THE MALABSORPTION SYNDROMES
Some Clinical Problems

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I HAVE BEEN interested in the malabsorption syndromes for a long time and one of the fascinations of a continued interest over the years is to watch the emphasis change as new knowledge is added and old problems are solved. When I reviewed the subject in 1960 the classical idea that all the signs and symptoms of the malabsorption syndromes were due to failure of absorption of essential substances still held the field, but even then this was difficult to sustain. It was held, for example, that the dermatitis, glossitis and cheilosis that occurred in some patients, were due to faulty absorption of B vitamins and yet it was known that with one or two notable exceptions the absorptive capacity of the small intestine for the water soluble vitamins was enormous, and that even in the presence of gross steatorrhoea enough could be absorbed to satisfy the body's needs. Gradually, we have had to come to realise that malabsorption is only one facet of the problem, even if it is the easiest to recognise.

In the presence of gross disorganisation of the small intestine not only are substances poorly absorbed but the normal losses by secretion and exudation into the lumen of the gut may be greatly increased either by direct seepage into the lumen or as a result of increased exfoliation of cells from the mucosal wall. Creamer and Croft (1970) have estimated that in normal man 60,000,000 cells may be lost daily from the small intestine together with 80 gms. of protein. Sixteen per cent of the protein lost is contained in the exfoliated cells. The greater quantity of this, of course, is digested and reabsorbed but in coeliac disease the loss of cells and protein may be increased six-fold and may contribute significantly to the hypoproteinaemia which occurs. It is known that not only protein but also iron and vitamin B_{12} are lost both by exfoliation and exudation and it may well be that there is an increased loss of many other essential substances when the mucosa is damaged.

Moreover, the patient with malabsorption is at a double disadvantage because substances which are lost into the lumen of the gut are likely to be less well-absorbed than in normal persons. Finally, in coeliac disease and other conditions associated with malabsorption, failure of absorption and increased loss into the lumen of the bowel may not be the only factors of importance. It is quite possible that abnormal substances, the result of faulty digestion or bacterial action, may be absorbed and give rise to far-reaching effects. Perhaps the first pointer to this came from an observation by England, French and Rawson (1960) some years ago. They studied a patient with Whipple's disease and a light sensitive dermatitis who was found to be excreting abnormal porphyrins in the stools. Treatment with antibiotics abolished the porphyrins from the stools and cured the dermatitis. The exact reason for the improvement remained uncertain but it could have been due

to the destruction of bacteria that were the source of the abnormal porphyrins.

For the clinician, the observation of Dickie (1950) that the removal of wheat and rye protein from the diet of children with coeliac disease will cure the patient still holds the centre of the stage. Much fundamental research stems from this single fact but it is chastening to realise that in spite of all efforts the exact nature of the defect in the small intestine and the way in which this normal dietary protein exerts its damaging effect is still unknown.

In 1959 Fraser and his colleagues showed that a peptic/tryptic hydrolysate of gluten was toxic to patients with coeliac disease, but if this hydrolysate was further digested by fresh hog intestinal mucosa the product was no longer capable of damaging the intestinal mucosa and inducing malabsorption in coeliac patients. As a result of these experiments it was concluded that coeliac disease was due to the congenital absence of a peptidase from the intestinal mucosa (Fraser et al, 1959). Unhappily, sixteen years later this peptidase still eludes all efforts to find it. Perhaps the most damaging blow to the supporters of the "absent peptidase" theory of the aetiology of coeliac disease was struck by Douglas and Booth (1970). They showed that the activity of leucyl-leucine hydrolase was depressed in the mucosa of untreated coeliac patients but after treatment with a gluten-free diet or even after treatment with steroids while the patients continued to take gluten in the diet, no difference in activity between the coeliac patients and the normal controls could be found.

However, the absent peptidase theory cannot be disposed of as easily as that. Amino-acids are absorbed by more than one system and even the di- and tripeptides can be absorbed into the mucosal cell in several different ways, and, as Matthews (1971) has pointed out, the only single biochemical lesion which could impair the absorption of protein would be a failure of release of the amino acids produced by digestion from the mucosal cell into the bloodstream. It is known that amino acid transport defects, even when they involve several amino acids, do not produce any clinical signs directly referable to the impairment of protein absorption. The mucosal peptidases are so numerous and have so many overlapping specificities that a single defective peptidase might be very difficult to detect by present assay methods.

The second major hypothesis to explain gluten sensitivity invokes a disturbance of immune reactions and stems from two observations. The first was the observation that precipitating antibodies to gluten or to its derivatives can be found in the serum of some patients with coeliac disease (Berger, 1958), and, the second, was the demonstration that treatment with steroids could bring about improvement in these patients even if they continued to eat a diet that contained gluten (Katz et al, 1968). Personally, I believe that the second prop in the argument is not necessarily secure because there could be other reasons for the effects of steroids, for example they induce non-specific changes in the permeability of cells and they are known to alter the activity of lysozymes Nonetheless, in recent years our understanding of the immune defences of the gut has increased and this has lent impetus to a study of the disturbance that occurs in intestinal disease. We know, for example, that the plasma cells of the gut chiefly synthesize IgA which is released into the sub-epithelial pool as a 7s monomer. Some of this is transported across the gut epithelium becoming dimerised in the process and to this dimer

is added "secretory piece" which is formed in the epithelial cells. The 11s secretory IgA thus formed reached the lumen of the gut and it differs from 7s IgA in two important ways. The secretory IgA is resistant to normal intestinal pH and enzymes and it can fix complement and damage the lipoid membrane of bacteria (Hobbs, 1971).

The results of studies of the abnormalities of the immune globulins which are present in patients with coeliac disease have been conflicting and the picture has been complicated still further by the fact that patients with either primary deficiency of immune globulins or a deficiency secondary to other disease such as leukaemia, often have malabsorption. Both deficiency of IgA and IgM and an increase in IgA and IgM have been described. Many of the results are conflicting and it seems to depend largely on whether the author has been studying the serum, the mucosal wall of the intestine or the intestinal secretions within the lumen itself. Moreover the differences between coeliac disease and patients with other diseases of the gut are not absolutely clear cut. The changes seem to depend on whether or not the patient has been under treatment with a gluten-free diet. Recently, Hobbs and his colleagues, summarised what is known of the subject. In their view the only significant difference between patients with coeliac disease and those with other diseases involving the small intestine was that patients with coeliac disease, whatever the levels of IgA or IgM in their plasma, showed an increase in the density of jejunal plasma cells containing IgM while the density of plasma cells containing IgA was either normal or decreased (Hobbs et al, 1969).

It is known that antibodies of the IgA type provide the main defence of the gut against virus infection. Beale and his colleagues (1971) have shown that whereas coeliac patients can produce normal IgG antibodies in response to a challenge with tetanus toxoid, they produce subnormal amounts of IgA in response to an oral dose of poliomyelitis vaccine. Beale suggests that in coeliac disease the ability of the patient to produce IgA antibodies is depressed. In its place IgM antibodies are produced and these, unlike the IgA antibodies, are capable of damaging the intestinal mucosa (Beale et al, 1971).

The exact relationship of the relative deficiency in the synthesis of IgA to the aetiology of coeliac disease remains unclear. Certainly, enough evidence has already accumulated to show that a quantitative decrease in IgA does not occur in every patient. Perhaps in the future it will be more profitable to look at the quality of the IgA which is produced and to follow up the work which has been done on patients with giardiasis and nodular lymphoid hyperplasia of the gut. In some of these, although the levels of IgA and IgM have been normal, the IgM has been found to be of poor quality and inadequate to protect the wall of the gut from the parasite (Hobbs, 1971).

Personally, I think it may be some time before we understand fully the cause of the gluten sensitive enteropathy. The one unassailable fact is that one chemical compound or a small group of chemical compounds have been shown to do the damage while as far as we know, once the mucous membrane has been restored to normal, all other substances present in the food are harmless. This being so, it seems odd to me that a failure of the normal IgA immune response, which one

would expect to involve a whole series of potentially damaging substances, should be so restrictive in its action.

In the last five years we have learnt a great deal about the processes of digestion that go on within the mucosal cell of the small intestine and it may yet be shown that the two hypotheses, on the one hand the alleged absence of a peptidase, on the other the abnormalities in the immune response, may yet be closely interrelated and that the prime cause of the immunological abnormality is a disturbance of the chemistry within the cells of the mucous membrane itself.

Whatever its cause it is a fact that immuneparesis does occur in some patients with the coeliac syndrome and as Austad and his colleagues have emphasised there is a profound disturbance of the lymphoreticular system (Austad et al, 1967). There may be splenic atrophy with Howell Jolly bodies in the red blood cells and an increased red cell survival time. There is hypoplasia of the peripheral lymph nodes and an increase in size of the nodes in the mesentery, and the lamina propria of the gut, and even the epithelial cells may be infiltrated with lymphocytes. Austad and his colleagues have postulated that the immunological insufficiency may be the result of a prolonged overactivity of antibody formation aggravated in some way by the sensitivity to gluten. Whatever its cause there is no doubt that immuneparesis does occur and it is perhaps of more than theoretical interest that it also occurs in Hodgkin's disease and other lymphomata. It is now well recognised that lymphomata occur more often in patients with the coeliac syndrome than in the population at large, and Whitehead (1968) has suggested that in these patients there may be a progressive hyperplasia of the lymphoreticular system with a gradual appearance of abnormal reticulum cells ending in the clinical manifestation of reticulosarcoma. He believes that this may be an expression of an auto-immune process that goes on to malignancy, and that it can be compared with the reticuloses that complicate some cases of Hashimoto's disease of the thyroid.

The incidence of carcinoma, especially of the foregut, is also higher in patients with coeliac disease than in the general population and I suppose it is possible that here, too, the development of an immuneparesis may predispose to the neoplastic change.

There is another aspect of the clinical picture of coeliac disease which may be linked to the immuneparesis. Everybody who has studied patients with steatorrhoea has encountered a few with a lesion of the spinal cord which can progress despite full supportive therapy including vitamin B_{12}, a gluten-free diet and steroids. I have had five totally unexplained cases and Cooke and Smith in 1966 published an account of sixteen. Their patients, eleven male and five female, were aged 26 to 68 at the onset of the neropathy. The main changes were a sensory ataxia chiefly involving the legs, a peripheral neuropathy, posterior column loss, muscle weakness but little wasting and no tenderness. Three of the patients had cerebellar dysfunction and five had unexplained transient attacks of loss of consciousness. In ten the neuropathy had been steadily progressive, nine had died and in four the neuropathy was the main cause of death. In another four it was a major contributory factor. It is of interest that one died of a reticulosarcoma. At autopsy in these patients the pathological changes are widespread and diffuse involving the cortex, the anterior horn cells and the spinal cord. There is patchy atrophy and loss of cells and focal areas of demyelination. The changes most closely resemble

those seen in the multi-focal leucoencephalopathy that occurs in association with neoplastic disorders.

As I have mentioned, one patient in Cooke's series died of a reticulosarcoma and there are at least two other cases in the literature in which this has happened. One, reported by Brain, Croft and Wilkinson in 1965, had steatorrhoea and a reticulosarcoma with neurological signs resembling motor neurone disease and another, published by Missen in 1966, with steatorrhoea and a malignant lympoma of the intestine suffered from cerebellar cortical dysfunction towards the end of his life. This is a surprising association and for some time I have been wondering whether these facets of the clinical picture of the coeliac syndrome, the immune-paresis, the increased incidence of malignant change and the progressive and lethal neuropathy might be related. Nobody knows the cause of the immuneparesis but once established might it not allow a slow virus to attack the central nervous system or perhaps even allow the development of a neoplasm which as Missen, himself, has suggested might further impair the immune defence by massive replacement of the lymphoreticular system by malignant cells and thus lay the way open for a neurotropic virus. Clearly, the neuropathy of the coeliac syndrome should be a fruitful field for study. It is certainly not due to a deficiency of any known vitamin. It can be progressive and lethal in spite of all attempts at treatment and it is associated with a neoplasm more commonly than seems possible by chance alone. It remains a complete enigma.

The next aspect of the malabsorption syndromes that I wish to consider today is the derangement of function that accompanies the short gut syndrome. The pattern of ileal dysfunction which follows resection of the bowel is particularly interesting because it has led to a better understanding of much of the pathophysiology of malabsorption but here also there are some unsolved problems. Börgstrom and his co-workers showed that after a test meal not only sugar and protein but also fat are almost completely absorbed in the first metre of the jejunum (Börgstrom et al, 1957). This being so it is perhaps surprising that the loss of part of the small intestine should be associated with such a profound disturbance of function. However, the situation is not always too desperate. It is known that 70 per cent of the small intestine can be resected without steatorrhoea if the terminal ileum and ileocaecal valve are preserved. If these are resected the position is very much worse and a loss of just over 50 per cent will lead to persistent diarrhoea and steatorrhoea.

The simple sugars and many water soluble substances are absorbed in the high small bowel and proteins, fats and fat soluble vitamins are absorbed in the upper and mid-small bowel, but cholesterol, vitamin B_{12} and the bile salts are chiefly absorbed by an active transport system selectively localised to the ileum. When the lower small bowel is resected the sites of active transport of these substances are lost and it is the failure of the absorption of bile salts and consequent bile salt deficiency that explains why steatorrhoea is much more prone to occur after ileal resections than after resections of the jejunum.

Under normal condition 98 per cent of the bile salts that are secreted into the lumen of the intestine are reabsorbed and find their way back to the liver via the portal stream for recirculation in the bile. The bile salts are recirculated several

times a day and under normal conditions the amount of new bile acid synthesised from cholesterol just equals the loss of bile acids in the faeces. Anything that interrupts the enterohepatic circulation of bile salts will lead to a rapid depletion of the pool with consequent failure of the micellar phase of fat absorption. The four main causes of depletion of the pool of circulating bile acids are obstructive jaundice, the contaminated bowel syndrome in which bacteria bring about excessive deconjugation of the bile salts, the binding of bile salts within the lumen of the gut by ion-exchange resins such as cholestyramine, and resection of the ileum or the short gut syndrome. Following a resection of the ileum loss of the active absorptive site for bile salts causes them to reach the colon in larger quantities than normal where they block the active absorption of water and electrolytes from the bowel and make the diarrhoea worse (Mekhjian et al, 1968).

If the resection of the bowel is complicated by the presence of strictures, blind loops of gut or fistulae, bacteria will flourish and abnormal deconjugation of even those bile salts that remain will occur. This will deplete the pool of bile salts still further and make it even more difficult to form the micelles necessary for fat absorption. The damaging effect of depletion of the bile salt pool is not limited to the absorption of fat. There is some evidence that when free bile acids are present in excess within the lumen of the gut they interfere also with the active transport of sugars and amino acids although the exact way in which they do this remains unknown (Baraona et al, 1968).

In the absence of gross bacterial contamination jejunectomy does not produce a continuing clinical defect in the transport of proteins, sugars or electrolytes because the active transport sites for these substances are present throughout the small intestine. Similarly, the removal of the ileum does not produce a major primary defect in absorption unless changes in motility, or abnormal bile salt loss with consequent steatorrhoea supervene.

Usually there is plenty of reserve capacity for active absorption but sometimes it is possible to saturate a limited active transport system. For example, after massive resection of the gut a solute overload at meal times can lead to tiresome postprandial diarrhoea which takes months to subside.

It would be very useful if passive transport played a greater part in normal absorption but unhappily its place is limited. Sugars, electrolytes, amino acids, fatty acids, pyrimidines, bile salts, cholesterol, vitamin B_{12} and folic acid all require an active transport system. A notable and useful exception involves the medium chain triglycerides which are absorbed largely by passive diffusion. Many substances that are primarily absorbed by an active process can also be absorbed in small amounts by passive diffusion and, if the body's requirements are small, enough may be absorbed by this route. This probably applies to some vitamins, trace elements and drugs.

The main cause of failure of absorption in the short gut syndrome is the loss of specialised absorptive sites especially those localised to the ileum, but there are also some secondary effects of resection of the gut which contribute to the disturbance in function. The worst of these is the alteration in gastric secretion and the disturbance of gastric and intestinal motility that develops. In man and

in experimental animals after resection of the small intestine gastric hypersecretion occurs.

The aetiology of the gastric hypersecretion is still in doubt. It is more marked after proximal than distal resections. It is possible, I suppose, that the small bowel remnant elaborates a gastric secretagogue. It has been shown that patients who have had a portacaval shunt secrete abnormal amounts of acid and that this is caused possibly by a secretagogue elaborated in the jejunum, but after resection of the bowel the excessive secretion of acid from the stomach seems more likely to be due to the loss of an inhibitor of gastric secretion, an enterogastrone. It is interesting that both serotonin and histaminase are localised in the upper small intestine and if the secretion of either of these were reduced gastric hypersecretion might result.

In 1956 Reynell and Spray in Oxford showed that after massive resection of the small gut in rats there was a marked increase in motility and a shortened transit time. This effect, in contrast to the gastric hypersecretion, is more marked if the distal small bowel is removed. Its cause is unknown but here, too, the loss of an inhibitory hormone could be responsible.

In coeliac disease in particular abnormalities of function resulting from the loss of gastrointestinal hormones are probably much more common than we realise. It is self-evident if you stop to think about it. In the gluten enteropathy the villi are destroyed, the mucosa is flattened, the brush border has vanished and the epithelial cells are debased and distorted. When this occurs we are quite ready to accept that there will be a failure of the intramural phase of digestion. On the other hand the concept that there must also be a loss of production of any intestinal hormones which are ebalorated in the mucosal cells or in the brush border is relatively new and is still not widely accepted.

In the past year or so evidence has been accumulating that loss of these gastro-intestinal hormones may indeed be important. In normal persons the physiological stimulus for the secretion of pancreozymin is the presence of amino-acids in the lumen of the upper intestine. In 1969 DiMagno, Go and Summerskill showed that in patients with coeliac disease the perfusion of the jejunum with amino-acids produced a subnormal secretion of pancreatic enzymes. They deduced that this was because the amino-acids present within the lumen had led to the release of abnormally small amounts of pancreozymin from the intestine. If the pancreozymin was injected parenterally the outflow of enzymes from the pancreas was normal. Similarly, Low-Beer and his colleagues (1971) from Bristol have demonstrated inertia of the gall bladder in response to a fatty meal in patients with coeliac disease. They have suggested that the failure of the gall bladder to contract resulted from an impairment of the release of cholycystokinin, and they postulate that the steatorrhoea in coeliac disease may be aggravated by a delay in the secretion of bile salts and pancreatic enzymes after a meal, which contributes to the failure of micelle formation. In this context it is interesting to recall that patients with the short gut syndrome and ileal dysfunction have a much higher incidence of gall stones than the population at large, and it may be that bile is sequestered in the biliary tree because of gall bladder inertia resulting from the loss of an intestinal activator.

It has been recognised for some time that patients with intestinal disease and especially those who have had a resection of the small bowel are more prone than the general population to the development of stones not only in the gall bladder but also in the kidneys. In the United States the incidence of renal stones in patients in hospital is estimated to be about 1 : 1,000 but Gelzayd and his colleagues in 1968 reviewed 885 patients with bowel disease and found the incidence of nephrolithiasis in them to be 7.2 per cent.

Initially, it was thought that the increased incidence of renal stones was caused by the fact that many of these patients lose quantities of water, sodium and bicarbonate into the gut and as a result secrete an acid urine of low volume which would favour stone formation, but in 1970 Hofmann and co-workers described two patients with previous small bowel resection and nephrolithiasis who had hyperoxaluria. In 1971, Dowling, Rose and Suter reported eleven patients with ileal dysfunction, eight of whom had hyperoxaluria and three of whom had calcium oxalate stones in the renal tract.

Several hypotheses have been put forward to explain the hyperoxaluria and in 1972 at the meeting of the British Society for Gastroenterology at Aviemore Chadwick, Modha and Dowling produced an interesting paper that did much to settle the dispute. It has been suggested that bile salt glycine spilling into the colon because of ileal dysfunction was deconjugated by bacteria, converted to glyoxalate, absorbed and then oxidised to oxalate with the production of hyperoxaluria. Dowling and his colleagues fed cholyl glycine labelled with radio-active carbon to control subjects and patients after ileectomy. The amount of radio-active carbon dioxide recovered from the breath of those with ileectomy was much increased when compared with the control subjects, but in both groups the amount of the dose of labelled cholyl glycine excreted in the urine as oxalate was the same. This would appear to exclude the excess bile salt glycine as the precursors of the excessive amounts of urinary oxalate.

It has also been suggested that after ileal resection the increased drain on hepatic glycine for bile salt conjugation might be met by an increased conversion of glycollate through glyoxalate to glycine. However, Dowling and his colleagues showed that after the intravenous injection of glyoxalate labelled with radio-active carbon the conversion to bile salt glycine, carbon dioxide and urinary oxalate was the same in the controls as in the patients with ileal resection and hyperoxaluria. They also fed oxalate labelled with radio-active carbon to normal controls and to patients with an ileectomy with and without hyperoxaluria. In the controls 28 per cent of the radio-active oxalate was recovered from the urine in the first 36 hours, 29 per cent was recovered from the patients with ileectomy without hyperoxaluria and 52 per cent over the same period from those with an ileectomy with hyperoxaluria. This suggested strongly that the hyperoxaluria following ileectomy was the result of an increased absorption of oxalate from the bowel. Finally, Dowling and his co-workers confirmed this hypothesis by the demonstration that if the oxalate was removed from the diet of those patients with hyperoxaluria excessive urinary excretion of oxalate ceased.

Why some patients with an ileal resection should absorb excessive amounts of oxalate from the diet and others should not remains in doubt and there is still

the interesting but unexplained observation by Smith, Fromm and Hofmann (1972) that cholestyramine will decrease the excretion of oxalate in patients with the short gut syndrome, and as yet it is far from clear why an ion-exchange resin should block the absorption of oxalate from the bowel.

Before we leave the short gut syndrome we must not forget the possibility that patients with ileal resection seem to be more prone to the malabsorption of essential substances than even those with the coeliac syndrome. In the past we have concentrated too much on the recognised vitamins and have attributed any unexplained symptoms to their lack. However, Press and his colleagues (1972) have shown that in patients with ileal resection the percentage of essential fatty acids in the lecithin, triglyceride and cholesterol ester in fasting plasma is lower than in normal persons. It has been shown that a deficiency of essential fatty acids can cause diarrhoea and dermatitis in human infants and in one of Press' patients with low levels of linoleic acid in the blood fats and a severe dermatitis the intravenous administration of "intralipid" cured the skin lesions. There is also the interesting observation that deficiency of essential fatty acids leads to the development of gall stones in hamsters and perhaps the increased incidence of gall stones in patients with ileal resection is due not only to gall bladder inertia but also to a shortage of essential fatty acids.

Several attempts have been made to lessen the diarrhoea in patients with the short gut syndrome. Considerable adaptation occurs with time and the diarrhoea and steatorrhoea tend to decrease as the remnant of bowel hypertrophies. In those in whom the diarrhoea persists probably the most useful regime is the substitution of medium chain triglycerides for the long chain fats in the normal diet (Zurier et al, 1966). These medium chain triglycerides can be absorbed without prior emulsification and solublisation by bile salts and they form a useful source of calories and decrease the steatorrhoea. An interesting feature of the treatment is that the steatorrhoea and diarrhoea does not decrease for a week or ten days after the treatment has begun. At the moment there is no clear explanation why this should be so, but it could be due to a gradual reduction in the amount of irritating long chain fatty acids being delivered to the colon. It is important to know that improvement takes time because the slow response may lead to the treatment being abandoned prematurely because it appears to be unhelpful.

Sometimes treatment with oral bile acids will reduce the diarrhoea, but in my experience more commonly the cathartic effect of the bile salts potentiates the diarrhoea without reducing the steatorrhoea appreciably. Oxbile in a dose of 3–6 gms. daily seems the best preparation to use but I have not had much success with it myself.

Calcium carbonate has also been used in the treatment of patients with ileal resection (LeVeen et al, 1967). The rationale of its use is that the calcium carbonate forms non-irritating soaps with free fatty acids, but to be effective the dose may have to be very large, up to 30 gms. a day, and there is a danger of the development of the milk-alkali syndrome. As an alternative cholestyramine can be used. It acts by binding bile salts within the lumen of the intestine and it may reduce the diarrhoea but at the cost of aggravating the deficiency of bile salts still further and making the absorption of fat even more difficult.

Of these measures, the substitution of medium chain triglycerides for the long chain fats in the diet offers the most physiological approach to a difficult problem and if they are introduced slowly the fat intake can usually be built up to a level that provides enough calories for adequate nutrition.

The medium chain triglycerides are useful in other forms of malabsorption also. They are helpful in children with fibrocystic disease and in those with biliary atresia. They have a place in the treatment of patients with a contaminated bowel syndrome when this is not amenable to surgery, they have revolutionised the management of a number of rare forms of malabsorption including a β-lipoproteinaemia in which the sufferer is unable to form chylomicrons and they can reduce the gross steatorrhoea of patients with intestinal lymphangiectasia. They have also proved helpful in children with steatorrhoea resulting from disaccharidase deficiency (Gracey et al, 1970).

The final topic I wish to consider is the relationship of drugs to malabsorption. Today the clinician is becoming increasingly aware of the toxic effects of drugs and the gastro-intestinal tract has not escaped unscathed. The classical example is the malabsorption produced by Neomycin. This drug produces a malabsorption of fat, protein, glucose, d-zylose, cholesterol, carotine, sodium, calcium, vitamin B_{12} and iron. The effect can be produced by as little as 3 g. a day. Neomycin induces morphological changes in the mucosa, precipitates bile salts, inhibits intra-luminal hydrolysis of long chain triglycerides presumably by inhibiting pancreatic lipase. It also reduces intestinal lactase activity and lowers serum cholesterol possibly by blocking cholesterol synthesis within intestinal crypts or by interfering with its absorption. Neither steroids nor a gluten-free diet improves the malabsorption induced by Neomycin. Neomycin is not the only drug which can bring about malabsorption. Other antibiotics, notably tetracycline, Kanamycin, Polymyxin and Bacitracin, produce minimal malabsorption in man. Alcohol can inhibit folate absorption, anti-convulsants may reduce the absorption of vitamin B_{12}, folate and also d-zylose. Cathartics in excess can produce steatorrhoea as well as diarrhoea and malabsorption has resulted from the use of colchicine, PAS, Phenindione, mannitol and calcium carbonate, while MER 29 (Triparanol) once used in the treatment of hypercholesterolaemia produced a severe steatorrhoea and a mucosal lesion indistinguishable from that seen in the coeliac syndrome.

In the gluten enteropathy and other conditions which cause widespread damage to the small intestine drugs, like other substances, may be involved in the general malabsorption. The best documented is digitalis which needs to be given in large doses if a therapeutic level is to be attained (Heizer et al, 1971) but no doubt others are similarly affected. Finally, there are other even more complex ways in which drugs may interfere with the normal processes of absorption. For example, calcium is necessary for the absorption of vitamin B_{12} and vitamin B_{12} deficiency itself may contribute to its own malabsorption (Chanarin, 1971). Enzymes induction may lead to malabsorption more often than has been realised. Recently, it has been shown that anti-convulsant drugs induce hepatic enzymes which lead to the inactivation of vitamin D with the consequent failure of absorption of calcium and osteomalacia (Richens and Rowe, 1970). The possible interactions are legion and in the future, just as we have to consider a failure of secretion of intestinal hormones when we are faced with an unexplained clinical situation in a patient

with malabsorption, so I think will we have to consider that the clue to the problem or the source of the trouble may lie on the treatment chart at the foot of the bed.

The small bowel is a difficult organ to study even today. The gluten enteropathy, Crohn's disease and other states of malabsorption are nature's experiments in the physiology and pathology of intestinal function. They still have much to teach us and if, like the Prince of Serandib, we can see when we are not looking then each time we treat one of these patients we may be able to add a little to our knowledge of this fascinating field.

References

AUSTAD, M., CORNES, J. S., GOUCH, K. K., MCCARTHY, C. F., READ, A. E. A. (1967). *Amer. J. dig. Dis.*, **12**, 475.

BARAONA, E., PALMA, R., NAVIAE, E., ORREGO, H., ESPINOZA, J. (1968). *Acta physiol. Lat. Amer.*, **18**, 291.

BEALE, A. J., DOUGLAS, A. E., PARISH, W. E., HOBBS, J. R. (1971). *Lancet*, **2**, 1198.

BERGER, E. (1958). *Ann. Pediat., Suppl.* 67, 1.

BÖRGSTROM, B., DAHLQVIST, A., LUNDH, G., SJOVALL, J. (1957). *J. clin. Invest.*, **36**, 1521.

BRAIN, W. R., CROFT, P. B., WILKINSON, M. (1965). *Brain*, **88**, 479.

CHADWICK, V. S., MODHA, K., DOWLING, R. H. (1972). *Gut*, **13**, 840. (Abstr.).

CHANARIN, I. (1971). *J. clin. Path.*, **24**, Suppl. 5, (Roy. Coll. Path.), 60.

COOKE, W. T., SMITH, W. T. (1966). *Brain*, **89**, 683.

CREAMER, B., CROFT, D. N. (1970). *Coeliac Disease*. Editiors Booth, C. C., Dowling, R. H. Edinburgh and London: Churchill-Livingstone.

DICKIE, W. K. (1950). COELIKIE, Utrecht M.D. Thesis.

DIMAGNO, E. F., GO, V. L. W., SUMMERSKILL, W. H. J. (1969). *Gastroenterology*, **56**, 1149. (Abstr.).

DOUGLAS, A. P., BOOTH, C. C. (1970). *Clin. Sci.*, **38**, 11.

DOWLING, R. H., ROSE, G. A., SUTOR, D. JUNE (1971). *Lancet* **1**, 1103.

ENGLAND, Margaret T,. FRENCH, J. M., RAWSON, Annette B. (1960). *Gastroenterology*, **39**, 219.

FRASER, A. C., FLETCHER, R. F., ROSS, C. A., SHAW, B., SAMMONS, H. G., SCHNEIDER, R. (1959). *Lancet*, **2**, 252.

GELZAYD, E. A., BREUER, R. I., KIRSNER, J. B. (1968). *Amer. J. dig. Dis.*, **13**, 1027.

GRACEY, M., BURKE, Valerie, ANDERSON, Charlotte M. (1970). *Arch. dis. Child*, **45**, 445.

HEIZER, W. D., SMITH, T. W., GOLDFINGER, S. E. (1971). *New Eng. J. Med.*, **285**, 257.

HOFMANN, A. F., THOMAS, P. J., SMITH, L. H., MCCALL, J. T. (1970). *Gastroenterology*, **58**, 960. (Abstr.).

HOBBS, J. R., HEPNER, G. W., DOUGLAS, A. P., CRABBE, P., JOHNASSON, S. G. O. (1969). *Lancet*, **2**, 649.

HOBBS, J. R. (1971). *J. clin. Path.*, **24**, Suppl. 5, (Roy. Coll. Path.), 146.

KATZ, J., KANTOR, F. S., HERSKOVIC, T. (1968). *Ann. Intern. Med.*, **69**, 1149.

LeVEEN, H. H., BOREK, Blanche, AXELROD, D. R., JOHNSON, A. (1967). *Surg. Gynec. Obstet.*, **124**, 766.

LOW-BEER, T. S., HEATON, Susan T., HEATON, K. W., READ, A. E. (1971). *Lancet*, **1**, 991.

MATTHEWS, D. M. (1971). *J. clin. Path.*, **24**. (Suppl. 5), 29.

MEKHJIAN, H. S., PHILLIPS, S. F., HOFMANN, A. F. (1968). *Gastroenterology*, **54**, 1256.

MISSEN, G. A. K. (1966). *Guys Hosp. Rep.*, **115**, 359.

PRESS, M., KIKUCHI, H., THOMPSON, G. R. (1972). *Gut*, **13**, 879. (Abstr.).

REYNELL, P. E., SPRAY, G. A. (1956). *Gastroenterology*, **31**, 361.

RICHENS, A., ROWE, D. J. F. (1970). *Brit. med. J.*, **4**, 73.

SMITH, L. H., FROMM, H., HOFMANN, A. F. (1972). *New Eng. J. Med.*, **286**, 1371.

WHITEHEAD, R. (1968). *Gut*, **9**, 569.

ZURIER, R. B., CAMPBELL, R. G., HASHMIN, S. A., VANITALLIE, T. B. (1966). *New Eng. J. Med.* **274**, 490.