BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 24 1960

STEATORRHOEA IN THE ADULT*

BY

J. BADENOCH, D.M., F.R.C.P.

Consultant Physician, United Oxford Hospitals

My interest in this subject stems from two main sources. Firstly, after the war I was privileged to work in Professor Witts's department in Oxford, where the main lines of study have been in haematology and gastro-enterology, and patients with one or other of the malabsorption syndromes forged a link between these two and lay at the focal point of our research. Secondly, it seemed to me that clinically the steatorrhoeas marched across the whole field of medicine and surgery in the way that syphilis used to do in the old days, and there was hardly a special department which could not produce a number of cases from its records.

Steatorrhoea is a convenient marker of small-intestinal insufficiency, but we now know that the condition is one of panmalabsorption, and it is this universal failure of function which gives rise to the wide variety of symptoms and signs and makes the condition so interesting to physicians in all branches of medicine.

My purpose in these lectures is to present the clinical picture of steatorrhoea as I have seen it in Oxford, to survey the widely differing conditions which may lead to its development, and to use this framework to indicate the present limits of our knowledge.

A Retrospective Glance

But let us first look back at the origins of our subject. The classical and mediaeval physicians, with their great interest in urinoscopy and excreta generally, could hardly fail to have been struck by the cardinal signs of steatorrhoea. Indeed, Aretaeus the Cappadocian, who practised possibly in Rome in the second century A.D., has left us an account of a disease which closely resembles the clinical picture of steatorrhoea as we know it to-day (Adams, 1856). He writes: "In the coeliac affection the heat does not digest the food nor convert it into its proper chyme but leaves its work half unfinished. The food then being deprived of this operation is changed to a state which is bad in colour as well as consistence. For its colour is white and without bile and it is liquid from no part of the digestive process having been properly done except the commencement."

This has an authentic ring about it, and how interesting it is to learn that even in classical times research had its problems; for the scholars tell us that Aretaeus may well have copied this account from an earlier authority, possibly Archiagenes, without acknowledging his debt.

1,500 years later, in 1669, Vincent Ketelaer, a Dutch physician who was rector of the Gymnasium at Zierickzee, published a treatise in which he described cases of stomatitis which were occurring in the Low Countries. The lesions in the mouth were accompanied by a phalanx of symptoms, among them a most pernicious diarrhoea which left behind scarcely any juice for the body, with faeces so voluminous that several basins could scarcely hold them (Hanes, 1938).

From the descriptions of the classical diarrhoea, there seems little doubt that both Aretaeus and Ketelaer were describing patients with steatorrhoea, but it was not until 1776 that William Hillary gave the first clear account of the sprue syndrome. In his *Observations on the Changes of the Air and the Concomitant Epidemical Diseases in the Island of Barbados* he described the pallor and emaciation of the sufferers, the soreness of the mouth, and the diarrhoea with pale foul stools, and noted that the disease pursued a relapsing course and often proved fatal. In 1864 Julien, working in the French Colonies in Asia, stated his belief that the "diarrhoea alba," or Cochin China dysentery as it was then known, was a specific condition different from other forms of dysentery. Finally, in 1880, van der Berg in Java and Manson in China, writing independently, described the disease which Hillary had observed a century before and defined it as a distinct clinical entity.

By the end of the last century many physicians practising in the tropics had become familiar with sprue and were adding to our knowledge of it, and yet the fact that there was a curiously similar condition occurring in the home countries of Europe went unremarked. It is true that both Aretaeus and Ketelaer had described cases with bulky diarrhoea, but in modern times no further description appeared until Samuel Gee (1888) published his classical paper on the coeliac affection. In four short pages he gives an account which will stand comparison with any written to-day. He described the natural history of the disease as slow with a relapsing course, sometimes fatal, often leaving the children weak and stunted even if recovery took place. He mentioned that occasionally Englishmen returned from India sick with the coeliac affection and that seldom it was met with in adults who had never left this island. At necropsy he could find nothing to explain the severity of the condition, and his paper ends with the prophetic statement that "if the patient can be cured at all it shall be by means of diet." One can imagine how interested he must have been when a child who was fed upon a quart of the best Dutch mussels daily throve wonderfully, but relapsed when the season for mussels was over. Unhappily the controlled experiment was incomplete, because the next season the child could not be prevailed upon to eat the mussels again.

*The first of two Goulstonian Lectures delivered before the Royal College of Physicians of London on January 19 and 21, 1960.

To-day, as in the time of Gee himself, the nature of the fundamental defect in the absorption of fat still eludes us, but, as I hope to show, our knowledge of the causes of steatorrhoea and the pathogenesis of its clinical signs and symptoms has grown rapidly in recent years, and it may not be long before the final door yields to the steady pressure which is being put upon it.

Present Investigation

In Oxford I have had the opportunity to study 163 patients with steatorrhoea (Table I).

TABLE I.—*Number of Patients Studied*

Idiopathic steatorrhoea (onset in childhood 32)	106
Regional ileitis	11
Pancreatic disease	8
Gastric operations	8
Diverticulosis of the jejunum	8
Tropical sprue	7
Tabes mesenterica	4
Blind loops of intestine	3
Gastro-colic+ileo-colic fistulae	2
Mesenteric thrombosis	2
Whipple's disease	1
Unclassified	3
Total	163

The majority, 106, were suffering from idiopathic steatorrhoea, and in the remainder the failure of fat absorption was due to a variety of other causes. The three unclassified cases provided insufficient data for a certain diagnosis.

About one-third of the patients in the idiopathic group first developed their symptoms in childhood and are probably cases of coeliac disease whose symptoms have continued into adult life. Ten years ago I would have defined the remainder of these with confidence as a single entity. Now I am not so sure. The difficulty is that, traditionally, idiopathic steatorrhoea has been a diagnosis that is made by exclusion. It is what is left when all other possible causes have been eliminated. In the past two years new methods of study, particularly the peroral biopsy of the mucosa of the small intestine, has enabled the diagnosis to be made with greater precision. Already it appears that while some, probably the majority, of the cases of idiopathic steatorrhoea are in fact adult cases of coeliac disease, as their response to the gluten-free diet would suggest, yet the pathological changes in the intestine may not be the same in all, and there may be more than one cause for the breakdown in function.

Nevertheless, it is convenient for the moment to consider them as a clinical group, so long as this does not imply a common aetiology which is not yet proved, or suggest that the dangerous deficiencies which may arise are limited to the idiopathic cases. This view, widely held in the past, has prevented the acceptance of the fact that a crippling osteomalacia may accompany chronic pancreatitis or that subacute combined degeneration of the cord may follow an intestinal anastomosis for Crohn's disease.

In the 74 patients with idiopathic steatorrhoea, whose illness began after childhood, symptoms most commonly developed between the ages of 30 and 39 (Table II). If, as appears to be the case, most of these patients are suffering from an adult form of coeliac disease, it seems curious to me that the majority do not break down in adolescence or early adult life, but do so in the fourth and fifth decades, when the major metabolic demands of growth and child-bearing are on the wane. In patients with other forms of steatorrhoea the age of onset varied with the underlying disease. In every series the presenting symptoms depend in large measure on the way in which the cases are collected, and perhaps my own have a bias because of our special interest in the anaemias.

TABLE II.—*Age at Onset of Symptoms of 74 Patients with Idiopathic Steatorrhoea*

Age in years	10–19	20–29	30–39	40–49	50–59	60–69	70–79
No. of patients	4	12	25	19	10	3	1

On the other hand, my findings emphasize once again the danger of putting too much reliance on the disturbance of the bowels (Table III). In 106 patients with idiopathic steatorrhoea tiredness or breathlessness were as common as diarrhoea as a presenting symptom, and a significant number mentioned that soreness of the tongue occurred long before other symptoms developed.

TABLE III.—*Presenting Symptoms of 106 Patients with Idiopathic Steatorrhoea*

Tiredness or breathlessness	38
Diarrhoea	35
Soreness of the tongue	12
Indigestion	10
Flatulence	6
Dermatitis	3
Heart failure	1
Rectal haemorrhage	1

Most of the patients are underweight and small in stature, and this is particularly true of those in whom the disease dates from childhood. Possibly because we are close to some good galloping country, steatorrhoea has become known locally in Oxford as the jockey's disease—there were five in this series; and more than once I have been accused of spoiling a promising future by making a young man grow again.

Usually the diagnosis of steatorrhoea is easy. The classical patient with pallor, wasted limbs, and distended belly, complaining of diarrhoea with large, pale, foul stools and soreness of the tongue could hardly be missed. But we have learnt that many patients with impaired fat-absorption have normal bowel habits and pass formed stools of normal colour, and in these the diagnosis may be overlooked until a near disaster has occurred. No fewer than 11 out of the 163 patients in this series denied that they had ever had any significant disturbance of the bowels; but in three of these, although the bowels were opened once daily and the patient thought his stools were normal, the ward sister commented on their size and pallor.

The most common gastro-intestinal symptoms are diarrhoea, flatulence, and abdominal distension. Although usually the diarrhoea is relatively painless, this is not always the case, and in some patients attacks of subacute intestinal obstruction produce violent colic and may endanger life. This occurred in 15 patients in my series (Table IV), and if we exclude the five with regional ileitis who had organic strictures, there remain 10 who suffered from recurrent colic with distended loops of bowel without obvious permanent narrowing of the lumen of the gut. Three of them died as a result of volvulus. This syndrome of chronic obstruction has multiple causes. In the absence of organic stricture it may depend on the disorder of motor function that seems common in patients with jejunal diverticulosis,

TABLE IV.—*Incidence of Intestinal Obstruction. Figures in Parentheses Indicate the Number of Patients in Each Group in the Series*

Regional ileitis (11)	5
Diverticulosis of jejunum (8)	5
Idiopathic steatorrhoea (106)	2
Partial gastrectomy (8)	1
Tabes mesenterica (4)	1
Mesenteric thrombosis (2)	1

on impairment of the blood supply, possibly on disturbed autonomic control as in the patient recently described by Naish and Capper (1960), or on the impaction, in widely dilated bowel, of a mass of pultaceous contents which cannot be moved on by peristalsis.

Loss of Vitamins

Steatorrhoea due to any cause may lead to loss of the fat-soluble vitamins A, D, E, and K in the stools. Clinical deficiency of vitamin A is rare, and I have no definite examples in my series, although lack of the vitamin may have contributed to the dryness and hyperkeratosis of the skin which is often noted, and to the reduced resistance to infection. Similarly, deficiency of vitamin E must occur, and in patients coming to necropsy we have seen a brown pigment in the muscle layers of the intestine and elsewhere which has been attributed to a deficiency of the vitamin. On the other hand, there are no clinical signs which could be attributed to lack of vitamin E. The obstetric history of patients with steatorrhoea on full vitamin supplements, with the exception of vitamin E, is normal, and my efforts to relieve muscular weakness and wasting with large doses of the vitamin have been without avail.

In considering the lack of vitamin D, I am on much firmer ground. In this series, osteomalacia of sufficient degree to cause skeletal pain occurred in 26 patients (Table V).

TABLE V.—*Incidence of Osteomalacia. Figures in Parentheses Indicate the Number of Patients in Each Group in the Series*

Idiopathic steatorrhoea (106)	20
Regional ileitis (11)	2
Partial gastrectomy (8)	1
Tabes mesenterica (4)	1
Diverticulosis of jejunum (8)	1
Pancreatic disease (8)	1

Twenty of them were in the idiopathic group, but the condition was not limited to steatorrhoea due to disease of the intestine, it also occurred after partial gastrectomy and in pancreatic steatorrhoea where the prime fault lies in fat-digestion. Many of these cases are tragic. Widespread skeletal pain, the absence of true arthritis, and the failure of our usual remedies for muscular strain, often brand the patient as neurotic for years before the correct diagnosis is made. Rapid growth in adolescence or the strain of pregnancy may precipitate symptoms and the cause of the steatorrhoea is unimportant, for softening of the bones may occur whenever fat-absorption is impaired. Not all have diarrhoea or pale, bulky stools, and these patients with osteomalacia, without other symptoms suggesting malabsorption, form one of the most important occult groups among the steatorrhoeas.

Role of Hypocalcaemia

A great deal of interest continues to be focused on the cause of the bone disease in steatorrhoea. The classical theory (Fig. 1) was that the absorption of calcium was impaired, partly because of a deficiency of vitamin D and partly because the calcium itself was lost in the stools in the form of insoluble soaps of fatty acid. This led to a negative calcium balance and a fall in blood calcium. In a proportion of cases tetany occurred, but in the remainder the parathyroids responded to the stimulus and a secondary hyperparathyroidism raised the calcium in the blood to safer levels at the expense of the bones. As Davies, Dent, and Willcox (1956) have shown, this secondary hyperparathyroidism may proceed to the length of tumour formation, and the resulting adenomata may have to be removed surgically before the softening of the bones can be halted. In the elderly, in post-menopausal women, and in the presence of gross malnutrition, disturbance of the protein matrix of the bone and osteoporosis may complicate the picture still further.

This classical theory may require modification in the future. It has been shown by Nassim and his colleagues that the calcium balance does not correlate well with the degree of steatorrhoea, possibly because of variation in the activity of the parathyroids (Nassim, Saville, Cook, and Mulligan, 1959), or because of changes in the volume, and hence in the calcium contents of the large quantities of digestive juices which are poured into the lumen of the gut.

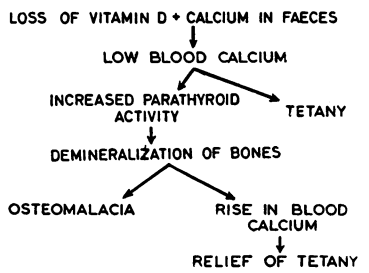

FIG. 1.—Pathogenesis of osteomalacia and tetany in patients with steatorrhoea.

Whatever the cause of the failure to absorb calcium, it is clear that some patients will respond to vitamin D and others will not, whether the vitamin is given orally or parenterally. I believe that in our thinking about this problem we have been guilty of falling into a trap, similar to the one that beset us in our studies of the absorption of vitamin B_{12} in steatorrhoea. Knowing that vitamin D is involved in the normal absorption of calcium, we are prone to believe that it is this specific mechanism that has broken down in the malabsorption syndromes. In fact, if we assume that this is not the sole explanation we are more likely to make progress.

As long ago as 1931, Marble and Bauer showed that the absorption of calcium in steatorrhoea could be improved by treatment with liver alone. To-day there is good evidence that in idiopathic steatorrhoea a gluten-free diet or treatment with steroids will promote absorption of calcium when vitamin D has failed, presumably by removing some other barrier to transfer across the wall of the intestine (MacKay and Volwiler, 1955; Buchan, Marko, and Gerrard, 1958). That this double mechanism is operative is emphasized, firstly, by the fact that the response to steroids is far too rapid to be the result of increased absorption of vitamin D (MacKay and Volwiler, 1955), and, secondly, by the demonstration that the serum of some patients with steatorrhoea and hypocalcaemia has normal antirachitic activity, suggesting that the low blood calcium cannot be due to lack of vitamin D (Morgan, quoted by Morse, Dickson, Nonamaker, and Embree, 1959).

The Parathyroids

It has been accepted that in some of these patients failure to absorb calcium leads to a fall in blood levels and tetany, but in others the parathyroids react to the stimulus and raise the blood calcium at the expense of the stores of calcium and phosphorus in the bones. If this occurs in some, why not in all? So far as I know there is no adequate explanation for this difference, but Bensley and Cameron (quoted by Morse *et al.*, 1959), have suggested that in some patients with steatorrhoea there is a diminished phosphaturic response to injections of parathormone, and it may be that in patients with steatorrhoea and tetany some inhibitor of parathyroid function is present.

There are other links between the parathyroids and steatorrhoea that are even less well understood. Some patients with hypoparathyroidism have steatorrhoea (Lowe, Ellinger, Wright, and Stauffer, 1950; Salvesen and Böe, 1953), and the failure of fat-absorption is not always due to infection of the bowel with yeasts, as was first thought to be the case. Sometimes the steatorrhoea precedes the failure of parathyroid function, and possibly both are the result of a common genetic defect.

Whatever its cause, the fall in blood calcium in steatorrhoea, in addition to producing tetany, may provoke mental disorientation and fits, as in the case described by Kant and Lubing (1947), and it is possible that protracted hypocalcaemia may contribute to the resistance to treatment of some of the skin lesions.

Haemorrhage in Steatorrhoea

Haemorrhage due to lack of vitamin K occurred in 17 patients in my series (Table VI), and, as with osteomalacia, it was not limited to those with idiopathic steatorrhoea. Considering that the haemorrhage may be disastrous, it is odd that it should have been overlooked by so many of the earlier writers. At first it was attributed to scurvy, but it soon became clear that this could not explain the tendency to bleed in every case. In 1927 Fanconi described three patients with a haemorrhagic diathesis which he felt must be due to some other cause. The coagulation time was prolonged and the clot retraction and platelet count were normal, and he concluded that the condition was allied to haemophilia. Eleven years later, when vitamin K had been discovered (Fanconi, 1938), he re-entered the lists and suggested that a deficiency of the vitamin might be the cause of the bleeding in steatorrhoea.

TABLE VI.—*Incidence of Haemorrhage Due to Deficiency of Vitamin K. Figures in Parentheses Indicate the Number of Patients in Each Group in the Series*

Idiopathic steatorrhoea (106)	13
Regional ileitis (11)	2
Tabes mesenterica (4)	1
Whipple's disease (1)	1

Purpura in the skin is the most common manifestation, but epistaxis, menorrhagia, haematuria, and melaena also occur, and in one of my patients, a man of 67, a sharp rectal haemorrhage was the presenting symptom of the disease. Most dangerous of all, the defect in coagulation may give rise to massive retroperitoneal haemorrhage simulating an acute abdominal catastrophe. I have seen two of these in the past year in patients who had not been under regular treatment, but mercifully the hospital notes provided the diagnosis in both before the surgeon operated in the face of incoagulable blood. In neither was there any external bleeding to suggest the cause of the acute abdominal symptoms and the collapse.

It is well recognized that much of the vitamin K required by man is synthesized within the lumen of the intestine. In patients with steatorrhoea, who may be in a precarious balance, an oral antibiotic may precipitate clinical deficiency by destroying the organisms which synthesize the vitamin within the gut (Heyeraas, 1949).

Glossitis and Dermatitis

Glossitis and dermatitis are prominent symptoms of the malabsorption syndrome. In this series 118 patients complained of soreness of the tongue at some time in the course of their illness, and in 12 it was the presenting symptom, while dermatitis occurred in 15 and antedated all other symptoms in 3 (Table VII). Traditionally these symptoms, and also the peripheral neuritis which occurs, have been ascribed to deficiencies of the B group of vitamins, but the picture is not nearly so clear-cut as it is, for example, in the haemorrhagic diathesis due to lack of vitamin K. It can be assumed that, in keeping with other water-soluble substances, the absorption of the B vitamins is impaired, or at least grossly delayed; but attempts by Girdwood (1956) to demonstrate this, in the case of pyridoxine, riboflavine, and aneurine, were unsuccessful.

TABLE VII.—*Incidence of Glossitis and Dermatitis in Series of 163 Patients*

Soreness of the tongue	118
Presenting symptom	12
Dermatitis	15
Presenting symptom	3

The second prop in the traditional argument is that, as many of these vitamins are synthesized within the lumen of the intestine in man, the abnormal bacteria assumed to be present in the upper gut in steatorrhoea either use them for their own metabolism or outgrow others on which their synthesis depends.

It may well be that this is the case in steatorrhoea associated with blind loops, or other anatomical abnormalities, in which the upper bowel is known to be teeming with organisms; but attempts to demonstrate bacterial invasion of the small intestine in coeliac disease and idiopathic steatorrhoea have been unconvincing (Gardner, 1957; Anderson and Langford, 1958).

Although vitamin B deficiency due to impaired absorption or bacterial competition may play a part in producing the dermatitis or the neuropathy, proof is lacking that this is the whole explanation. For example, peripheral neuropathy which responds to vitamin B_1 does occur in association with steatorrhoea, yet there are similar cases which progress to the point of incapacity in spite of full doses of all the known vitamins. Clearly other mechanisms must be involved, and the knowledge that lack of calcium can cause resistant eczema, and iron deficiency produce glossitis, suggests that there may be other deficiencies not connected with the vitamins of the B group which may be important. One of these may be lack of protein, for skin lesions are common in nutritional protein deficiencies in the tropics, and Leitner (1958) has described two interesting patients with severe protein malnutrition which followed gastric and pancreatic resections, who suffered from intractable dermatitis.

Moreover, the lesions need not be the result of a lack of a specific factor. They could be due to the absorption of toxic substances formed within the lumen of the intestine. That this can happen is illustrated by the observations of England, French, and Rawson (1960), who studied a patient with Whipple's disease and a light-sensitive dermatitis with excess of porphyrins in the stools. Sterilization of the gut with a broad-spectrum antibiotic led to a fall in the porphyrin excretion and a rapid cure of the dermatitis. Presumably the antibiotic had exerted its effect by destroying the organisms within the lumen of the intestine which were producing the toxic porphyrins.

If the glossitis and dermatitis are due to poor absorption of the B vitamins, it is curious that frank deficiency of the other important water-soluble vitamin, vitamin C, is so rare in steatorrhoea. Only one of the 163 patients in this series had clinical scurvy, and she is an elderly woman in whom a poor diet seemed to be playing the major part in producing the deficiency. It is true that

the level of ascorbic acid in the leucocytes is often low, and it may be that subclinical scurvy plays a part in producing the irritability and swings of mood of which these patients complain; but although the vitamin may be destroyed rapidly if the upper bowel is infected (Kendall and Chinn, 1938), the available evidence suggests that it can be absorbed without much difficulty in the presence of steatorrhoea (Boscott and Cooke, 1954).

Loss of Weight

Loss of weight is common in steatorrhoea, and 76% of the patients in this series who were weighed when they were first seen were one stone (6.4 kg.) or more below their optimum weight. This loss of weight depends partly on the diminished intake of food and partly on the loss of fat and other essential nutriments in the stools. Even amino-acids are poorly absorbed, and some of them may be involved in a breakdown of intermediary metabolism as well. Butterworth, Santini, and Perez-Santiago (1958) have shown that the level of serine in the blood in patients with steatorrhoea is abnormally high. They could not explain this finding, but serine is deaminated by a specific enzyme which requires pyridoxyl phosphate as its coenzyme, and in the presence of a deficiency of pyridoxine the process might be halted. Similarly the excess of *p*-hydroxyphenyl acetic acid, which is found in the urine, may depend on a disturbance of tyrosine metabolism resulting from lack of vitamin C (Boscott and Cooke, 1954).

In many patients the levels of plasma proteins are reduced, but it is probable that diminished absorption does not explain the fall in every case. Protein synthesis may also be disturbed, as is shown by the abnormal electrophoretic pattern. There may be a rise in the β-globulin and sometimes the γ-globulin, and a low albumin in the absence of proteinuria or overt hepatic damage (Adlersberg, Wang, and Bossak, 1957). Moreover, the results of studies on copper metabolism in steatorrhoea have indicated that the specific carrier protein, coeruloplasmin, is poorly synthesized (Butterworth, Gubler, Cartwright, and Wintrobe, 1958). Further evidence of disturbed protein synthesis is provided by the association of impaired fat-absorption with all forms of agammaglobulinaemia, both congenital and acquired (Firkin and Blackburn, 1958). The steatorrhoea usually develops after the abnormality in the plasma proteins, and has been ascribed, on too slender evidence, either to secondary infection of the gut or to blockage of the lymphatics of the mesentery by the underlying lymphomatous process. However, sometimes the steatorrhoea precedes the development of the hypogammaglobulinaemia, and in these patients no adequate explanation for the association has been put forward.

Finally, not only poor absorption and faulty synthesis, but also increased loss of protein into the gastro-intestinal tract may be important. Schwartz and Jarnum (1959) and Young, Levin, Fowler, and Miles (1959) have described cases with steatorrhoea and hypoproteinaemia in which studies with albumin and polyvinylpyrrolidone (P.V.P.), labelled with radioactive iodine, have revealed a very rapid turnover of albumin and considerable losses of protein into the gastro-intestinal tract. The use of radio-iodinated P.V.P. as a marker for protein loss into the bowel represents a very real advance, and should prove most useful in the study of other patients with hypoproteinaemia due to unknown cause.

Some years ago our interest was aroused by a patient with access to the ward scales, who demanded to know why, although he had not had his bowels open during the night, he was invariably 2 lb. (0.9 kg.) lighter in the morning than he had been when he went to bed. In fact, he was giving forthright expression to the observation, made by Wollaeger and Scribner (1951), that patients with steatorrhoea excrete large volumes of water during the night. Wollaeger believed that this was the result of delayed absorption of water drunk during the previous day, and that the delay depended on the presence of food within the lumen of the gut. Jackson, Linder, and Berman (1951), in their classical experiments on their patient with massive resection of the bowel, noted a similar delay in diuresis, but they doubted if slow absorption could be the explanation, because the same effect was noted if the water load was given intravenously. Later, Taylor (1955) showed that the delay in absorption could not be due to the presence of unabsorbed food within the bowel, because it occurred even if the subjects were fasting.

The picture is a complicated one. Higgins, Lee, Scholer, Reitemeier, Code, and Wollaeger (1957), using isotopically labelled water, have shown that absorption is slower than normal in steatorrhoea, but this does not account for the delay in diuresis. Flear, Cooke, and Quinton (1959) showed that fluid taken in the mornings in a fasting state, or with food, gave rise to a delayed diuresis the following night, but that if the same water load was administered to the same patients in the evening it was promptly excreted. They postulate that the nocturnal diuresis that occurs in patients with steatorrhoea is due to an inversion of the normal rhythm of excretion such as has been noted in congestive cardiac failure and cirrhosis of the liver.

Dehydration, weakness, and hypotension are common in all forms of steatorrhoea, and if the asthenia is accompanied by pigmentation of the skin difficulties in diagnosis may arise.

One of the patients in this series, a man aged 44, was admitted to the Radcliffe Infirmary under the care of Dr. A. M. Cooke in 1951. His main complaint was of great weariness; he had lost weight and had abdominal pain and diarrhoea. There was pigmentation of his skin and even of the mucous membranes of his mouth, and his blood-pressure was 90/50. He had been diagnosed as suffering from Addison's disease at another hospital, and both eucortone and D.C.A. had been given without effect. Clinically, he presented the picture of adrenal failure, but the appearance of his stools, which were silver-grey in colour, at once suggested the correct diagnosis and led to effective treatment.

The striking resemblance of some patients with steatorrhoea to sufferers with Addison's disease and the knowledge that the adrenal cortex may play a part in the normal process of fat-absorption have led in the past to repeated suggestions that adrenal cortical failure might be the cause of steatorrhoea (Gloor, 1930; Thaysen, 1932). Although patients severely ill with steatorrhoea and malnutrition may show a functional adrenal insufficiency, all the evidence points to the fact that the asthenia, hyponatraemia, and hypotension that are often encountered are not due to this cause. Prunty and Macoun (1943) have shown that sodium is retained normally by the kidneys in these patients, and Black (1946) demonstrated that replenishing the body stores

of sodium will restore well-being and raise the blood-pressure to normal without need of other measures.

The common occurrence of hypotension has aroused interest. It has been suggested that it might be due to failure of absorption of some substance necessary for the maintenance of normal blood-pressure (Salvesen, 1953). However, although a low blood-pressure is often found when the patient is ill, it is not invariable, and two of my patients had diastolic pressures of over 120 mm. of mercury during the course of their illness.

Potassium Depletion

For many years it has been known that patients with steatorrhoea could suffer from profound muscular weakness. In the records of the Radcliffe Infirmary we have the story of one patient who died of what was thought to be a creeping paralysis, which progressed to such an extent that terminally she was unable to lift her head from the pillow. At the time the cause of her distress was unknown, but Harrison, Tompsett, and Barr (1943) showed that the weakness of patients with steatorrhoea was often due to the loss of large amounts of potassium in the stools, and that supplements of the mineral would bring about improvement in muscle power. The loss of potassium parallels the bulk of the stool and it can be quite large even if the stools are semi-formed (Cooke, Thomas, Mangall, and Cross, 1953).

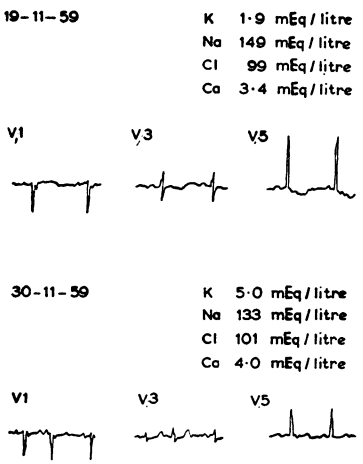

FIG. 2.—Electrolyte levels in blood and electrocardiograph of a patient with steatorrhoea and severe muscular weakness before (November 19, 1959) and after (November 30, 1959) supplements of potassium were given.

Fig. 2 shows the serum levels of electrolytes and the electrocardiographic findings in a patient with steatorrhoea who had profound muscular weakness due to hypokalaemia.

Before treatment was begun the level of potassium was low and the electrocardiogram showed the sagging ST segments and prominent U waves of hypokalaemia. When potassium supplements were given, her weakness improved, and the electrocardiographic trace became more normal.

Potassium depletion used to be one of the most dangerous complications of the malabsorption syndrome, and it was responsible for many deaths before its importance was realized. Apart from producing muscular weakness, it may contribute to atony of the bowel and abdominal distension, and may mask tetany due to low blood calcium. More than once I have seen enthusiastic treatment of the muscular weakness with potassium precipitate tetany because calcium supplements were not given at the same time.

Anaemia

From the earliest times it has been recognized that steatorrhoea is usually accompanied by anaemia. Gee (1888), in his classical paper, noted "that a fault of sanguification betokened by pallor and a tendency to dropsy is a constant symptom." To-day, largely as a result of the discovery of folic acid and vitamin B_{12}, we know more about the pathogenesis of the anaemia than about any other facet of the syndrome. It is recognized that it may be macrocytic and megaloblastic, iron-deficient, or a combination of both. Indeed, it is the occurrence of macrocytosis with hypochromia in the blood picture which often suggests an intestinal cause for the anaemia when bowel symptoms are minimal. Similarly, in the past, when the multiple nature of the defect was less well understood, treatment with one haematinic might unmask a deficiency of the others, as is shown in Table VIII. The first three patients presented with a macrocytic anaemia, and treatment with folic acid or liver unmasked the iron deficiency; while in the last two the initial hypochromic anaemia became macrocytic after treatment with iron. Occasionally, if the anaemia is severe, immature red and white cells may be seen in the peripheral blood. Leucopenia with a total white-cell count of less than 4,000 per c.mm. occurs in about a third of those with megaloblastic bone-marrow, and sometimes this can lead to troublesome agranulocytic lesions, as in Fig. 3, which shows an agranulocytic ulcer that has perforated right through the lip.

TABLE VIII.—*Change in Blood Picture in Five Patients with Idiopathic Steatorrhoea who were Treated with Folic Acid, Liver, or Iron Alone*

Case No.	Initial Blood Count	Treatment	Time Interval (Months)	Blood Count after Treatment
18	Hb 12·25 C.I. 1·3	Folic acid 20 mg./daily	23	Hb 10·85 C.I. 0·8
45	Hb 12·25 C.I. 1·25 M.C.V. 110 μ3	Folic acid 10 mg./daily	4	Hb 12·2 C.I. 0·8
44	Hb 10·4 C.I. 1·25	"Liveroid" ½ oz. (15 g.) q.d.s.	29	Hb 14·9 C.I. 0·8
30	Hb 7·0 C.I. 0·65 M.C.V. 82 μ3	Ferrous sulphate 0·4 g. t.d.s.	5	Hb 11·0 C.I. 1·2
33	Hb 8·3 C.I. 0·66	Ferrous sulphate 0·2 g. t.d.s.	5	Hb 14·2 C.I. 1·3

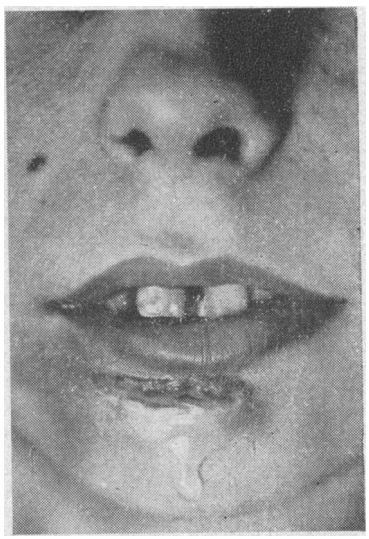

FIG. 3.—Agranulocytic ulcer of lower lip in a patient with steatorrhoea and leucopenia. (Reprinted from *Modern Trends in Gastroenterology*, series I. Butterworth, London.)

Although leucopenia occurs in all forms of megaloblastic anaemia, severe agranulocytic lesions are much more common in the steatorrhoeas where there is a combined deficiency of folic acid and vitamin B_{12} than in Addisonian pernicious anaemia itself.

The basic cause of the anaemia is failure to absorb folic acid, vitamin B_{12}, and iron. Theoretically at least, deficiencies of copper, vitamin C, and pyridoxine may also occur, but there is no evidence that lack of these substances plays a significant part in producing the anaemia.

Soon after it was introduced in 1945, folic acid was shown to be effective not only in the megaloblastic anaemia of tropical sprue and idiopathic steatorrhoea but also when the anaemia occurred in association with gross disease of the bowel (Darby and Jones, 1945; Moore, Bierbaum, Welch, and Wright, 1945; Heyeraas, 1949). Many of these cases had previously proved resistant to all forms of liver extract. The success of folic acid not only in these but also in the group of achrestic anaemias suggests that many of the latter patients may have been suffering from occult steatorrhoea or some other form of intestinal disease.

Initially, folic acid was hailed as the answer to all forms of intestinal megaloblastic anaemia, but we now know that lack of vitamin B_{12} also plays a prominent part in their aetiology.

Absorption of Vitamin B_{12}

In patients with megaloblastic anaemia and the malabsorption syndrome, particularly those cases due to blind loops of bowel or to diverticulosis of the upper intestine, the level of vitamin B_{12} in the serum is often as low as that found in untreated pernicious anaemia (Fig. 4) (Spray, 1960). There are several causes for this deficiency. Castle, Rhoads, Lawson, and Payne (1935), in one of their classical experiments, showed that patients with sprue in relapse are unable to secrete intrinsic factor, but that the secretion returns when the patient enters a remission. However, it is clear that the failure to absorb vitamin B_{12} which occurs in idiopathic steatorrhoea is not due primarily to lack of intrinsic factor.

Fig. 5 shows the percentage of an oral dose of 0.5 μg. of vitamin B_{12} labelled with radioactive cobalt recovered from the faeces of a group of normal persons, of patients with pernicious anaemia, and of seven patients with idiopathic steatorrhoea (Callender and Evans, 1955). The black columns indicate the percentage of the dose found in the faeces when the vitamin was given alone, and the shaded and cross-hatched columns the effect of adding intrinsic factor to the dose of the vitamin. When the vitamin is given alone many of the patients with idiopathic steatorrhoea excrete as much in the faeces as do the patients with pernicious anaemia. When intrinsic factor is added, some of those with steatorrhoea show an improvement in absorption, but the effect is not as dramatic or as consistent as in pernicious anaemia itself. These results suggest that the prime cause of the defect in absorption is not lack of intrinsic factor, but that the vitamin is involved in the general failure of absorption which occurs.

Finally, in some patients, notably those with blind loops of intestine or jejunal diverticulosis, bacterial destruction of the vitamin, or competition for it within the lumen of the gut, may play an important part in producing the deficiency.

Girdwood (1959) has shown *in vitro* that organisms from the gut of patients with a blind loop will take up

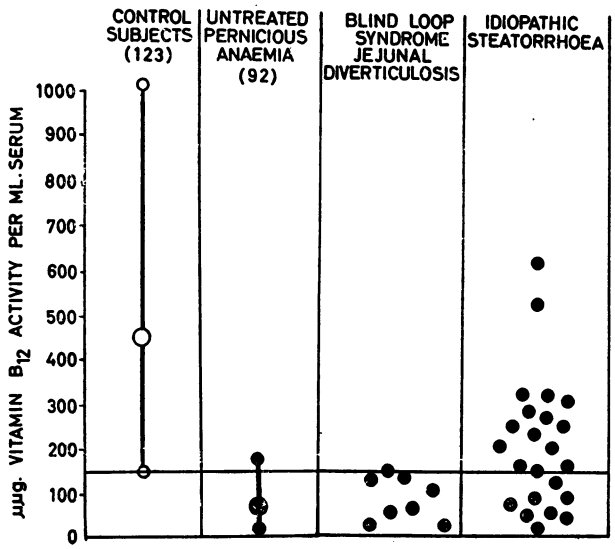

FIG. 4.—Levels of serum vitamin B_{12} in $\mu\mu$g./ml. in eight patients with jejunal diverticulosis and 23 patients with idiopathic steatorrhoea. Mean and range found in a group of control subjects and in untreated patients with pernicious anaemia are shown for comparison. (Data of G. H. Spray.)

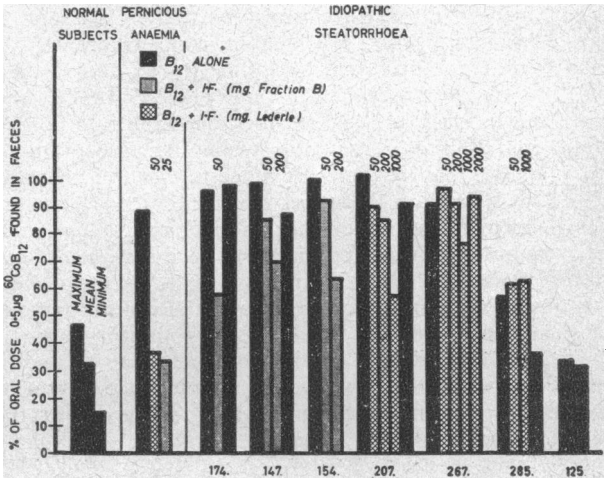

FIG. 5.—Percentage of oral dose of vitamin B_{12} labelled with radioactive cobalt recovered in faeces when given alone and with increasing doses of intrinsic factor. For comparison the excretion in normal subjects is shown and the response in a patient with pernicious anaemia to 25 mg. of Welch Fraction B and to 50 mg. of Lederle intrinsic factor. (Data of S. T. Callender and J. R. Evans, 1955.)

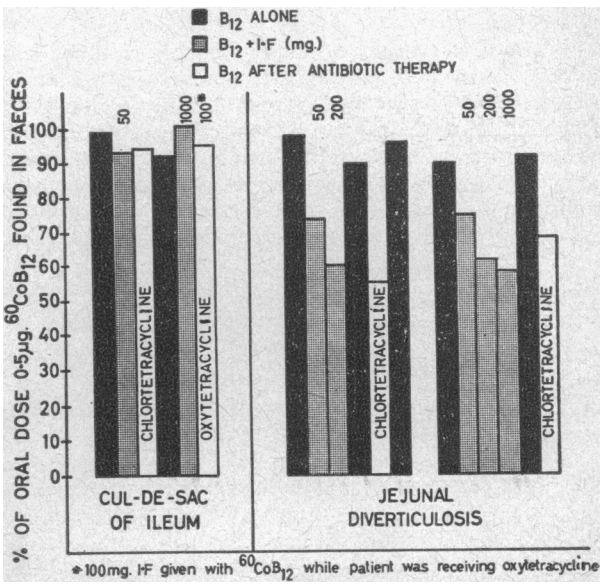

FIG. 6.—Effect of increasing amounts of intrinsic factor and of sterilization of intestine with antibiotics on absorption of oral dose of 0.5 μg. vitamin B_{12} labelled with radioactive cobalt in three patients with megaloblastic anaemia and structural abnormalities of small intestine. Figures above columns are weights in mg. of intrinsic factor preparation given. (Data of J. R. Evans, 1956.)

vitamin B_{12} readily from culture media, and Fig. 6 shows that sterilization of the bowel of these patients with an antibiotic will sometimes improve the absorption of the vitamin without need for other therapy (Evans, 1956). The black columns show the percentage of an oral dose of radioactive vitamin B_{12} recovered from the faeces when the vitamin was given alone to two patients with jejunal diverticulosis, and one with a blind loop. The grey columns show the effect of adding intrinsic factor, and the clear columns the result of treatment with an antibiotic. In both the patients with jejunal diverticulosis the antibiotic improved the absorption of the vitamin. In the patient with the blind loop neither the antibiotics nor the intrinsic factor had any effect, but she was desperately ill and the underlying process had involved most of the bowel (Badenoch, Bedford, and Evans, 1955).

In man, the evidence suggests that folic acid is absorbed mainly from the jejunum while vitamin B_{12} is absorbed from the ileum (Mollin, Booth, and Baker, 1957; Cox, Meynell, Cooke, and Gaddie, 1958); and the fact that in idiopathic steatorrhoea failure to absorb folic acid is almost universal while the absorption of vitamin B_{12} may be normal, suggests that the brunt of the disease falls on the upper small intestine. None the less, clinically the importance of deficiency of vitamin B_{12} cannot be overemphasized. The initial success of folic acid in correcting the megaloblastic anaemia overshadowed the dangers of damage to the central nervous system due to lack of vitamin B_{12}—a danger which is very real, especially in the steatorrhoeas due to anatomical lesions of the bowel where maintenance treatment is unlikely to influence significantly the power of the gut to absorb essential materials.

Iron Deficiency

The deficiency of iron which commonly occurs in idiopathic steatorrhoea is also the result of a failure of absorption. When a dose of 200 mg. of ferrous sulphate labelled with ^{59}Fe is given by mouth to a normal person (Fig. 7) some 5 to 8% appears in the blood, about 85% is recovered from the faeces, and the remainder goes to the body stores and cannot be recovered. If the same dose is given to a patient with simple iron deficiency a very much larger proportion appears in the blood (Badenoch and Callender, 1954a). Fig. 8 shows that, in contrast, in patients with idiopathic steatorrhoea almost all the oral dose is recovered from the faeces and very little appears in the blood, even in the presence of a severe iron-deficiency anaemia. The importance

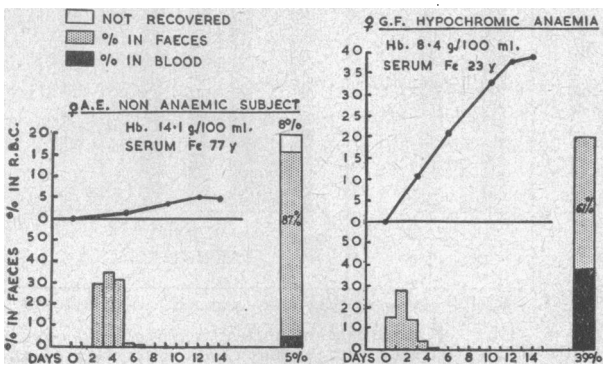

FIG. 7.—Radioactivity appearing in red cells and faeces of normal subject and one with hypochromic anaemia after an oral dose of 200 mg. of ferrous sulphate (5 μc. ^{59}Fe). (Data of J. Badenoch and S. T. Callender, 1954a.)

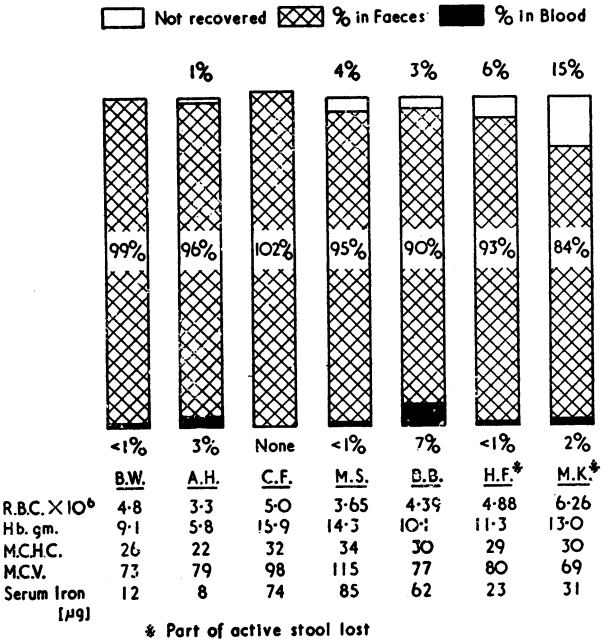

FIG. 8.—Recovery of oral dose of 200 mg. ferrous sulphate labelled with ^{59}Fe in seven patients with steatorrhoea.

of impaired absorption in producing the iron deficiency is emphasized by the response to treatment, for a course of parenteral iron will often restore the haemoglobin rapidly to normal after iron by mouth has failed (Fig. 9).

In some patients with idiopathic steatorrhoea poor absorption may not be the only cause of the iron deficiency, because Dr. Callender and I encountered a few who appeared to absorb enough iron to keep themselves in balance and yet suffered recurrent anaemia (Badenoch and Callender, 1954b). It may be that in these there was intermittent bleeding which we could not detect, but it is also possible that the loss of iron into the intestine from the seepage of serum or from increased desquamation of epithelium may be greater in the presence of steatorrhoea than in normal subjects. In any event, the impaired absorption of iron in idiopathic steatorrhoea and coeliac disease allows nothing for additional demands. I believe that this accounts for the fact that iron deficiency is the common cause of anaemia in the coeliac child, and explains why the symptoms of idiopathic steatorrhoea, in which tiredness and breathlessness are prominent, declare themselves at an earlier age in women than they do in men.

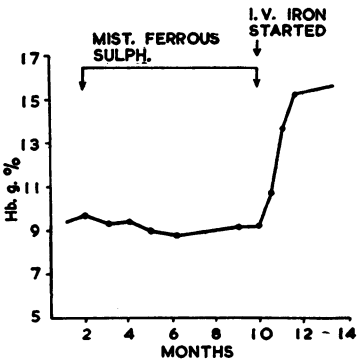

FIG. 9.—Woman, aged 36, with idiopathic steatorrhoea and hypochromic anaemia. Response to treatment with intravenous iron after failure to respond to iron by mouth.

In steatorrhoea due to anatomical disease of the bowel or to pancreatic failure the absorption of iron is usually normal, and when iron-deficiency anaemia occurs it is the result of bleeding.

Obscure Cases

In spite of advances in knowledge, there is still one part of the clinical picture of the malabsorption syndrome which we cannot explain. From time to time we see patients with a peripheral neuropathy, or damage to the central nervous system, which resist all our efforts to relieve them. There were four in my series, suffering respectively from idiopathic steatorrhoea, tabes mesenterica, Whipple's disease, and diverticulosis of the small intestine. The first three had progressive glove-and-stocking anaesthesia, with loss of reflexes, and the fourth had a myeloradiculopathy involving the cord. In two the C.S.F. was normal, in the other two the level of protein was raised, but there were no other abnormalities.

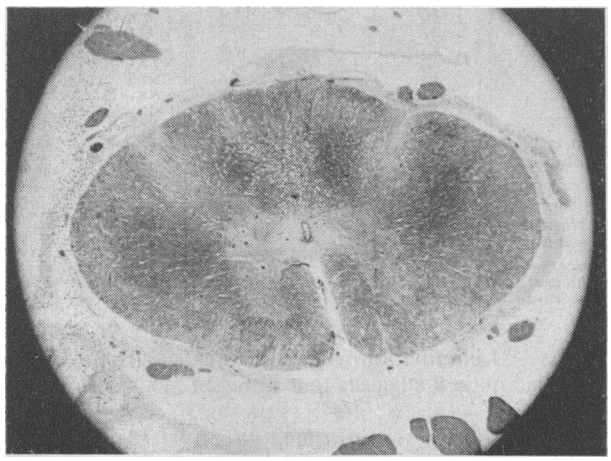

FIG. 10.—Section of lumbar spinal cord (stained for myelin) of patient with steatorrhoea and a myeloradiculopathy, showing generalized demyelination with some sparing of lateral columns.

Fig. 10 shows a section of the lumbar cord, stained for myelin, of the patient with the myeloradiculopathy. The black areas in the region of the pyramidal tracts are the only areas unaffected by the generalized demyelination which is maximal in the posterior columns. The curious thing about this syndrome is that it can occur while the patient is in haematological remission and in fair health, and it is totally uninfluenced by massive doses of all the known vitamins and minerals. It is tempting to assume that it is due to lack of an essential factor, but this is pure hypothesis. Its origin is entirely obscure and it presents a challenge for the future.

Fatal Cases

Before I leave the clinical part of my story, and lest I give the impression that, apart from a stubborn neurological syndrome, medical science has triumphed, it will be as well to remind ourselves that steatorrhoea is still a dangerous disease. In my series of 163, there have been 21 deaths, almost 13%. It is true that this study extends over a number of years, and to-day we would have saved some of these patients, but four of them died in 1959, in spite of our best efforts. Of the 21 deaths, nine occurred in the idiopathic group and 12 among the remainder.

To take first the 12 in which the steatorrhoea was symptomatic of a wider pathological process (Table IX). Three had cancer and a fourth developed massive gangrene of the bowel after mesenteric thrombosis.

TABLE IX.—*Causes of Death in the 12 Patients in Whom Steatorrhoea was Secondary to a Wider Pathological Process*

Case	Diagnosis	Cause of Death
K.F., C.J.	Carcinoma of pancreas	Carcinomatosis
L.M.	,, caecum-resection	Pneumonia
R.B.	Mesenteric thrombosis	Gangrene of bowel
E.B., J.M., I.R.	Diverticulosis of jejunum	Pneumonia; ,, ; Myelopathy
D.B., J.S.	Tabes mesenterica	Pneumonia; Volvulus neuropathy
V.R., M.S.	Crohn's disease	Perforated duodenal ulcer; steroids
B.F.	Whipple's ,,	Cachexia; ,, neuropathy

Among the eight remaining patients it is interesting to note that three suffered from progressive neurological disease, and one of these died of acute intestinal obstruction as a result of volvulus. Three of the eight patients with upper intestinal diverticulosis have died, not, I think, because it is a particularly dangerous syndrome, but because it occurs chiefly among the elderly whose days are numbered for other reasons. One of the patients with Crohn's disease, a woman, died of a perforation of a duodenal ulcer while receiving steroids.

TABLE X.—*Causes of Death in Nine Patients with Idiopathic Steatorrhoea*

Case	
M.W.	Oesophageal stricture-perforation
W.P.	Bronchopneumonia
L.F.	Pneumonia, Steroids
D.C., K.W.	Muscular weakness ? Hypokalaemia
G.E., S.P.	Hepatic failure
J.T.	Volvulus—acute obstruction
W.B.	Cachexia, neuropathy

Of the nine deaths in the idiopathic group (Table X), in only two, M.W. and W.P., could the deaths be said to be unrelated to the malabsorption syndrome. In one of these, M.W., attempts to dilate an oesophageal stricture led to a fatal mediastinitis; and W.P. was an old man who succumbed to bronchopneumonia.

L.F. was one of the first patients whom I treated with cortisone. She died of an uncontrollable respiratory infection which seemed to be related to its use. D.C. and K.W. suffered progressive muscular weakness and, in retrospect, almost certainly succumbed to potassium deficiency. G.E. and S.P. died in hepatic coma, and illustrate the point that the combination of liver disease and steatorrhoea is a lethal one. S.P. was all the more unfortunate because he was one of the two with massive retroperitoneal haemorrhage described earlier, and we had good reason to suppose that his hepatitis was due to homologous serum jaundice, resulting from the blood transfusions which he had received. Once again intestinal obstruction appears in the list. W.B. died in our wards last year of progressive inanition, in spite of full replacements of vitamins and minerals, a gluten-free diet, and treatment with steroids. Necropsy failed to reveal a malignant cause for his steatorrhoea, and we are forced to admit that we have no idea why he died. His death emphasized more strongly to me than anything else has done that for all our efforts, and in spite of much greater understanding of some facets of the problem, the basic defect in idiopathic steatorrhoea still remains unknown.

[The second lecture, together with a list of references, will appear in our next issue.]