measured, is the gastro-intestinal disturbance produced by larger doses. How far, if at all, this exceeds that produced by TC remains to be determined by further experience. This kind of tetracycline diarrhoea—as distinct from the much severer form due to infection of the gut by resistant staphylococci—deserves further investigation, and if some means could be found of overcoming it without interfering with the absorption of the drug all tetracycline therapy would be facilitated. Is it a chemical effect on the bowel mucosa or on the bowel contents, or does it operate through disturbance of the balance of the intestinal flora ? Is it promoted by relatively poor absorption and thus a higher concentration of the drug in the bowel ? If answers could be found to these questions, this nuisance factor might cease to operate in the choice between one tetracycline and another, or between tetracyclines generally and other drugs.

Summary

This paper reviews all the existing literature on demethylchlortetracycline (DMCT) and the results of other unpublished studies.

The significant properties of DMCT are: (1) high stability ; (2) an activity against most bacteria exceeding that of tetracycline (TC) by approximately twofold ; and (3) a rate of renal excretion less than half that of TC, with the result that therapeutic concentrations are maintained in the blood for a much longer time after a dose.

It may be concluded from these facts that DMCT can be administered at longer intervals than other tetracyclines—two daily doses should suffice ; and that a smaller dose of DMCT than of TC should achieve an equivalent therapeutic effect.

Larger doses of DMCT are apt to cause diarrhoea : whether this liability exceeds that of TC is not certain.

A phototoxic reaction peculiar to DMCT may occur in treated patients exposed to bright sunlight.

We are indebted to Lederle Laboratories Ltd. for the supplies of DMCT (" declomycin," " ledermycin ") used in our own studies.

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STEATORRHOEA IN THE ADULT*

BY

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In this lecture I propose to survey the causes of steatorrhoea, and to consider the differential diagnosis and treatment of the malabsorption syndromes.

The pathogenesis of steatorrhoea is a very large subject and the number of conditions that can give rise to it is formidable. For this reason I shall deal with them in tabulated form and select from the list, for closer scrutiny, the subjects in which recent advances have been made, or on which further work is needed.

Group 1

Coeliac Disease. Idiopathic Steatorrhoea. Tropical Sprue

Until a short time ago the only justification for grouping these three together was that the cause of each was unknown.

It is possible, as Adlersberg (1957) believes, that all are due to a constitutional genetic defect which is unmasked by a number of different trigger mechanisms. In the case of coeliac disease and idiopathic steatorrhoea at least, the evidence for a common genetic background is quite strong. Cooke, Peeney, and Hawkins (1953) noted that many of their adult patients seemed to conform to a particular somatic type. Other workers, who

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were careful to exclude cases of pancreatic failure, showed that diarrhoea and intolerance of fats were more common among relatives of patients with coeliac disease than in control families (Boyer and Andersen, 1956), and that coeliac children were born to older mothers and in later child ranks than was likely to be due to chance (Thompson, 1951). Moreover, there is a significant increase in the incidence of blood group O among patients with idiopathic steatorrhoea, and both idiopathic steatorrhoea and coeliac disease occur quite often in more than one member of a family (Joske and Benson, 1958; Carter, Sheldon, and Walker, 1959). This happened three times in my series, and in one of these families one member had tropical sprue and the other idiopathic steatorrhoea.

Further evidence linking coeliac disease with idiopathic steatorrhoea is provided, firstly, by the fact that in many adult cases the disease begins in childhood; secondly, by the response to treatment with the gluten-free diet; and, thirdly, by the observation that the histological lesion in the small intestine is probably identical in the two diseases.

The exact way in which wheat and rye gluten cause symptoms in patients with the gluten-enteropathy remains unknown. Gluten added to the diet not only increases the amount of dietary fat excreted but also increases the amount lost from endogenous sources. Weijers and van de Kamer have shown that feeding gluten or gliadin raises the bound forms of glutamine in the blood to higher levels in children with coeliac disease than it does in normal controls. They also showed that if the gluten is totally hydrolysed to its component amino-acids it is harmless and that free glutamine by itself is non-toxic. They concluded that the harmful fraction is a glutamine-peptide complex (van de Kamer and Weijers, 1955; Weijers and van de Kamer, 1955).

Frazer (1956) has been unable to demonstrate any difference *in vitro* between the digestion of wheat gluten by juices obtained from children with coeliac disease and from normal subjects, but the product of such digestion, although harmless to normal individuals, is toxic to patients with coeliac disease. He has shown, further, that if the toxic fraction is incubated with an extract of pig's intestinal mucosa it loses its toxic properties. In recent experiments he and his colleagues have demonstrated that the harmful effect is not due to the chemical treatment that the flour has received or to residual gluten still present in the enzymic hydrolysate. As a result of their studies, they have suggested that the basic defect in the gluten enteropathy is the absence of an enzyme from the wall of the intestine, lack of which makes it impossible for a patient with the coeliac syndrome to break down glutamine containing peptides (Frazer, Fletcher, Ross, Shaw, Sammons, and Schneider, 1959). Such a mechanism would explain the high levels of bound glutamine in the blood in patients with the coeliac syndrome; but, curiously, it is the glutamine in the form in which it is bound in wheat and rye protein which does the damage, for it occurs in considerable quantities in bound forms in other proteins, such as casein, and yet these are harmless.

In spite of these interesting experiments, and until the aetiology is precisely known, we should be wary of assuming that idiopathic steatorrhoea and coeliac disease are one and the same. Some, probably the great majority, of the adult cases are due to a gluten-induced enteropathy, but there remains a small number that do not respond to the gluten-free diet, and yet no other cause for the steatorrhoea can be found. It is tempting to assume that these patients have not adhered to their diet strictly; but French, Hawkins, and Smith (1957), in their careful study of 22 patients, found six who failed to improve, and they were unwilling to accept that breaks in the dietary regime were always responsible. It is possible that in these patients the disease had progressed too far for recovery to take place, but it is also possible that they represent a separate entity with a different aetiology. In future, careful correlation between the response to treatment and the histology and perhaps the histochemistry of the small intestine may provide the answer.

It is clear that tropical sprue differs from idiopathic steatorrhoea, for it will not respond to the withdrawal of gluten from the diet, but it will to treatment with antibiotics. The results obtained by French, Gaddie, and Smith (1956) were so definite that I have been surprised that they have not been confirmed by other workers in India or the Far East with access to larger series of cases; but perhaps our dwindling political and medical contact with the sprue areas is the cause of this. In view of the different therapeutic response, it is odd that the histological picture of the small intestine in tropical sprue is so similar to that in idiopathic steatorrhoea and coeliac disease. This could be used as an argument in support of Adlersberg's idea of a common genetic background, but it may be that the atrophy of the mucosa and the loss of villous pattern can result from a number of different causes and need not imply a common aetiology.

Group 2.—Failure of Digestion of Fat

Obstructive Jaundice. Disease of the Pancreas (Alcoholic Cirrhosis). Gastric Operations

In this group the steatorrhoea is primarily the result of impaired fat-digestion. I have linked alcoholic cirrhosis with the pancreatic steatorrhoeas because here the failure of fat-absorption is due to pancreatic damage and not to the primary liver disease (Fast, Wolfe, Stormont, and Davidson, 1959). Traditionally, the steatorrhoea in this group has been regarded as a nuisance which causes considerable loss of weight, but it has not been thought to be of any real significance. This idea is both false and dangerous. It is true that, at least in the first two, anaemia does not usually occur and water-soluble substances are absorbed normally, but in all three loss of fat-soluble vitamins in the stools may lead to serious symptoms.

Fig. 1 shows the pelvis and right hip of a patient who developed steatorrhoea after a by-pass operation on her stomach. Her serum calcium was low and biopsy of the bone revealed osteomalacia. The bones were so soft that the pin used to fix the fracture protruded right through the neck of the femur.

Interest in the role of the pancreas in the malabsorption syndromes has been reawakened as the result of recent work on fibrocystic disease. Originally it was thought to be solely a disease of the pancreas, but it is now known to be a widespread disorder of exocrine glands involving as well as the respiratory tract the liver, Brunner's glands in the intestine, and the sweat and salivary glands (Di Sant'Agnese, 1956). It is hereditary and is transmitted as a recessive. Several theories have been put forward to explain its manifestations, the most ingenious being that, as all the affected glands are cholinergic, the symptoms might be the result of their continued over-

secretion due either to liberation of excessive quantities of acetylcholine or lack of the enzymes which destroy it (Roberts, 1959).

Fibrocystic disease comes within my terms of reference because, although it is an important cause of death in childhood, the sufferers may survive into adult life. The involvement of the pancreas is clinically silent and painless, and the true cause of the defect in secretion is easy to overlook. Some of the patients have bronchiectasis and emphysema, others cirrhosis of the liver, and it has been recorded in association with transposition of the viscera and Kartagener's syndrome. After childhood the pathology of the pancreas is a lipomatosis, and the pathognomonic cystic fibrosis is seen only in infancy (Andersen, 1958; Brown and Smith, 1959).

Yet another syndrome which has recently come to the fore is the triad of non-insulin-secreting islet-cell tumours of the pancreas, marked gastric hypersecretion, and recurrent ulceration of the stomach and small bowel, first described by Zollinger and Ellison (1955). In many of the cases the tumours are multiple and involve other endocrine glands, including the pituitary, parathyroids, and adrenals, in addition to the pancreas.

The main emphasis in the first papers was on the severity of the gastro-intestinal ulceration, but Maynard and Point (1958) drew attention to a patient in whom the gastric hypersecretion was accompanied by malabsorption and steatorrhoea. The cause of the steatorrhoea is believed to be due either to inactivation of pancreatic enzymes at the low *p*H induced by the overwhelming flow of acid, or to an outpouring of mucus by the

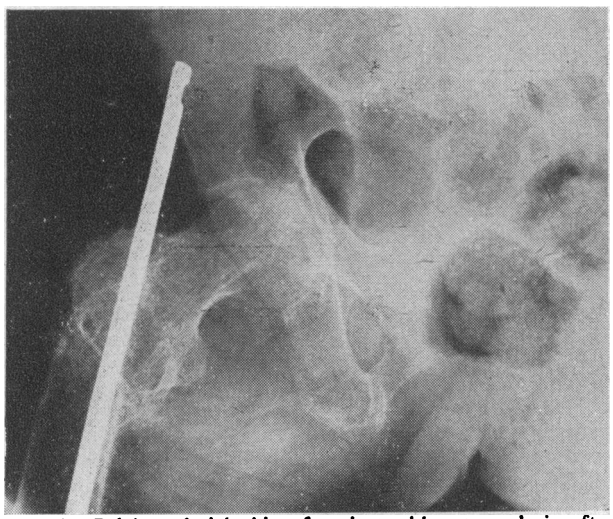

FIG. 1.—Pelvis and right hip of patient with osteomalacia after a by-pass operation on the stomach.

intestine in response to this. Whichever is correct, England, French, Rawson, and Stammers (1960) have shown that if the pancreatic tumour can be totally removed the secretion of acid falls to normal and the steatorrhoea disappears. However, Zollinger and Elliott (1959) believe that the safest course is to carry out a total gastrectomy and remove the acid-secreting mucosa completely, because if metastasis of the tumour has occurred the hypersecretion of acid will continue from any gastric mucosa that remains.

The steatorrhoea that follows partial and total gastrectomy is also chiefly the result of faulty digestion, and it has two main causes. The first is that in total gastrectomy, in Polya partial gastrectomy, and in by-passed stomachs the food does not enter the duodenum, and thus the natural stimulus for the secretion of pancreatic juice and the release of bile into the intestine is lacking. The second is that in all gastric resections, including Billroth's first operation, the gastric reservoir is reduced and food is shot into the upper small intestine too rapidly for adequate mixing (Brain, 1953; Main and Gobbel, 1960). In these patients meals rich in carbohydrate make the steatorrhoea worse, possibly by promoting the reflex secretion of adrenaline which inhibits the flow of pancreatic juice. Sometimes the steatorrhoea can be decreased by giving pancreatin or bile salts by mouth, but in adequate doses they are likely to make the diarrhoea worse. However, Vanamee, Lawrence, Levin, Peterson, and Randall (1959) have shown that as little as an ounce (28 ml.) of N/10 HCl given before meals will reduce the steatorrhoea and stop the diarrhoea by providing the physiological stimulus for the secretion of pancreatic juice. Presumably this is the explanation for the old clinical observation that very small doses of acid will exert a dramatic effect on the diarrhoea of achlorhydric patients.

A third mechanism which may cause steatorrhoea in some of these patients in whom gastro-duodenal continuity has not been preserved is dilatation of the afferent loop and stagnation of its contents. It has been shown that when this occurs coliform organisms can be cultured from the dilated bowel and the steatorrhoea can be decreased by antibiotics (Wirts, Goldstein, Calaresu, Kramer, and Concannon, 1959).

Group 3.—Derangement of Normal Anatomy Alteration in Bacterial Flora of Gut

Blind Loops. Fistulae. Diverticulosis of Jejunum. Resections

In Oxford we have always been interested in this group, which traditionally is closely bound up with the pathogenesis of the megaloblastic anaemias.

Most of the earlier reports were concerned with the ill effects of strictures of the small intestine or with the results of anastomoses which had isolated loops of gut and shortened the effective length of the bowel. Recently we have learnt that similar symptoms may be produced by massive diverticulosis of the small intestine.

In 1930 Taylor reported the case of a patient with pernicious anaemia and a gastro-enterostomy in whom numerous diverticula of the jejunum were found at necropsy. Montuschi (1949) and Zingg (1950) each described cases of jejunal diverticulosis with steatorrhoea, and in 1954 Bedford and I were lucky enough to encounter two patients with the triad of jejunal diverticulosis, steatorrhoea, and megaloblastic anaemia (Badenoch and Bedford, 1954). It occurred to us that the narrow-mouthed diverticula might be acting as stagnant pools where bacteria could flourish, and that the condition could well be regarded as a variant of the blind-loop syndrome.

The classical views of Faber (1895) and Meulengracht (1921), that the anaemia and disturbance in intestinal function which occur in these patients are the result of bacterial invasion of the bowel, have been amply confirmed. Experiments on animals have shown that if strictures are made in the upper intestine the incidence of anaemia is greater if the bowel becomes infected (Seyderhelm, Lehmann, and Wichels, 1924), and, as Cameron, Watson, and Witts (1949) have demonstrated, blind loops more often give rise to anaemia and steatorrhoea if they are designed so that normal peristalsis

cannot empty them and they become dilated with stagnant contents.

In the human cases, studies of the absorption of vitamin B_{12} have also emphasized the importance of infection, for sterilizing the bowel with antibiotics or restoring the normal anatomy by surgery will often improve absorption and cure the anaemia (Halsted, Lewis, and Gasster, 1956; Mollin, Booth, and Baker, 1957).

The cause of the steatorrhoea in patients with the blind-loop syndrome, or diverticulosis of the jejunum, is more difficult to explain. None the less, it must be related to the presence of bacteria, because it, too, can be improved by antibiotics or by removing the offending loop or the segment of bowel bearing the diverticula (Watkinson, Feather, Marson, and Dossett, 1959).

In patients who have suffered massive resection of the gut, the removal of up to two-thirds of the small intestine is followed by little incapacity so long as the remaining bowel is normal, and survival with only 7 inches (18 cm.) of jejunum has been recorded (Jackson, Linder, and Berman, 1951). There are a number of interesting differences between these patients and those with blind loops of bowel. Initially, there is profound loss of weight with impairment of absorption of all foodstuffs except alcohol, which is absorbed from the stomach. However, in man as in animals, hypertrophy of the remaining bowel usually occurs and the defect in absorption lessens with time. Megaloblastic anaemia is very uncommon, but in cases where the ileum has been totally removed Mollin, Booth, and Baker (1957) have shown that there is gross failure to absorb vitamin B_{12}; so presumably there must be a danger that subacute combined degeneration of the cord will develop, even if anaemia is prevented by adequate supplies of folic acid. Similarly, iron deficiency is rare unless there is bleeding, because the iron can be absorbed from the intact duodenum.

Usually hypocalcaemia and tetany are not a marked feature of massive resections. In this context (Morse, Dickson, Nonamaker, and Embree, 1959) have reported an interesting case in which the surgeon resected all but the proximal 3 feet (90 cm.) of jejunum and made small blind pouches of jejunum and colon at the time of the anastomosis. Tetany developed, and oral and intramuscular injections of calcium and large doses of vitamin D had little effect on the serum calcium. Reconstitution of the anastomosis seven months later to eliminate the blind loops of gut produced a striking improvement in the blood calcium and abolished the tetany, although the steatorrhoea continued.

In patients that survive for any length of time after massive resection, the picture is complicated by a gradual failure of pancreatic function which in turn contributes to the steatorrhoea. The cause of the atrophy of the pancreas is not known, but it may be the result of chronic malnutrition, especially of protein as occurs in kwashiorkor, or it may be due to lack of stimulation of the pancreas by secretin (Jackson, Linder, and Berman, 1951; Dreiling, 1957; Leitner, 1958).

Group 4.—Infiltration of Intestinal Mucosa (Blockage of Lymphatics)

Crohn's Disease. Tabes Mesenterica. The Lymphomata. Amyloid Disease. Systemic Sclerosis (Scleroderma). Whipple's Disease

Traditionally the steatorrhoea in this group has been attributed to blockage of lymphatics, but involvement of the mucosa is probably more important because, even in Hodgkin's disease and other lymphomatous conditions of the mesentery, not only fat but also sugar is poorly absorbed (French, 1955). In Crohn's disease and other chronic granulomata the ill effects of the underlying disease are often increased by those of resection of the gut and the formation of blind loops of bowel. In such patients the margin of safety is much less than in normal individuals, and symptoms may worsen after the removal of quite a short length of intestine. Tabes mesenterica is a much less common cause of steatorrhoea than it used to be; there were only four cases in my series. However, from time to time massive mesenteric calcification will suggest the diagnosis.

Diarrhoea and steatorrhoea have long been recognized as part of the syndrome of secondary amyloidosis, but the gut may also be involved in primary systemic amyloidosis, although such cases are rare (Bassett, Adams, Goldman, and Fishkin, 1952; Mamou, Savoie, and Damblon, 1955).

Another rare condition which may involve the intestine and lead to the development of steatorrhoea is diffuse systemic sclerosis (scleroderma). The involvement of the bowel is usually a late manifestation and is less common than changes in the skin or oesophagus. Heartburn and abdominal pain are prone to occur and diarrhoea may alternate with constipation. *X*-ray examination of the bowel shows distended coils of gut and diminished peristalsis (Rosenthal, 1957; Sommerville, Bargen, and Pugh, 1959).

It is over 50 years since Whipple first described the disease which bears his name. He reported the case of a young physician who in life had suffered from cough, loss of weight, arthralgia, and diarrhoea. At necropsy the macrophages of the lymph nodes of the mesentery and of the intestinal wall were distended with material which at first was thought to be fat (Whipple, 1907). There are now over 60 well-documented cases in the literature, and the major landmarks in our understanding of the disease have been the demonstration by Black-Schaffer (1949) that the material in the macrophages is a glycoprotein, and the discovery that the peripheral nodes and many other tissues are involved in the process (Puite and Tesluk, 1955).

We have had the opportunity to observe one of these cases closely.

The patient was admitted to hospital in 1956 at the age of 48, with a history of diarrhoea, loss of weight, and anaemia of two years' duration. Investigation revealed a profound iron deficiency and steatorrhoea; but a raised E.S.R., the presence of occult blood in the stools, and the fact that radio-iron was absorbed normally, all pointed to the steatorrhoea being secondary to an anatomical lesion of the bowel. Mr. Corry kindly carried out a laparotomy, and the typical changes of Whipple's disease were found. Fig. 2 shows the appearance of the mucosa of the jejunum with club-shaped villi containing numerous macrophages with large foamy cytoplasm distended with P.A.S.-positive material. Over the next three years his illness pursued a stormy course. Steroids failed to bring about improvement, and, although *x* rays to the abdomen seemed to produce benefit for a time, he gradually went downhill. There were episodes of severe hypokalaemia and subacute intestinal obstruction, and, finally, in his last year he developed a total gaze paralysis and episodic mental confusion. He died in November, 1959, five years after the onset of his illness. At necropsy P.A.S.-staining material was found in many tissues. Particularly interesting were the vegetations on the heart valves, which in section showed the P.A.S-positive material, and the demonstration of the involvement of the brain and cord. Fig. 3 is a section of the thalamus

showing the presence of P.A.S.-positive material. Some of it is extracellular, but most is in close association with clumps of microglia. Fig. 4 shows the accumulation of the material in the grey matter of a pontine nucleus, also in association with microglial cells. The white matter is relatively normal.

The cause of Whipple's disease is still unknown, but three main theories have been advanced to explain it. The first, now no longer held, was that there was a basic defect in fat metabolism. The second was that an abnormal mucoprotein was produced within the lumen of the intestine and that this was absorbed and gave rise to the symptoms. This was difficult to sustain because of the fact that the arthralgias and other systemic symptoms often preceded the involvement of the gut by many years, and also because the level of seromucoids was often just as high in idiopathic steatorrhoea as in Whipple's disease. The third theory of aetiology is that

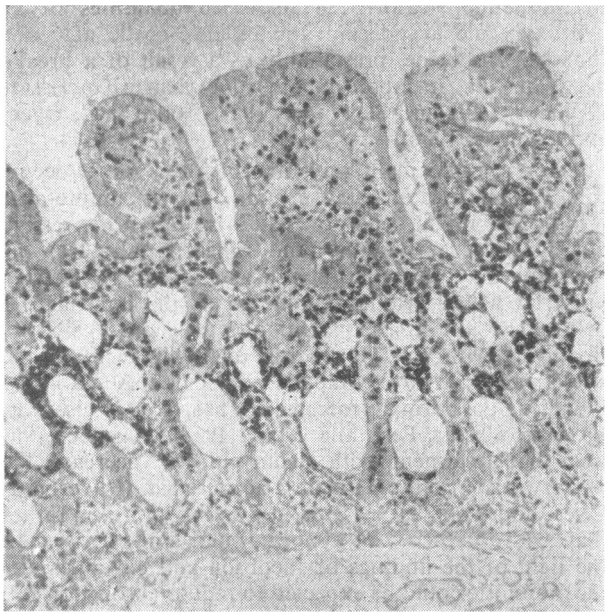

FIG. 2.—Section of jejunal mucosa (P.A.S. stain) from patient with Whipple's disease, showing club-shaped villi filled with macrophages containing P.A.S.-positive material.

Whipple's disease should be classed as a collagen disease. In support of this, Taft, Liddelow, and Ralston (1959) have put forward evidence that the abnormal material present in the macrophages may not be phagocytosed but perhaps is formed *in situ*. They showed with appropriate staining that some of the cells of the reticulo-endothelial system seemed to be producing ribonucleic acids normally, while others were producing glycoprotein, and in some there was a transition from one to the other. They could not explain why the change had occurred, but thought that it might be due to a genetic defect, as has been suggested by Puite and Tesluk (1955), or to a low-grade neoplastic process.

The idea that the disease is due to a change in the nature of the ground substance of the cells is attractive, and the pattern of distribution of the P.A.S.-positive material in the brain of my patient is more in keeping with this than with the suggestion that some abnormal substance had been filtered off from the blood-stream.

Group 5.—Infection of Bowel by Pathogens

Giardia lamblia. Candida. Coccidioides. Proteus vulgaris

This is an unimportant group numerically. The flagellate *Giardia lamblia* will produce a steatorrhoea, and the ease with which it can be eradicated by treatment with mepacrine makes it worth while to look for the cysts in the stools or for the flagellates in the duodenal aspirate (Cortner, 1959).

The part played by infection with other known pathogens is less certain. They may be important in the few cases where the steatorrhoea accompanies agammaglobulinaemia, or when the normal flora of the gut has been destroyed by a broad-spectrum antibiotic (Merliss and Hoffman, 1951).

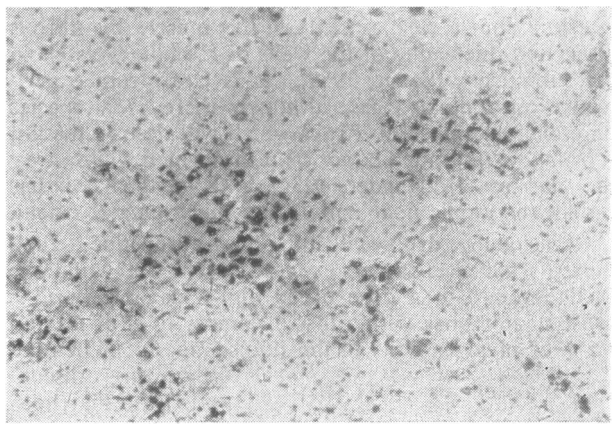

FIG. 3.—Section of thalamus from patient with Whipple's disease (P.A.S. stain), showing most of the P.A.S.-positive material is in close association with clumps of microglia.

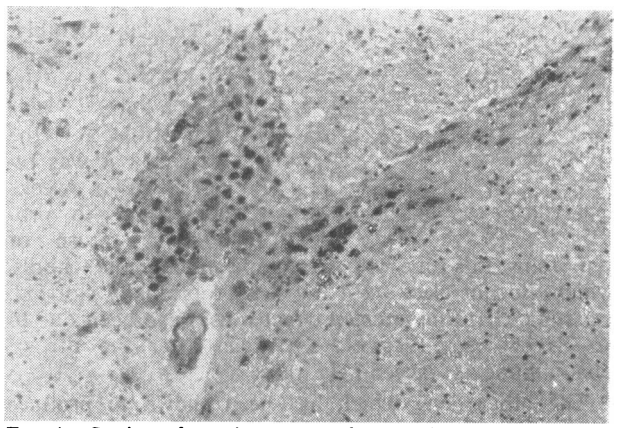

FIG. 4.—Section of pontine nucleus from patient with Whipple's disease (P.A.S. stain), showing accumulation of P.A.S.-positive material in the grey matter. The white matter is relatively normal.

Group 6.—Failure of Blood Supply

Coeliac and Mesenteric Thrombosis or Embolism

Experiments in animals have shown that failure of absorption may occur in states of shock, but it is only in the past two years that mesenteric arterial disease has been recognized as a cause of steatorrhoea in man. In 1958 Joske, Shamma'a, and Drummey reported two interesting cases in which the block in the artery was removed surgically, in one 34 hours and in the other 12 hours after the obstruction had occurred. In both, although the blood supply was restored, failure to absorb fat and other substances developed and the defect took months to recover although the acute symptoms of ischaemia rapidly subsided.

Patients with mesenteric arterial disease are prone to suffer from crampy postprandial abdominal pain, and it is likely, as occurred in one of the two in my series, that they will be diagnosed as suffering from chronic pancreatitis unless the alternative diagnosis is considered.

Group 7.—Iatrogenic Steatorrhoea

X-radiation. Drugs (Phenindione, Neomycin)

In view of the intense metabolic activity of the intestine, it is perhaps not surprising that *x*-radiation to the abdomen will impair absorption. Reeves, Sanders, Isley, Sharpe, and Baylin (1959) found that steatorrhoea developed in 13 out of 29 patients with tumours of the cervix who were given prophylactic radiation to the abdomen. In chronic cases subacute intestinal obstruction may be a problem. Histological examination of the intestine shows replacement of the muscle by fibrous tissue and thickening of the walls of the blood-vessels in the submucosa (Sauer, 1959). It is clear from experiments on animals that, although there is a species difference, the dose of *x* rays which will destroy the gut is probably not much larger than that which will destroy the marrow (Hollaender, 1954), and yet the latter has caught the public imagination to a much greater extent.

Occasionally, drugs will impair fat absorption. Juel-Jensen (1959) has reported a case in which phenindione ("dindevan") in a dose of 50 mg. a day produced a gross steatorrhoea with a loss of almost 40 g. of fat and 3.5 g. of nitrogen daily in the stools (Fig. 5). When the drug was discontinued the diarrhoea decreased and within a week the stools were normal and the fat excretion had fallen considerably. Because we were not convinced that the phenindione was responsible for the diarrhoea it was restarted two weeks later, only to produce a return of symptoms, this time with blood and mucus in the stools, which did not clear until the drug was finally stopped. I assume that this unusual effect must have been due to an idiosyncrasy, because diarrhoea after the use of phenindione is exceedingly rare.

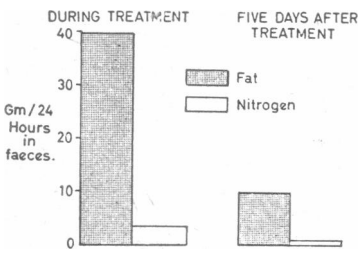

FIG. 5.—Steatorrhoea due to phenindione, showing daily excretion of fat and nitrogen in the faeces while the patient was receiving 50 mg. of phenindione daily and the fall in excretion five days after the drug was stopped.

The other drug which has been shown to produce steatorrhoea is neomycin. This interesting observation by Jacobson and his colleagues may provide the reason for the paradox that while the tetracyclines will produce an improvement in the absorption of vitamin B_{12} in patients with the blind-loop syndrome, neomycin, the most powerful intestinal antiseptic of all, will not (Doscherholmen and Hagen, 1954; Halsted, Lewis, and Gasster, 1956). The way in which it produces the steatorrhoea remains completely unknown, but there is a failure in the absorption not only of fat but also of sugar, iron, and vitamin B_{12}; and histological examination of the jejunal mucosa of the treated patients has shown varying degrees of clubbing of the villi, round-cell infiltration, and oedema of the lamina propria.

Apparently the defect in intestinal function recovers quite quickly once the antibiotic is stopped (Jacobson, Chodos, and Faloon, 1959; Jacobson, Chodos, Prior, and Faloon, 1959).

Group 8.—Miscellaneous Causes of Steatorrhoea

Diabetes Mellitus. Malignant Carcinoid Tumours. Schönlein–Henoch Purpura. Infectious Mononucleosis. Pneumatosis Cystoides

Steatorrhoea may occur in the course of diabetes mellitus. In some of the cases both are due to pancreatic failure, but in others the external secretion of the pancreas has been shown to be normal. The association of the steatorrhoea with diabetic neuropathy has led to the suggestion that the failure of absorption may be due to involvement of the autonomic nerve supply of the bowel (Berge, Wollaeger, Scholz, Rooke, and Sprague, 1956).

Steatorrhoea may occur in association with malignant carcinoid tumours of the intestine (Kowlessar, Law, and Sleisenger, 1959). The cause of the malabsorption is uncertain, but the large amount of 5-hydroxytryptamine circulating in the blood increases gastro-intestinal movements and leads to an outpouring of mucus which could well interfere with absorption (Haverback, 1958). The observation that steatorrhoea may occur in patients with carcinoid tumours may help to shed some light on one of the causes of diarrhoea in idiopathic steatorrhoea itself. In idiopathic steatorrhoea increased quantities of 5-hydroxyindole acetic acid and indole-3-acetic acid are found in the urine, presumably as a result of a breakdown in the metabolism of tryptophan (Kowlessar, Williams, Law, and Sleisenger, 1958; Haverback, Dyce, and Thomas, 1960).

There are two main ways in which this might occur. Firstly, the delay in absorption of the amino-acid tryptophan might lead to the formation of excessive quantities of tryptamine and other metabolites, or, secondly, they might be formed as a result of excessive bacterial action within the lumen of the intestine. I believe that the first explanation is the more likely, for treatment with the gluten-free diet will decrease the excretion of 5-hydroxyindole acetic acid, presumably by favouring the normal processes of absorption (Sleisenger, Law, Kowlessar, Pert, and Almy, 1958). The observation that treatment with neomycin will decrease the urinary excretion of indole-3-acetic acid (Haverback, Dyce, and Thomas, 1960) is in keeping with this rather than with the theory of abnormal bacterial activity. In the light of the findings of Jacobson and his colleagues the antibiotic could be expected to reduce absorption still further (Jacobson, Chodos, Prior, and Faloon, 1959).

The remainder in this group—infectious mononucleosis (Abrahamsen, 1954), Schönlein – Henoch purpura (Eilersen, 1959), and pneumatosis cystoides intestinalis (Yunich and Fradkin, 1958)—are very rarely associated with steatorrhoea, and I have included them only because I wish my clinical picture of the malabsorption syndromes to be complete.

Diagnosis

Now to the problem of diagnosis. The wide spectrum of possible clinical signs at first sight might well seem to make the task a hopeless one. In fact, most patients with malabsorption do pass large, pale, foul stools, and in these the diagnosis is easy. Even if the stools are normal it is decidedly unusual for the patient to complain of a single symptom, and usually the association of several, which could be due to a deficiency state, will suggest the diagnosis. Such is the variation in these cases that at one end of the scale we have patients with a resistant anaemia, or an obscure dermatitis, in whom the diagnosis is considered almost as a policy of despair, and, at the other, patients with the classical stools in whom the estimation of fat-excretion does no more than give numerical respectability to a firm clinical impression. In a syndrome as varied as this can be, the importance of a full and accurate history is paramount,

for the clues may lie as far back as a prolonged illness in infancy or a distant abdominal operation for an appendix abscess.

The results of Annegers, Boutwell, and Ivy (1948) have shown that 95% of normal persons on diets containing up to 150 g. of fat daily excrete less than 7 g. of fat per day in the stools. It is therefore possible to make the diagnosis of steatorrhoea by measurement of the excretion of fat alone without the need for elaborate balance techniques.

There is little doubt that the estimation of the output of fat in the stools is still the most certain way of making the diagnosis, but there is a real need for quick screening tests that can be applied to large groups of subjects. One of these which has given promise is measurement of the absorption of triolein and oleic acid labelled with radioactive iodine. In spite of early doubts about the suitability of radiotriolein as a test, it has been shown that the bond linking the iodine to the fat is unaffected by gastric or pancreatic juice, that there is a good correlation between the absorption curves obtained and those of vitamin A, and that it is handled, in animals at least, in the same way as tripalmitin labelled with ^{14}C.

In idiopathic steatorrhoea the absorption of both radiotriolein and radio-oleic acid is impaired. In pancreatic steatorrhoea, where the fault is primarily in the digestion of fat, triolein is poorly absorbed but oleic acid absorption is normal. In other forms of steatorrhoea the results are inconsistent (Kaplan, Edidin, Fruin, and Baker, 1958; Berkowitz, Sklaroff, Woldow, Jacobs, and Likoff, 1959; Playoust, Wyatt, and Blackburn, 1959).

In the malabsorption syndromes the impairment of fat absorption usually parallels that of other substances, but even in idiopathic steatorrhoea this is not always the case. For this reason it is important to test the absorption of more than one substance in suspected cases. Traditionally, in spite of their disadvantages, a group of oral tolerance tests have been employed for this purpose. The earliest to be used was the glucose-tolerance test, but this has fallen into disfavour with the demonstration that a high proportion of normal persons show flat curves. Butter-fat, vitamin A, and carotene have all been used, but probably the best is the D-xylose absorption test (Hunter and Prevatt, 1958).

Although xylose is not the inert substance it was formerly thought to be, in the absence of renal damage the amount appearing in the urine after an oral dose provides a good index of absorption (Christiansen, Kirsner, and Ablaza, 1959). In normal persons (Fig. 6), after an oral dose of 25 g., from 3.2 to 8.9 g., with a mean of 5.8 g., is excreted in the urine within the first five hours. In untreated idiopathic steatorrhoea the amount excreted is very much less, ranging from 1.2 to 2.1 g., with a mean of 1.7 g. In treated idiopathic steatorrhoea the excretion approaches normal, while in steatorrhoea due to gastric operations and pancreatic disease the mean excretion is exactly the same as in the normal subjects (Perry, unpublished observations). These figures are comparable to those reported by Butterworth, Perez-Santiago, Martinez-de-Jesus, and Santini (1959), who have confirmed that faulty absorption is the cause of the difference between the results obtained in untreated patients with idiopathic steatorrhoea and normal subjects; for, if the xylose is given intravenously, the urinary excretion in the next 24 hours is the same in the two groups.

In difficult cases further information may be obtained by the use of the folic-acid-excretion test (Girdwood, 1953) or from studies of the absorption of radioactive vitamin B_{12} or iron (Badenoch and Callender, 1954a; Callender and Evans, 1955).

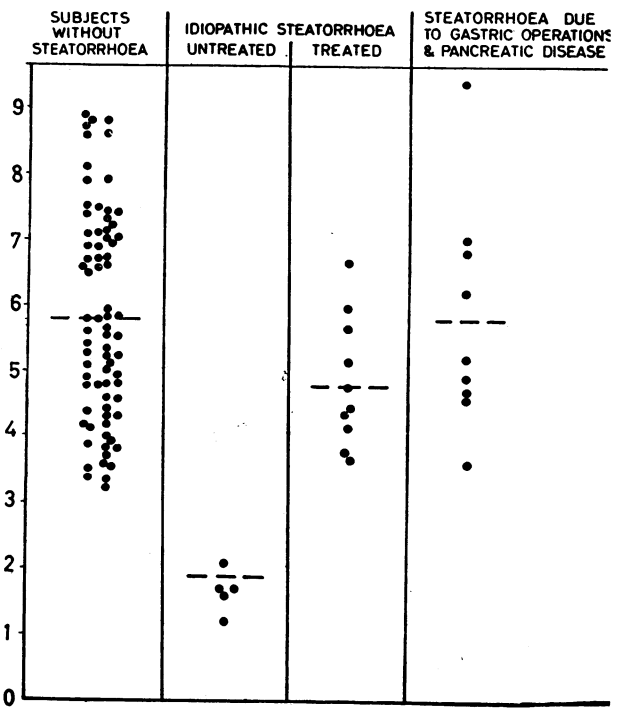

FIG. 6.—Grammes of D-xylose excreted in the urine in the first five hours after an oral dose of 25 g. in 75 control subjects without steatorrhoea, in five untreated and 10 treated patients with idiopathic steatorrhoea, and in nine patients with steatorrhoea due to pancreatic disease or gastric operations. The interrupted horizontal lines indicate the mean in each group (data of S. Perry).

The problem of the differential diagnosis of steatorrhoea has been complicated in the past by the fact that patients with idiopathic steatorrhoea have had to be diagnosed by exclusion. Unless a special search was made for pancreatic failure, occult blood was found in the stools, or one of the screening tests gave an unexpectedly normal result, as in our patient with Whipple's disease, mistakes could easily be made. For this reason careful radiological examination of the bowel should be made in every patient. There is evidence that the radiological changes which are found in idiopathic steatorrhoea depend on the presence of an excess of mucus within the lumen of the gut, and may be either clumping of barium, as is shown in Fig. 7, or a transformation of the normal feathery appearance into a ladder pattern resembling a stack of coins (Fig. 8). The type of pattern found depends, at least in part, on the barium suspension used, the ladder pattern being more common if a non-flocculable barium is employed (Ardran, French, and Mucklow, 1950). The changes are not confined to the idiopathic group, and it is not possible to make the differential diagnosis between idiopathic steatorrhoea and pancreatic steatorrhoea with safety on the *x*-ray pattern of the bowel alone. *X*-ray studies may also show an unsuspected stricture or reveal the presence of regional ileitis or systemic sclerosis.

Some of the structural lesions which can lead to steatorrhoea are extremely difficult to demonstrate. Blind loops can be overlooked and fistulae are often difficult to find, and the clumps of barium within the diverticula of the jejunum may be mistaken for floccules of medium within the lumen of the gut.

Pancreatic steatorrhoea presents a special problem in diagnosis. The output of nitrogen in the faeces is no longer accepted as a safe index of pancreatic failure. It can be high in other forms of steatorrhoea (Taylor, Wollaeger, Comfort, and Power, 1952). The most reliable screening test is measurement of the absorption of radio-oleic acid and triolein, but the only certain way of confirming the diagnosis is to intubate the patient and measure the output of bicarbonate and enzymes in the duodenal juice after stimulation with secretin and pancreozymin. A normal response to secretin does not exclude pancreatic disease, but it makes it virtually certain that it is not the cause of the steatorrhoea (Dreiling, 1957).

In all cases where pancreatic failure is found fibrocystic disease should be excluded by estimation of the chloride content of the sweat. In 140 cases reported by Di Sant'Agnese (1956), with one exception, the range of chloride in the sweat was 50 to 160 mEq/l., with a mean of 106 mEq/l. In contrast, in normal controls it was only 4 to 60 mEq/l., with a mean of 27 mEq/l.

Finally, pancreatic failure can be secondary to malnutrition resulting from steatorrhoea due to some other cause, and an abnormal result to the secretin test must be accepted with reserve in severely ill patients (Dreiling, 1957).

Biopsy of the Mucosa of the Intestine

Here the difficult matter of differential diagnosis rested until biopsy of the mucosa of the small intestine became a practical possibility. It is true that many of the earlier authors, notably Manson-Bahr (1924), thought that there were histological changes in the small intestine at least in tropical sprue, and that in 1954 Paulley published some beautiful pictures of the mucosa of the intestine in idiopathic steatorrhoea which had been obtained at laparotomy. They showed blunting of the villi, atrophy of the mucosa, and infiltration with plasma cells, but the difficulty of obtaining useful material prevented general acceptance of his views. However, the position was radically altered when Shiner (1956) introduced her peroral biopsy tube. For the first time histological examination of the mucosa was possible with little inconvenience to the patient.

Her observations fully confirmed those of Paulley. In contrast to the beautiful finger-like projections of the villi of the normal jejunum (Fig. 9), the mucosa of the small intestine in idiopathic steatorrhoea and coeliac disease is flattened and there is a reduction in absorptive surface (Fig. 10). The villi are short and blunted, there is a variable increase in the cells of their stroma, and the surface epithelium is reduced to a low columnar type with small irregular nuclei (Shiner, 1957; Sakula and Shiner, 1957). Mitoses are more common than usual, and Shiner and Doniach (1959) have suggested that in the coeliac syndrome the cells of the mucosa of the intestine may have a shorter life-span than in normal persons and that desquamation takes place at a faster rate.

In other forms of steatorrhoea when the malabsorption is secondary to pancreatic failure, follows gastric resection, or is symptomatic of a wider pathological process, the mucosa of the jejunum is usually normal and villous atrophy is variable and inconsistent (Shiner, 1957; Baird and Dodge, 1957; Paulley, Fairweather, and Leeming, 1957; Joske and Blackwell, 1959).

Rubin and his colleagues, in two careful studies, have taken the matter further (Rubin, Brandborg, Phelps, and Taylor, 1960; Rubin, Brandborg, Phelps, Taylor, Stemler, Murray, Howry, and Volwiler, 1960). They

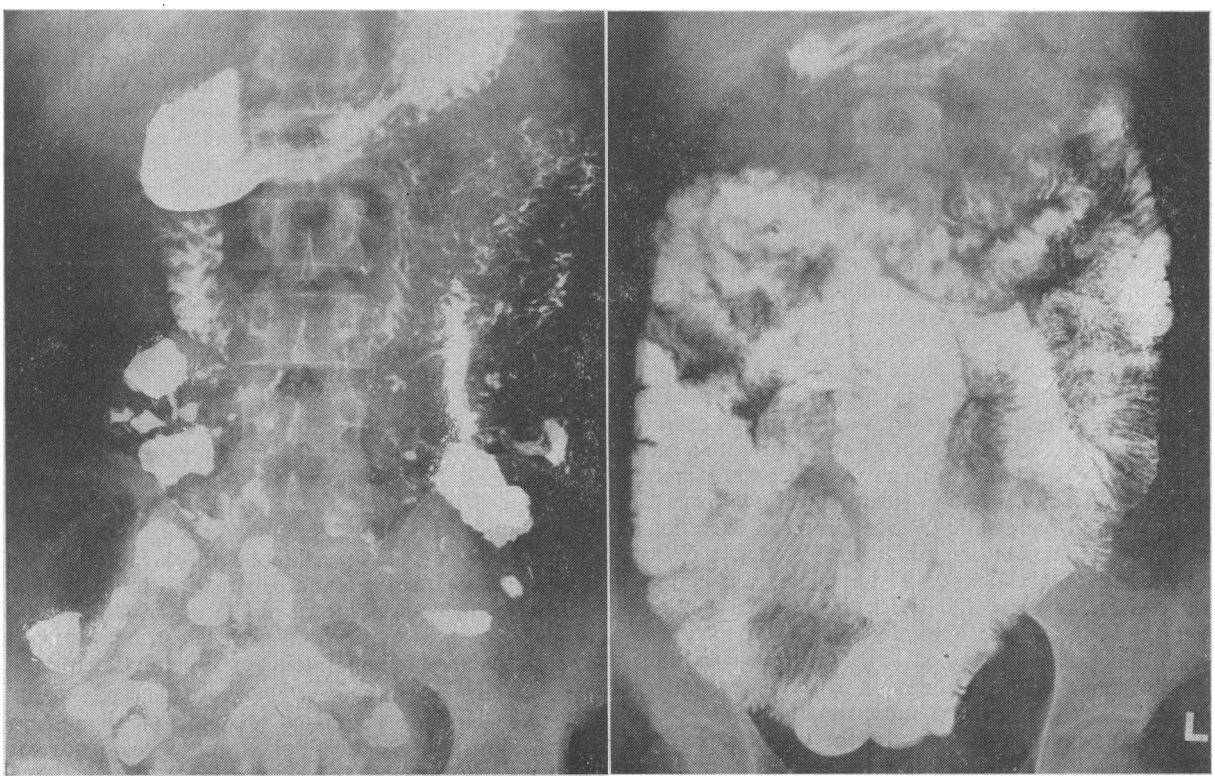

FIG. 7 FIG. 8

FIGS. 7 AND 8.—Small-bowel patterns in the presence of steatorrhoea showing either clumping of barium (Fig. 7, left) or transformation of the normal feathery appearance into a ladder pattern (Fig. 8, right).

agree that the lesion in idiopathic steatorrhoea and coeliac disease, and probably also in tropical sprue, is the same, although in the latter there may be a heavier infiltration with inflammatory cells. They maintain that the best criterion on which to base the diagnosis is a decrease in the overall length of the absorptive surface of the jejunum. By taking up to 10 biopsies from different areas of bowel in the same individual they showed that the degree of change could vary from one part of the duodenum and jejunum to another, but that the lesion was clearly diffuse and involved the whole of the upper small intestine. To their surprise, in two patients in whom the jejunum showed the lesion, biopsies of the ileum were normal. They stress the importance of taking multiple biopsies, because blunted flattened villi were sometimes found in normal persons over Brunner's glands or over lymphoid follicles, and occasionally a very similar picture was found in Crohn's disease, although here the changes were patchy and not diffuse.

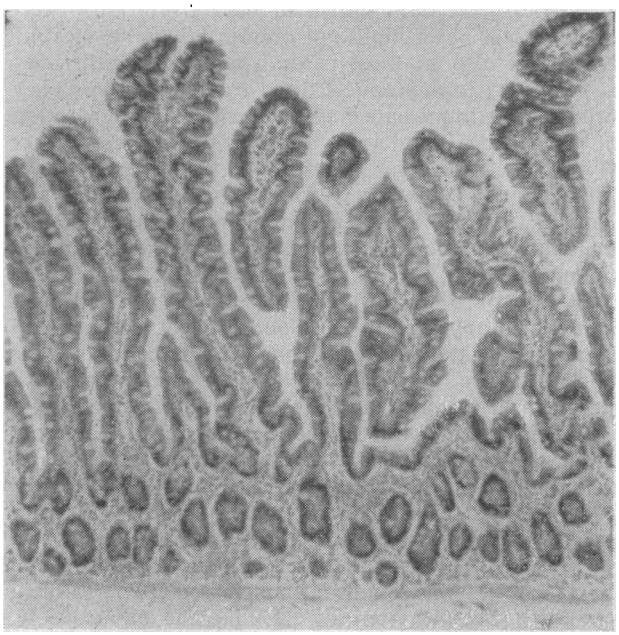

FIG. 9.—Section of normal jejunum stained with H. and E., showing finger-like villi lined with tall columnar epithelium.

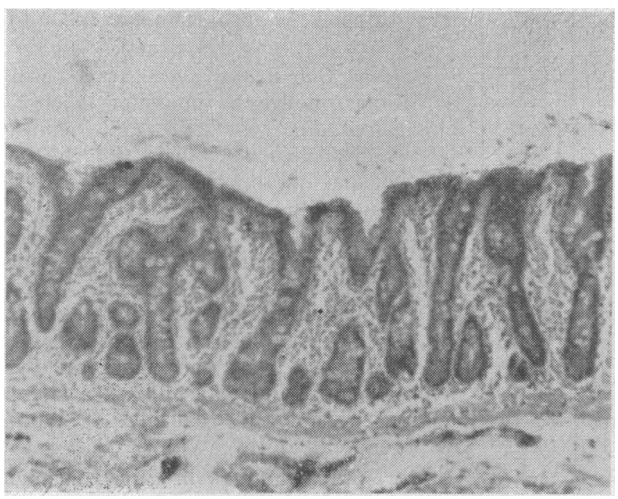

FIG. 10.—Section of jejunum from idiopathic steatorrhoea stained with H. and E., showing blunting of villi, reduction of absorptive surface, and cellular infiltration of stroma.

The effect of treatment with the gluten-free diet or steroids on the histological picture of the small intestine in the coeliac syndrome is still uncertain, but the weight of evidence suggests that in the majority of patients the lesion persists throughout life and is uninfluenced by treatment. Kelley and Terry (1958) found no improvement in one case after 14 months' treatment with steroids and a gluten-free diet, and neither Rubin and his colleagues nor Shiner and Doniach could detect any differences between the treated and untreated cases. Rubin did, however, biopsy the jejunum in six children who were clinically normal but were said to have had coeliac disease in the past, and found the mucosa normal in every case. It may be, therefore, that if the patients are put on a gluten-free diet early enough in the course of the disease, histological recovery can take place.

In tropical sprue the available evidence suggests that the state of the mucosa improves with treatment. It is not yet known whether it becomes entirely normal when the patient is cured (Shiner and Doniach, 1959; Butterworth, Smith, and Perez-Santiago, 1959).

Peroral biopsy of the intestine has been a big advance, but in patients with progressive disease in whom the histology of the gut is normal, laparotomy may still be needed to establish the diagnosis. That this is more than an academic exercise is underlined by the few patients in whom the discovery of an unsuspected fistula, or an adenoma of the pancreas, has led to effective treatment when other measures have failed.

Treatment

The management of idiopathic steatorrhoea has been revolutionized by the introduction of the gluten-free diet. In view of the country of origin of Gee's miraculous mussels so many years ago, it is fitting that it is to a Dutch paediatrician that we owe this major advance in treatment (Dicke, 1950). The effectiveness of the diet is now well established, not only in the cases in childhood, but also in the great majority of those who develop the disease in adult life, although in the adults the time taken to recover may be measured in months rather than days or weeks (French, Hawkins, and Smith, 1957). In the patients that respond the effect is dramatic. Fat-absorption improves, the nitrogen and calcium balances become positive, and the high faecal losses of sodium, potassium, phosphorus, and magnesium are reduced (Schwartz, Sleisenger, Pert, Roberts, Randall, and Almy, 1957). There is improvement in the absorption of vitamin B_{12} (Mollin, Booth, and Baker, 1957) and iron (Badenoch and Callender, 1960), and the levels of plasma proteins rise and oedema disappears (Forshaw, 1957). The absorption of xylose is also increased (Finlay and Wightman, 1958), and I suspect that the flat glucose-tolerance curves which sometimes persist in patients on the gluten-free diet are an indication not of impaired absorption but of the increased tolerance to sugar which was present before treatment was begun.

When I look at the flattened, shrunken epithelial surface of the intestine in the gluten enteropathy, I am lost in wonder at the functional reserve which allows substances of every kind to pour across the mucous membrane once the offending agent is removed from its surface. Presumably the site of action is the mucosal surface, and yet some contend that the sensitivity to wheat gluten may involve a disturbance of intermediary metabolism as well.

Paediatricians have remarked that the temperament of children on the gluten-free diet changes too quickly to be the result of improved absorption, and others have noted the great speed of the haematological response. Personally, I still have to be convinced. Many must have watched the change that can occur in a patient with pernicious anaemia after parenteral vitamin B_{12} long before the blood improves, and it may well be that, in the coeliac syndrome, immediately the barrier is down the body can replenish stores of vitamins long since depleted.

The gluten-free diet has proved so successful that it has supplanted all other forms of treatment in suitable cases. On the other hand, its very success has brought new dangers. Fletcher and McCririck (1958) have pointed out that wheat flour provides almost one-third of the protein, calcium, and iron in our national diet, and, in growing children at least, supplements of these, and of the B vitamins also, will be necessary if wheat flour is withdrawn.

The restriction of wheat gluten has to be virtually absolute if the diet is to be effective, and the second danger is that the patient will take the diet intermittently, and, lacking the vitamin and mineral supplements provided by the traditional regime, will suffer a relapse. This happened to one of our patients who had a severe haemorrhage from vitamin-K deficiency. In the majority the diet will induce a full clinical remission, but the power to absorb fat and other substances may not always be fully restored, and further experience may indicate that vitamin supplements are still required (Green, Wollaeger, Scudamore, and Power, 1959). Moreover, no one will deny that it is a troublesome regime for those who have to eat away from home. For those patients as well as for all with structural disease of the bowel, the traditional high-protein and low-fat diet with vitamin and mineral supplements still has its place. Multiple vitamin deficiencies are so common that this syndrome provides one of the few rational indications for shotgun therapy (see Table). Whole B complex, vitamins C, A, D, and K, the last in water-soluble form, and vitamin E, are all required. Calcium to be effective must be given in very large doses —15 to 20 g. a day. As the anaemia is usually the result of a combined deficiency of folic acid, vitamin B_{12}, and iron, all three haematinics should be given. In severe cases, when the function of the bowel is grossly disorganized, it may be necessary to give all the substances parenterally if a rapid remission is to be obtained.

Medical Regime for Treatment of Steatorrhoea

High-calorie, high-protein, low-fat diet (supplemented with high-protein milk powder)

Tab. aneurin. co. fort.	1	t.d.s. by mouth
Folic acid	20	mg. daily by mouth
Ascorbic acid	50	,, ,, ,,
Vitamin A	4,000	I.U. ,, ,,
,, D	10,000	,, ,, ,,
,, K (water-soluble)	20	mg. ,, ,,
,, E	100	,, ,, ,,
Calcium gluconate	15	g. ,, ,,
Ferrous gluconate	1·0	,, ,, ,,
Potassium chloride	2·0	,, ,, ,,
Vitamin B_{12}	100	µg. monthly intramuscularly

Since they were first introduced nine years ago, A.C.T.H. and cortisone, and more recently its newer analogues, have been shown to exert a profound effect on intestinal absorption, not only in idiopathic steatorrhoea but also in most cases where the steatorrhoea is secondary to anatomical disease of the bowel. They bring about immediate improvement in the absorption of fat, nitrogen, calcium, and many other substances (Taylor, Wollaeger, Comfort, and Power, 1952; MacKay and Volwiler, 1955; Drenick, Hvolboll, and Halsted, 1955). Dr. Callender and I have studied their effect on the absorption of iron (Badenoch and Callender, 1960). Fig. 11 shows the percentage of an oral dose of 5 mg. of ferrous sulphate labelled with ^{59}Fe which appeared in the blood of eight patients with idiopathic steatorrhoea and one with resection of the bowel, before and after five days' treatment with steroids. The mean and observed limits found in a group of patients with simple iron deficiency, who were given the iron alone is shown for comparison. The maximum absorption without steroids, even in the patients with severe iron deficiency, was 8% as compared with an average of 60% in simple iron deficiency. With one exception (B.W.), absorption was significantly increased after treatment with steroids. Unlike the others, G.K. had been on the steroids for a year, and during treatment she absorbed 37% of the dose. One week after the steroids were stopped the absorption had fallen to 8%.

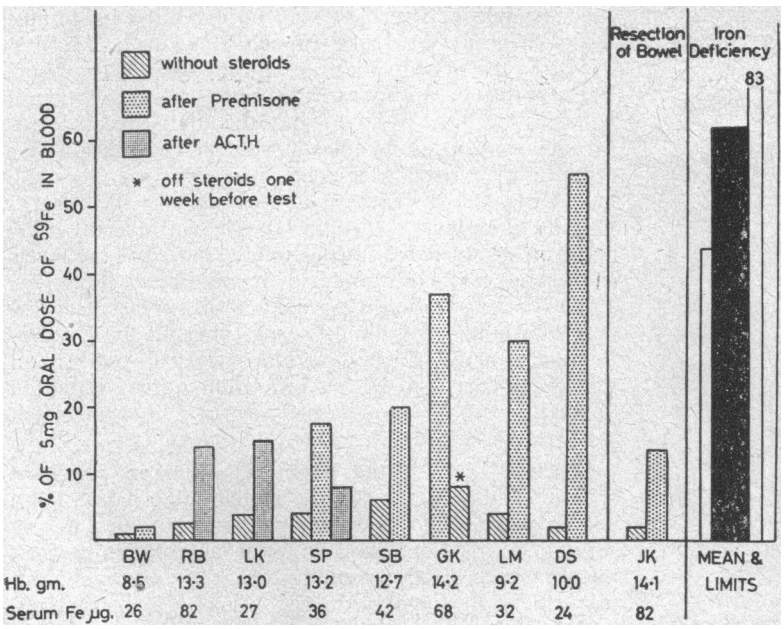

FIG. 11.—Effect of administration of prednisone and A.C.T.H. on absorption from oral dose of 5 mg. ^{59}Fe in eight patients with idiopathic steatorrhoea and one with resection of bowel. Mean and observed limits found in a group of patients with simple iron deficiency not receiving steroids is shown for comparison.

In idiopathic steatorrhoea steroids will sometimes induce a remission when a gluten-free diet has failed, and Lepore (1958) has advocated their use in the maintenance treatment of severe cases. This is not without risk. Water retention is particularly prone to follow their use, and I have seen fits and transient papilloedema due to this cause. They may contribute to softening of the bones by adding osteoporosis to an existing osteomalacia. They can aggravate the hypokalaemia, and may unmask a latent tetany, possibly by causing a hypochloraemic alkalosis.

More important, as in other chronic inflammatory conditions of the stomach and intestine, perforation and peritonitis may occur with minimal warning, and

there is a report in the literature of one fatal case in which there seemed to be a link between protracted treatment with steroids and the extensive ulceration of the bowel which caused death (Himes, Gabriel, and Adlersberg, 1957).

There are some types of steatorrhoea which require special treatment.

In biliary obstruction and pancreatic failure, replacement of bile salts and pancreatic ferments may help a little if diarrhoea can be avoided. These patients often thrive better on a fairly high fat intake so long as the diarrhoea is not too troublesome and fat-soluble vitamins are supplied.

The steatorrhoea occurring after gastric operations can be minimized by retaining as big a pouch of stomach as possible, by designing operations to avoid dilatation of the afferent loop, by avoiding high-carbohydrate meals, and by the use of small doses of acid to stimulate the pancreas.

In regional ileitis and other granulomata when surgery is necessary, as much of the bowel should be preserved as possible, and it is better to anastomose the cut end of the small intestine to the lower ascending colon rather than to make the traditional ileo-transverse colostomy. Above all, the creation of blind loops should be avoided unless they are a surgical necessity.

Jejunal diverticulosis often gives rise to troublesome abdominal pain, and it may be possible to bring relief by resecting the affected segment of bowel (Watkinson, Feather, Marson, and Dossett, 1959).

Finally, steroids may bring about a temporary remission in Whipple's disease. If they fail, some improvement may follow *x* rays to the abdomen or a course of nitrogen mustard (Gross, Wollaeger, Sauer, Huizenga, Dahlin, and Power, 1959).

Conclusion

In conclusion let me look back across the ground that has been covered in the past decade, for there must lie the keys to future progress.

On a humble plain, we have learnt much about the clinical picture of steatorrhoea and are now aware that dangerous symptoms may arise whenever fat-absorption is impaired.

More important perhaps, we have begun to break with the tradition that the manifestations of steatorrhoea are always due to the failure of absorption of essential substances. We are learning that they can be the result of increased loss into the gastro-intestinal tract, and new evidence has given added point to the old idea that some of the symptoms, at least, might be due to the absorption of toxins formed within the lumen of the intestine by chemical degradation or abnormal bacterial action.

As so often in the past, it is to the careful clinical observation of one man that we owe the major breakthrough in recent years.

It may seem a far cry from a group of hungry children in the German-occupied Netherlands to the careful research which is defining ever more closely the basic defect in the gluten-enteropathy, but the links in the chain are there.

Gradually a new concept is arising, and it may be that in future years we will classify the coeliac syndrome as an inborn error of metabolism differing from others that we recognize only the fact that the lesion lies not in the liver or the kidney but in the wall of the small intestine.

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Research grants totalling over $523,000 have already been made to 40 scientists in 1960 by the Tobacco Industry Research Committee of the United States of America. Among the factors being studied are the possible interaction of viruses and tobacco smoke, environmental factors and pulmonary disease, coronary artery disease, psychological differences between smokers and non-smokers, characteristics of aromatic hydrocarbons, the effect of tobacco derivatives on arterial and myocardial tissue cultures, the role of the nucleolus in normal and malignant cells, and the effect of negatively charged ions on human tracheo-bronchial ciliary action. All grants are made by the Scientific Advisory Board, composed of nine doctors, scientists, and educators, who retain their institutional affiliations, under the chairmanship of Dr. K. MERRILL LYNCH, chancellor of the Medical College of South Carolina, Charleston.