easily flushed from the lavatory. A bloated abdomen, excessive flatus, and gross weight loss are other features of the condition. In the less severe cases malaise, general ill-health, and dyspepsia resembling peptic ulcer are common, as are mental apathy and depression, and at first the patient may be thought to be suffering from a psychiatric disease. Patients frequently complain of symptoms referable to anaemia, osteoporosis, osteomalacia, and vitamin deficiencies, and many are found to have recurrent glossitis with a sore raw-looking tongue or aphthous ulceration. Bone pain and failure in the healing of fractures are sometimes encountered. Tetany may also be present. Nocturnal diuresis and hypothermia occasionally occur. In cases due to chronic pancreatitis the main complaints may be of abdominal pain radiating to the back, polyuria, and polydipsia. An example of a patient with chronic pancreatitis and severe malabsorption is shown in Figs. 1 and 2. The syndrome should be included in the differential diagnosis of every case of iron-deficiency anaemia which fails to respond to iron after elimination of hookworms, and in all cases of macrocytic (megaloblastic) anaemia, due to either folic-acid or vitamin-B_{12} deficiency.

Signs are often few and rarely give much help in diagnosis. The muscle mass is diminished, often grossly, and there is loss of subcutaneous tissue. The hair is soft, often sparse over the occipital region, and lacks its usual elasticity. Cheilosis, angular stomatitis, and glossitis are often present. Hyperkeratotic skin changes, often accompanied by hypopigmented patches, are common. Iron-deficiency anaemia may be present, but this is widespread in the tropics owing to other causes. Signs which are present in some cases include oedema, finger-clubbing, splenomegaly, pigmentation, and hypotension. Evidence of other vitamin deficiencies is often present. There are no signs which give a clear-cut distinction from protein-calorie malnutrition.

In children the picture may be very similar to that in the adult. In protein-calorie malnutrition, especially kwashiorkor, part of the clinical picture is due to failure of absorption from the severely damaged small-intestinal mucosa ; pancreatic dysfunction is also present. Failure to grow is common, and weight is affected more than height. There is muscular wasting and hypotonia. The child is often fretful and irritable. The eyes, face, hands, and feet may be puffy, and there may be oedema of the penis and scrotum. The abdomen is distended and the hair is depigmented and becomes brown or straw-coloured. The skin may be coffee-coloured with reddish-brown areas instead of its usual black coloration. Circumoral pallor may be present and there is a generalized thickening and flaking of the skin.

Other causes of severe weight loss should always be considered in the differential diagnosis. Gastrointestinal signs and symptoms in the malabsorption syndrome are not always obvious

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on clinical examination. Low blood pressure, skin pigmentation, and muscular weakness may suggest adrenal cortical failure.

Aetiology

Table II gives the main causes of the syndrome. Although many of these factors may be present in any area of the world, the causes particularly important in tropical countries are indicated. Hitherto there has been a tendency to regard the syndrome as a chronic one. It is now clear that it may take an acute form following, for example, acute gastroenteritis of bacterial or virus origin. Malabsorption is transient in most such cases. In a few, however, a significant degree of malabsorption may persist for weeks or months after the initial acute attack.

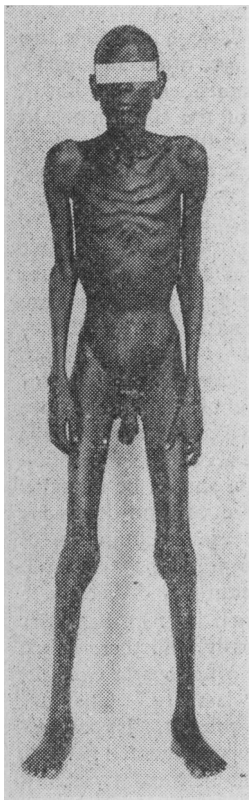

FIG. 1.—The general appearance of a 52-year-old Ugandan male from the Baganda tribe with severe chronic calcified pancreatic disease. Daily faecal fat excretion was 16 g. He also had moderately severe diabetes mellitus.

FIG. 1

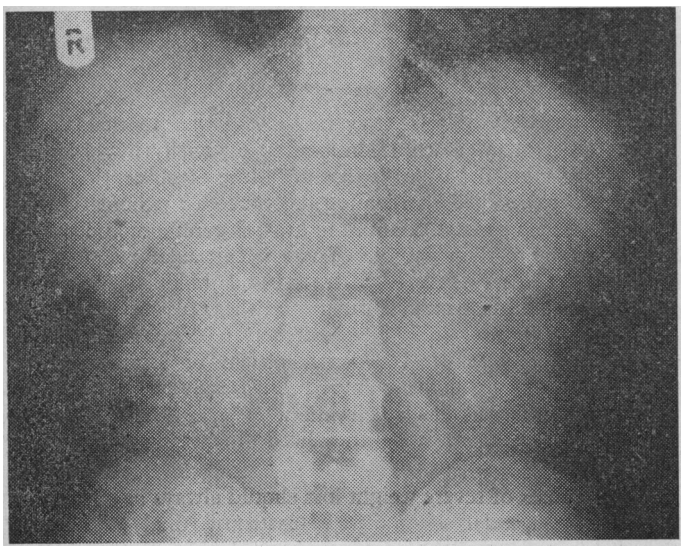

FIG. 2.—Straight x-ray of the abdomen of the same patient showing extensive pancreatic calcification.

FIG. 2

Disease of the Pancreas or Biliary System

In Uganda, Nigeria, and probably throughout tropical Africa, and possibly the Far East also, chronic pancreatitis accounts for a high proportion of cases of chronic malabsorption. The presentation is usually either with gross weight loss and steatorrhoea or with the symptoms of diabetes mellitus. Some cases present with generalized oedema. In pancreatitis the main defect is in digestion, and though deficiency of fat-soluble vitamins may occur water-soluble vitamins are usually well absorbed. Anaemia and deficiency of vitamin B_{12} and folic acid are uncommon. Patients often complain of recurrent severe upper abdominal pain, and parotid gland enlargement occurs in some; but parotid enlargement is in any case a frequent finding in some populations living in the tropics. The pathological changes in the pancreas consist of fibrosis and lithiasis. There is increased iron absorption, which may lead to haemosiderin deposits in the liver. The disease may occur at any time from childhood to late adult life and is possibly more common in males. The cause is unknown; both malnutrition and excess alcohol have been incriminated.

Throughout tropical Africa (East and West Africa, and the Congo) gall stones are uncommon, and prolonged extrahepatic obstructive jaundice does not seem to be as common as in most temperate zones. Cases due to chronic pancreatitis or carcinoma of the head of the pancreas are occasionally seen. Prolonged intrahepatic cholestasis and transitory steatorrhoea following cholestatic virus hepatitis or hepatotoxic agents does not appear to be more prevalent than in temperate zones. Gall stones are common in some parts of the Far East.

Intestinal Causes

In the small intestine mucosal damage of any cause, diminution in the absorptive area, or alteration of the luminal *milieu intérieur* may produce the syndrome. Although minor mucosal damage is often found in indigenous populations in many parts of the tropics, this does not in most cases give rise to much malabsorption, although D-xylose absorption may be impaired in some otherwise healthy subjects. Biopsy specimens of the mucosa contain many more leaf-shaped than finger-shaped villi in patients from these areas; the cause of this is not yet clear.

TABLE II.—*Causes of Malabsorption Syndromes*

DEFECTIVE GASTRIC FUNCTION
- Gastritis, peptic ulcer, total gastrectomy, gastrojejunostomy, gastrocolic fistula. } inadequate mixing; intestinal hurry.

DEFECTIVE DIGESTIVE GLANDS
- * Pancreas—e.g., chronic calcified pancreatitis.
- Liver—e.g., prolonged biliary obstruction.

LESIONS INVOLVING THE SMALL INTESTINE
- *Mucosal lesions*
  - * Tropical sprue.
  - * Jejunitis, ileitis.
  - * Infiltrative lesions—e.g., tuberculous enteritis, Crohn's disease, Whipple's disease, systemic sclerosis, leukaemia, reticuloses, amyloidosis, abnormal lymph drainage.
  - * Enzyme defects—e.g., disaccharidase deficiencies.
  - Coeliac disease, adult coeliac disease (gluten-induced enteropathies).
- * *Resection of part of the small intestine* (i.e., absorptive-surface deficiency).
- *Intraluminal abnormalities*
  - * Parasites—e.g., *Giardia lamblia, Strongyloides stercoralis, Diphyllobothrium latum, Ankylostoma duodenale.*
  - Stagnant loops, strictures, fistulae, jejunal diverticulosis.
- *Vascular lesions of the small intestine*
  - * Constrictive pericarditis.
  - * Endomyocardial fibrosis.
  - Congestive cardiac failure.
  - Superior mesenteric thrombosis.

IATROGENIC CAUSES
- Neomycin, triparanol, phenindanedione, phenolphthalein, colchicine, para-amino salicyclic acid, radiation.

ENDOCRINE DISORDERS
- Addison's disease, hypoparathyroidism, diabetes mellitus, Zollinger-Ellison syndrome.

MISCELLANEOUS CAUSES
- Cystinuria, Hartnup disease, acanthocytosis, agammaglobulinaemia, pneumatosis cystoides, malignant carcinoid syndrome.

* Indicates causes which are more common in the tropics than in temperate zones.

Conditions in which the ileum is involved often have vitamin-B_{12} deficiency as part of the clinical picture ; absorption of this vitamin is confined to the terminal ileum.

Tropical sprue was first described in the eighteenth century. Until recently it was thought to be a chronic form of malabsorption occurring solely in expatriate subjects living in the tropics, but it is now known that acute cases are very common. Sprue is widely found in many parts of the tropics, including the Far East, India, Indonesia, the West Indies, and South America. It is probably unusual in Africa, although only on rare occasions has it been looked for seriously. It has a characteristic local distribution, occurs in epidemics, and may have a seasonal incidence. The mode of onset is variable. Anorexia, lassitude, and diarrhoea are usual initially. Weight loss, glossitis, stomatitis, anaemia (usually megaloblastic), and other vitamin deficiencies follow. A pre-existing folic-acid deficiency is usual in most patients owing to an inadequate diet ; it is also often seen after pregnancy. Folic-acid deficiency seems to be uncommon in the normal Ugandan and this may explain the rarity of tropical sprue here. It is probable that the syndrome is set off by an acute insult to the intestinal mucosa, such as acute gastroenteritis of bacterial, viral, or helminthic origin. In the presence of a deficiency of folic acid, which is required for the rapid production of cells in the small-intestinal mucosa, persistent damage and malabsorption result. It is possible that the severity of the disease is dependent on the degree of folic-acid deficiency ; recently a correlation between the severity of malabsorption and the degree of mucosal damage in acute cases has been noted. In some, folic-acid deficiency may play only a minor part, in which case the disease starts with a gastrointestinal infection and folic-acid deficiency follows.

Acute or subacute cases of jejunitis (enteritis necroticans), usually in children, have been reported in New Guinea and Uganda. Presentation is as an acute episode with colic, diarrhoea, and even melaena. There is segmental ulceration with necrosis of the jejunum. *Clostridium perfringens* is the probable pathogen. Death in the acute stage is usual, but a few survive long enough to suffer from malabsorption.

Tuberculosis of the small intestine (tabes mesenterica) accounts for some cases of malabsorption in very many parts of the tropics.

Lactase Deficiency

Digestion of disaccharides is dependent on the presence of disaccharidases in the mucosal cells of the small intestine. Discovery of widespread lactase deficiency in some populations living in the tropics has led to the recognition of many cases of diarrhoea which are occasionally accompanied by steatorrhoea, presumably due to intestinal hurry. The deficiency seems to occur in some populations as an isolated, probably genetically controlled, defect. It is common in Uganda and parts of the Far East. In some Ugandan tribes a high level of the enzyme exists at birth, but this falls at varying times during the first three or four years of life. Failure to thrive in infancy may be caused by this defect in some cases owing to failure of absorption of lactose, which constitutes about 50% of the calories in breast milk. Lactase deficiency may also exist as part of a general depression of disaccharidases when the jejunal mucosa is severely damaged, as in severe protein-calorie malnutrition or severe gastroenteritis. Other enzyme defects responsible for intolerance to certain foodstuffs will probably come to light in the future.

Massive small-intestinal resection involving much of the small intestine is frequently seen in some parts of Africa after either strangulated hernia, trauma, or volvulus of the intestine. The latter condition is common in some parts of tropical Africa. Survival is possible if only a few feet of small intestine remain. A patient with an abdominal scar and malabsorption will probably be suffering from a lack of intestinal mucosa, or a structural abnormality.

The two most important parasitic diseases which can certainly cause malabsorption are caused by *Giardia lamblia* and *Strongyloides stercoralis*. The clinical picture in the latter condition may be associated with an irritating rash, pulmonary symptoms, and an eosinophilia. *Necator americanus* almost certainly does not produce malabsorption. There is some evidence that *Ankylostoma duodenale* may be responsible in some cases. Tape-worms do not cause this syndrome.

Cardiac lesions, especially constrictive pericarditis and endomyocardial fibrosis, are common in many areas of Africa and these may produce malabsorption by an indirect disturbance of the vascular supply to the small intestine, though this has not yet been adequately investigated.

Adult coeliac disease and coeliac disease are the commonest small-intestinal causes of malabsorption in Great Britain. They are probably related, since they are both precipitated by the same factor—gluten. Adult coeliac disease occasionally occurs in patients who have had coeliac disease in infancy. There is increasing evidence that the two diseases are also by no means uncommon in both indigenous and expatriate populations in the tropics.

Investigations

There are no simple tests for differentiating protein-calorie malnutrition from the malabsorption syndromes ; in the former secondary mucosal damage is relatively common. Careful macroscopic inspection of the stool will often strongly suggest steatorrhoea. A gross excess of fat in the stool is unusual in uncomplicated malnutrition.

Urine examination may show glycosuria in patients with a pancreatic cause for the malabsorption syndrome. Haematological investigation will reveal an iron-deficiency anaemia in very many patients in the tropics, but a macrocytic anaemia due to folic-acid or vitamin-B_{12} deficiency or both may be caused by a malabsorption syndrome—e.g., tropical sprue. If it is possible to perform a gastric test meal, the presence of free acid will rule out pernicious anaemia and make malabsorption a much more likely cause of the anaemia.

Estimation of faecal fat will only rarely be possible at up-country stations. If this is possible a 72-hour collection in a patient receiving a normal diet containing 50–100 g. of fat daily should be done to establish the presence of steatorrhoea. Daily excretion of more than 6 g. will indicate malabsorption. Microscopy of a random stool may be of value.

A specimen of faeces is emulsified on a glass microscope slide with ethyl alcohol and stained with alcoholic Sudan 3. In severe pancreatic steatorrhoea large numbers of yellow or orange neutral fat globules may be seen ; they may also occur, however, after liquid paraffin ingestion. If a specimen of stool in tropical sprue is treated with 36% acetic acid and three times gently heated to boiling point, soaps and glycerides are converted to free fatty acids which can also be demonstrated as spherical droplets with Sudan 3. Large numbers of fatty acid crystals may also be seen when there is gross faecal fat loss, as in tropical sprue. Microscopy may also reveal undigested meat fibres in pancreatic disease. An absence of trypsin in the stool in severe chronic pancreatitis may occasionally be demonstrated by placing a specimen of faeces on an exposed *x*-ray film ; removal of the black emulsion will not usually occur ; this test must, however, be interpreted with caution. Microscopic examination of the stool may also be of value in detecting intestinal infestations. Hookworm ova and larvae of *Strongyloides* should be found. In some, but not all, cases of *Giardia lamblia* infestation this is also helpful.

In cases of severe disaccharidase deficiency—i.e., when there is either a primary deficiency of lactase, or severe mucosal damage—the appropriate disaccharides are not hydrolysed and an excessive amount of reducing substance may be detected in the stool. An approximate estimate is obtained by the "Clinitest" technique. A specimen of liquid stool is

diluted with its own volume of water, and five drops of the suspension are mixed with ten drops of water and a "Clinitest" tablet in a test-tube. The result can be expressed as g. per 100 ml. stool. Amounts of 3 g. per 100 ml. stool may be present in severe cases of disaccharidase deficiency, although the presence of any reducing substance is abnormal. In such cases stool *p*H which can be measured with *p*H paper may be acid (less than *p*H 6.0) owing to the presence of lactic and other volatile fatty acids derived from bacterial action on the unabsorbed lactose and other disaccharides.

If *x*-ray facilities are available straight *x*-ray of the abdomen may reveal calcification within the pancreas in chronic pancreatic disease. This varies from fine disseminated calculi in the tail and body of the pancreas to larger discrete calculi which may be so diffuse that the whole pancreas is outlined (Fig. 2). In tuberculosis of the small intestine diagnosis may be facilitated by finding evidence of tuberculosis in the chest *x*-ray or calcified lymph glands in the straight film of the abdomen.

Other investigations may be required to reach a firm diagnosis of the cause of malabsorption. These include oral glucose tolerance, D-xylose absorption, tests of pancreatic function (e.g., the secretin-pancreozymin provocation test), serum folate, formiminoglutamic acid excretion, serum B_{12}, and the Schilling test. A barium meal, radiology of the small intestine by small bowel enema, and peroral jejunal and ileal biopsy are also of great value. An augmented histamine test meal and a vitamin-A absorption test may be helpful. In long-standing cases estimation of the serum calcium and skeletal *x*-rays may reveal osteomalacia. Most of these tests, however, will be performed only in large well-equipped hospitals, of which there are few in tropical countries.

Management

Table III gives a summary of the principles of management of a patient with the malabsorption syndrome. An accurate diagnosis should if possible be made in all cases before treatment is started, and this will in very many necessitate transfer of the patient to a larger hospital with good diagnostic facilities. As soon as diagnosis is reached management is usually fairly straightforward.

During the phase of active malabsorption general replacement therapy is indicated. A high-calorie, high-protein, low-fat diet with adequate replacement of minerals and vitamins is necessary. Symptomatic treatment may be necessary if diarrhoea is particularly troublesome.

Pancreatic disease is difficult to manage and there is no cure. Pancreatic extract (pancreatin *B.P.*) may be given orally before meals, and increase in weight usually occurs. The diabetes mellitus which often accompanies this disease is usually fairly easily managed either with insulin or occasionally with oral hypoglycaemic agents. Some patients, however, require an astonishingly high dose of insulin for stabilization.

In tropical sprue initial treatment should be carried out in hospital. Spontaneous recovery may occur, although the overall mortality rate in untreated cases is very high. It was formerly thought that expatriates who contracted the disease had to be moved to temperate climates. Recent evidence indicates that if a satisfactory cure is obtained recurrence is unusual even if the patient is left in the tropics; there is as yet, however, no really satisfactory follow-up study available. Most cases respond to folic acid alone (Table III). Response is usually dramatic, often in the first few days, and the megaloblastic anaemia improves immediately; the intestinal mucosa returns to normal in 12–18 months. Owing to involvement of the ileum in tropical sprue (unlike adult coeliac disease), if folic acid is given and vitamin B_{12} is not, cases of subacute combined degeneration of the cord may be encountered. Broad-spectrum antibiotics produce a slower and less spectacular response than folic acid. Both folic acid and antibiotics may be used in a severe case. Failure of response to folic acid and antibiotics may indicate that the diagnosis of tropical sprue is wrong. Tropical sprue does not respond to a gluten-free diet. The long-term outlook is very good.

Where malabsorption is due to intestinal resection, if the terminal ileum is involved, vitamin-B_{12} supplements will be required, as this is the only site of absorption of this vitamin.

It is often worth trying a gluten-free diet if this is possible, as gluten-induced enteropathies (adult coeliac and coeliac disease) undoubtedly occur in the tropics. The dietary restrictions must be very rigidly observed. Response may be delayed for up to six months after diagnosis. Some seem to be perpetuated by an abnormal bacterial flora, and broad-spectrum antibiotics are then of value. In a minority A.C.T.H. or corticosteroids may be necessary to produce a remission, but here careful supervision and constant awareness of the complications of this form of treatment are required. Continuation on a gluten-free diet throughout life is usually necessary.

In cases of lactose intolerance a non-lactose diet is required. Treatment must be rigidly carried out, for even small amounts of lactose in milk products will precipitate diarrhoea in a severe

TABLE III.—*Management of a Patient with Malabsorption*

GENERAL PRINCIPLES		
High-calorie, high-protein, low-fat diet.		
(a) *Replacement* (during period of *active malabsorption*)		
Tab. aneurin. co. fort.	1 t.d.s.	Oral
Folic acid	20 mg. daily	,,
Vitamin B_{12}	100 µg. monthly	Intramuscular
Ascorbic acid	50 mg. daily	Oral
Vitamin A	4,000 i.u. daily	,,
,, D	10,000 i.u. daily	,,
,, K (water soluble)	20 mg. daily	,,
,, E	100 mg. daily	,,
Ferrous gluconate	1·0 g. daily	,,
Calcium ,,	15 g. daily	,,
(b) *Symptomatic*		
Mist. kaolin. et morphin.	½ fl. oz. t.d.s.	,,
Codeine phosphate	30 mg. t.d.s.	,,
SPECIFIC TREATMENT		
Chronic pancreatitis		
Pancreatic extract, pancreatin *B.P.*	3 g. t.d.s. before meals	Oral
Insulin	..	Subcutaneous
or tolbutamide (to control diabetes mellitus)	..	Oral
Tropical sprue		
Folic acid	0·2 mg. daily (8 weeks)	Intramuscular
	5 mg. daily (6–12 months)	Oral
Vitamin B_{12}	100 µg. monthly (12 months)	Intramuscular
Succinyl sulphathiazole	10 g. daily (5 days)	Oral
Chlortetracycline	2 g. daily (5 days)	
Chloramphenicol	2 g. daily (5 days) (consecutively)	,,
Parasites		
Ankylostomiasis		
Ferrous sulphate	100 mg. t.d.s. (continue for 3/12 after Hb is normal)	,,
Bephenium hydroxynaphthoate (Alcopar)	5 g. daily on empty stomach (3 consecutive days)	,,
or tetrachlorethylene	4 ml. stat.	,,
Strongyloides stercoralis		
Dithiazanine	200 mg. t.d.s. (21 days)	,,
or thiabendazole	25 mg./kg. body weight (2 days)	,,
Giardia lamblia		
Mepacrine	100 mg. t.d.s. (5 days) (repeat after 1 week if stool still positive)	,,
or metronidazole	200 mg. t.d.s. (7 days)	,,
Lactose intolerance		
Lactose-free diet		,,
Milk, creams, ice-creams, milk powder, etc., must be excluded. Commercial yoghurt may contain some lactose (lactose is not hydrolysed by boiling)		
Gluten-induced enteropathy (adult coeliac disease, coeliac disease)		
Avoid all foods containing even traces of wheat or rye gluten indefinitely. Very many commercial foods, sweets, ice-creams, etc., contain wheat gluten. (A list of suitable foods is given in many textbooks of medicine.) Corticosteroids may be required in a few cases (e.g. prednisone, 10–15 mg. daily)		,,

case. In the secondary forms treatment can be discontinued as the mucosa recovers and lactase reappears.

Summary and Conclusions

Malabsorption syndromes are common in the tropics ; the causes have a definite geographical distribution. Protein-calorie malnutrition is the commonest and often most difficult differential diagnosis. Common causes in temperate regions (e.g., adult coeliac disease and coeliac disease) seem to be less common, but there is evidence that this is merely because they have not been properly looked for. In Africa chronic calcified pancreatic disease is undoubtedly a more common cause than in most temperate areas, and in the Far East tropical sprue accounts for many cases. Recent demonstration of disaccharidase deficiencies—either primary or secondary—in several parts of the tropics may lead to the more adequate treatment of some cases of diarrhoea and malabsorption. It is most important to exclude other causes, such as those commonly seen in temperate zones, for only by systematic exclusion will it become clear which are the truly common causes in any locality.

A full clinical history and examination, together with a simple haematological, biochemical, and radiological examination, will allow a reasonable diagnosis in some cases. Careful macroscopic inspection of the stool is of very great importance, though malabsorption may be present without gross abnormalities. In many cases it is impossible to arrive at the exact cause of the syndrome unless the diagnostic facilities of a large hospital are available. Treatment is often simple and can easily be maintained at up-country stations when the diagnosis has been made. It is essential to consider the entire differential diagnosis in every case.

TODAY'S DRUGS

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Nitrites and Nitrates in the Treatment of Ischaemic Heart Disease

Ischaemic heart disease or coronary failure results when the supply of oxygenated blood through the coronary arteries is inadequate to meet the demands of cardiac muscle. Occlusive disease of the coronary vessels is nearly always the result of atherosclerosis. This is a disorder affecting large arteries in which fatty deposits and fibrous nodules narrow the lumen of the artery, reduce the potential blood flow, and predispose to intravascular thrombosis and the clinical syndrome of angina of effort.

At rest there is little difference between the rate of coronary blood flow in the normal subject and in the patient with coronary artery disease. However, a normal individual can increase his coronary blood flow severalfold, but the patient with coronary artery disease is unable to do so, and indeed may not even be able to increase the resting blood flow at all.

The normal coronary circulation delivers more blood to the myocardium on demand, and the strongest physiological stimulus to coronary vasodilatation is hypoxia. Angina of effort develops only when there is severe myocardial hypoxia as a result of inadequate perfusion, and, under these circumstances, the affected coronary vessels are already under the maximum physiological stimulus to dilate.

Nitroglycerin and Nitrites

The drug that betters this physiological dilating mechanism does not exist. However, the beneficial effects of nitroglycerin (glyceryl trinitrate) in angina of effort are undoubted, and indeed have been known for over 100 years, but this is not the result of coronary vasodilatation.

The basic pharmacological property of nitrites is to relax smooth muscle, and it is the effect on vascular smooth muscle that is particularly relevant to the patient with ischaemic heart disease. The major effect of nitrites is on the small postcapillary vessels. As a result of relaxation of the smooth muscle of these vessels the mean systemic arterial blood pressure falls, and this reduces the oxygen requirements of the heart usually to a level which can be adequately supported by the unaltered coronary blood flow. While it is true that nitroglycerin dilates the coronary arteries of normal human beings, it does not increase the coronary blood flow in patients whose vessels are damaged by atheroma, and whose vessels are already maximally dilated as a result of local tissue hypoxia. It is therefore misleading to call nitroglycerin and other similar drugs coronary vasodilators. It is also unlikely that these drugs will stimulate the development of a collateral circulation, and, indeed, proof of any beneficial effect in promoting the development of such collateral vessels in patients with coronary artery disease is lacking.

Long-acting Compounds

The effects of nitroglycerin and amyl nitrite, though beneficial for the acute attack of angina, are short-lived, and attempts have been made to produce drugs with a prolonged action. Many preparations have been marketed claiming to be long-acting coronary vasodilators, but not only do they have no vasodilating effect on the diseased coronary arteries but none has been shown to have any greater effect on angina of effort than a placebo.

The problems of assessing these drugs are great. Objective evaluation of changes in the coronary circulation is difficult. Coronary arteriography cannot give the conclusive evidence, as even if an increase in the calibre of coronary arteries is demonstrated this does not prove that there is an increase in blood flow, as the smaller arterioles cannot be visualized, and these are the vessels that regulate blood flow. If isotope studies of coronary blood flow demonstrate an increase, this does not indicate that the increase in flow is to the ischaemic area. Indeed, this is unlikely, as the diseased vessel is probably not able to dilate further. The electrocardiogram is often used as an objective measure of the patient's exercise tolerance, but even this has pitfalls, as repetitive tests are executed with decreasing effort and anxiety.

These objective methods do not measure angina. Angina is a syndrome which cannot be measured objectively. Subjective methods are therefore essential to the clinical assessment of therapeutic agents, and only the controlled trial can determine the efficacy of a new drug.

A large proportion of patients with angina improve on placebo therapy. The knowledge that they are involved in a test of a potentially effective treatment reduces the incidence of angina in 50% of cases. Anxiety stimulates the sympathetic innervation of the heart and brings about the release of endogenous noradrenaline, which increases the oxygen requirement of the heart by increasing cardiac work and metabolism. Any drug given with enthusiasm will allay anxiety, and will therefore improve the patient's symptoms. It is thus essential that