Section of Medicine

President E R Cullinan MD

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Hypoproteinæmia in Gastrointestinal Disease [*Abridged*]

by A M Dawson MD and Roger Williams MD
(*London*)

Hypoalbuminæmia in disease may be due to a decreased synthesis of the protein or to an increased rate of destruction. In gastrointestinal disease the importance of decreased synthesis has been stressed. This may be due either to impaired digestion, absorption or metabolism of protein precursors, but little attention has been given to the possible role of increased catabolism. Recently, evidence has started to accumulate which shows that in fact synthesis is often normal or even slightly increased and destruction rapid (Citrin *et al.* 1957, Schwartz & Jarnum 1959, Gordon 1959, Steinfeld *et al.* 1960). First I shall discuss how standard methods of investigating protein metabolism in man may help to assess the relative importance of these two factors. The use of the nitrogen balance technique in clinical investigation is now well established and for the sake of this argument I shall merely consider the excretion of fæcal nitrogen as compared with the oral intake. For example, in a patient with severe small bowel disease and impaired absorption of protein one might expect an excretion of 5 g of fæcal nitrogen a day (normal <2 g); this is equivalent to 31·25 g of protein. The daily needs of the body may be generously put at 45 g and so a total of 76·25 g of protein would be needed to maintain a patient in balance. In fact, this is a normal dietary intake. Moreover many patients with hypoalbuminæmia in gastrointestinal disease do not even have a raised fæcal nitrogen. Thus theoretically, impaired digestion and absorption of protein products is an unlikely cause of hypoalbuminæmia unless dietary intake is very low.

By using ^{131}I-labelled albumin, the albumin synthesis has been shown to be normal or slightly increased, in a variety of gastrointestinal disorders, while destruction is often accelerated, but such data do not give a clue to the site of the increased degradation. One might suspect this site to be the diseased gastrointestinal tract and this has been demonstrated by direct intubation of the stomach in patients with giant rugal hypertrophy (Citrin *et al.* 1957) and intubation of the intestine in small bowel disease (Holman *et al.* 1959). In both these studies excessive albumin was shown to be leaking into the gut lumen. Presumably the leaking protein is digested and the peptides and amino acids so formed are reabsorbed so that the fæcal nitrogen is not raised. Similarly if albumin ^{131}I is used as a tracer for the serum protein, it leaks into the gut lumen, is broken down and the water-soluble radioactive products are reabsorbed so that negligible radioactivity appears in the fæces. The reason that hypoproteinæmia occurs at all is that the liver has a limited reserve in its ability to synthesize albumin.

The measurement of albumin turnover with simultaneous intubation of the bowel would be far too tedious for a routine clinical test. Gordon (1959) has partially overcome this problem by introduction of the use of polyvinylpyrrolidone (PVP) labelled with ^{131}I. When injected intravenously this substance, which has a similar molecular weight to that of albumin, can leak through similar sites to those which are permeable to albumin; in this case into the gastrointestinal tract. However, PVP is relatively inert to the digestive enzymes and so can escape into the fæces and there the radioactivity may be measured. The test is performed by injecting this substance intravenously after blocking the patient's thyroid with iodine, and then collecting the stools and urine separately for 4 consecutive twenty-four-hour periods; great care is taken to prevent contamination of the fæces with urine. Twenty-one patients with a variety of gastrointestinal disorders were also studied; these included idiopathic steato-

Metabolic Disorders in Gastrointestinal Disease

rrhœa (4), cryptogenic steatorrhœa (2), jejunal diverticulosis (2), ulcerative jejunitis (1), idiopathic hypoproteinæmia (2), giant rugal hypertrophy of the stomach (1), ulcerative colitis (2), polyarteritis nodosa (1), secondary amyloidosis (1), pancreatic steatorrhœa (1), total gastrectomy (1), Crohn's disease (1), scleroderma (1), biliary enteric fistulæ (1). Three patients with cirrhosis and 2 with a nephrotic syndrome (all of whom had a low serum albumin) as well as 18 normal persons who had neither disorders of the gastrointestinal tract nor abnormalities of their plasma proteins were also studied. In Fig 1 is shown the serum albumin of these patients with gastrointestinal disease plotted against the fæcal excretion of ^{131}I PVP, the mean excretion being 0·52% with a range of <0·05 to 1·6%. With decreasing serum albumin levels there is a tendency to an increased fæcal PVP. Taking the lower limit of serum albumin as 3·5 g/100 ml only one patient with a low albumin level had a normal PVP excretion. This man had a total gastrectomy and a very poor dietary intake and severe steatorrhœa; it is possible that this hypoalbuminæmia is purely nutritional in origin. On the other hand 4 patients with a normal serum albumin had a slightly raised PVP excretion. Apart from these patients the results were remarkably consistent. That such an overlap was observed is to be expected on at least three counts: (*a*) PVP, although similar in size to albumin, is not the same as the albumin molecule – the shape and the charge on the molecule are different. (*b*) Serum albumin does not necessarily reflect total body stores of albumin. (*c*) Gastrointestinal protein loss is probably intermittent so that such a loss may not be occurring during the test. Hypoalbuminæmia itself does not cause an increased loss of PVP, for 2 patients with a nephrotic syndrome and 3 with cirrhosis, all with hypoalbuminæmia, were found to have a normal excretion; similarly 4 patients with diarrhœa not associated with hypoalbuminæmia had a normal PVP excretion.

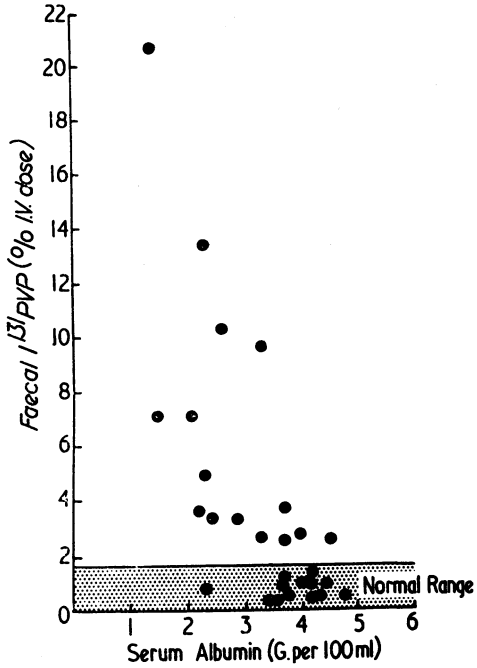

Fig 1 *Serum albumin plotted against ^{131}I PVP excretion in patients with gastrointestinal disease and idiopathic hypoproteinæmia. Hatched area represents normal range of PVP excretion*

We have studied 6 patients on more than one occasion (Table 1). In all these patients during the active phase of the disease when they had hypoalbuminæmia the fæcal excretion of PVP was

Table 1
Serial studies with ^{131}I PVP

Patient	*Age*	*Sex*	*Diagnosis*	*Serum albumin g/100 ml*	*Fæcal ^{131}I PVP % I.V. dose*	*Remarks*
1	43	M	Giant rugal hypertrophy of stomach	3·7 4·3	2·6 0·4	 After subtotal gastrectomy
2	53	F	Idiopathic steatorrhœa	3·3 4·8	9·7 0·5	 Gluten-free diet
3	56	F	Idiopathic hypoproteinæmia	2·6 3·3	10·3 2·7	
4	38	F	Regional ileitis	2·2 3·4	3·6 0·1	Active Quiescent
5	16	M	Cirrhosis and ulcerative colitis	3·5 2·4 4·2	0·05 3·4 0·4	Pre-colitis Active colitis Quiescent colitis
6	26	M	Ulcerative colitis	2·8 4·2	3·4 0·5	Active Quiescent

raised, while during a remission or following treatment there was a rise in serum albumin and an associated fall in the fæcal excretion.

These results support the view that protein leakage into the intestine, rather than impaired digestion and absorption, is often a dominant cause of hypoproteinæmia in a variety of gastrointestinal diseases. Further, in the occasional patient with hypoproteinæmia of unknown cause a careful search of the gastrointestinal tract must be made; this should include a ^{131}I PVP test, a small bowel biopsy and sometimes even laparotomy.

Acknowledgments: We should like to thank the physicians of The Royal Free Hospital for allowing us to study their patients and all others who have referred patients to us.

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Hæmatological Abnormalities

by Clifford F Hawkins MD FRCP (*Birmingham*)

Hæmatological changes may be due to deficiency of iron, folic acid or vitamin B_{12} (cyanocobalamin); and, also, to the inflammation which involves the bowel wall in colitis or Crohn's disease. Only the megaloblastic anæmias will be considered here, for this is where a break-through in our knowledge has taken place. In the past, most cases have been labelled 'pernicious anæmia'. Accurate techniques for studying fæcal fat excretion first encouraged separation of anæmia due to disease of the small intestine from true addisonian pernicious anæmia. The discovery of folic acid and vitamin B_{12} then stimulated methods of investigation which now allow cases of deficiency of B_{12}, of folic acid, or of both, to be distinguished.

Addisonian pernicious anæmia, a genetically determined disease resulting in atrophic changes in the gastric mucosa, can be regarded as the prototype of B_{12} deficiency. The patients are usually over 40 years old, but rare examples have been described in children. One boy suffered from lack of Castle's intrinsic factor but had a normal flow of hydrochloric acid and a normal gastric mucosa (Mollin *et al.* 1955); his father had pernicious anæmia with complete gastric atrophy. It is possible that pernicious anæmia is one of the diseases due to a specific enzyme deficiency. A congenital lack of intrinsic factor may result in prolonged subclinical B_{12} deficiency which causes the gastric atrophy. Iatrogenic pernicious anæmia follows total gastrectomy.

Another cause of B_{12} deficiency is the fish tapeworm, *Diphyllobothrium latum.* It absorbs radioactive B_{12} in preference to its host and so may compete for this vitamin. However, only a small number of infested persons develop the anæmia; it is thought that the anæmia is more likely if the worms are in the jejunum, but there is some evidence that the worm itself may cause a gastric atrophy (Siurala 1956).

More important in this country is the B_{12} deficiency due to anatomical lesions of the small intestine such as strictures, fistulæ, blind loops and diverticula of the small bowel. The common factor is stagnation or contamination of the small gut. Modern investigations and the use of antibiotics have vindicated the views of the older writers in indicting the bacteria as the cause. There is evidence that the coliform bacteria compete for B_{12} and so deprive the host of it (Doig & Girdwood 1960) but it is also possible that metabolites of the bacteria – the toxins of the older writers – could interfere with the absorption or utilization of B_{12} (Drexler 1958). This type of megaloblastic anæmia is rare and only occurs in a small percentage of patients with these bowel lesions. Corrective surgery may cure the anæmia (Watkinson *et al.* 1959). To-day it is seen particularly in Crohn's disease with fistula or blind loop formation. When one reads the autopsy reports of the tuberculous strictures of the bowel described earlier this century (Meulengracht 1932) it seems that many to-day would be regarded as Crohn's disease. Crohn's disease, when it causes anæmia, usually does so from iron deficiency, but B_{12} deficiency may occur from extensive involvement of the ileum (Meynell *et al.* 1957). Folic-acid deficiency is seen in the malabsorption syndromes, such as idiopathic steatorrhœa and tropical sprue, where the disease affects the jejunum. B_{12} deficiency may be present in up to half the cases; this may be due to extension of the disease to the jejunum, or possibly to bacterial contamination of the small bowel. The evidence suggests that folic acid is absorbed mainly in the jejunum and B_{12} in the ileum (McIntyre *et al.* 1956, Meynell *et al.* 1957, Booth & Mollin 1959).

Addisonian pernicious anæmia and the malabsorption syndrome have occurred in about equal numbers in a series of 61 unselected patients with megaloblastic anæmia admitted to The General Hospital, Birmingham (Bradley & Cooke

1960). Thirty-one cases were due to pernicious anæmia, 27 to idiopathic steatorrhœa, 2 resulted from operations on the alimentary tract, and 1 was due to drugs. The more complete the investigations, the less frequent is the diagnosis of pernicious anæmia. Cases of idiopathic steatorrhœa can often be collected by going through the files of patients labelled pernicious anæmia and investigating them more fully. The clinical picture of megaloblastic anæmia from either B_{12} or folic acid deficiency may be indistinguishable, but the presence of neurological lesions supports B_{12} deficiency. (The malabsorption syndrome occurs at any age and there may be multiple vitamin deficiencies; malnutrition is more likely, and many patients suffer from diarrhœa. Accustomed to mild diarrhœa over a long period, patients may reply 'yes' to the question 'Are your bowels normal?'; further questioning reveals a bowel movement three or more times daily. The appearance of the stool on the fingerstall or in the sluice often allows an immediate diagnosis of steatorrhœa. Further investigations, such as analysis of fæcal fat excretion (Kamer *et al.* 1949), radiological studies, and jejunal biopsy using the Crosby capsule (Crosby & Kugler 1957), are usually necessary to establish an exact diagnosis. The serum vitamin B_{12} level is helpful (Mollin & Ross 1954), as it is the first sign of B_{12} deficiency, occurring before macrocytosis or other changes in the blood. Tests of folic acid absorption and excretion are avoided initially as they involve treatment with folic acid, which confuses the response to the gluten-free diet.

For the patient with idiopathic steatorrhœa, the gluten-free diet offers the best hope of restoring the health and blood to normal (French *et al.* 1957). The anæmia of idiopathic steatorrhœa is usually macrocytic and slight, but the most striking example of the effect of this treatment is seen in the severe megaloblastic anæmia which is identical to pernicious anæmia and may be fatal. When gluten is withdrawn, a reticulocytosis occurs but is later and smaller than after folic acid. A rapid rise in the hæmoglobin and red cells takes place until the blood values, including the mean corpuscular volume, are entirely normal. Conversion of the marrow from megaloblastic to normoblastic occurs within a month without hæmatinics or other therapy. Iron deficiency may be unmasked and delay cure of the anæmia; then oral iron can be given as it appears to be absorbed normally in those responding to the diet. Dr J M French and I find that 34 out of 48 patients (71%) with idiopathic steatorrhœa have responded successfully. Fat excretion and other tests of intestinal function are normal in most, but sometimes power to absorb fat and folic acid is not restored in spite of apparent clinical and hæmatological cure. The jejunal mucosa, like the gastric mucosa in pernicious anæmia, fails to return to normal. The blood picture remains entirely normal while the patient is on the diet and this has been so in all successful cases, many of whom have been followed up regularly for six years or more. Response to the gluten-free diet is probably connected with the folic acid deficiency as vitamin B_{12} levels may be normal or low; if low, it may take up to a year before normal levels are reached. It is curious that a rapid response in the blood may precede any improvement in the fat excretion or other tests. It is not possible to predict which patients will respond and the trial may have to go on for three or six months. A course of antibiotics has, in an occasional patient, seemed suddenly to aid response to the diet.

When the megaloblastic anæmia is so severe as to threaten life it may be necessary to give a hæmatinic immediately, before a definite diagnosis has been made. Most megaloblastic anæmias respond temporarily to folic acid but it is usually preferable to know exactly which deficiency exists and then it is best to give a single injection of vitamin B_{12}. The fall in serum iron after forty-eight hours will give a quick indication of the response (Hawkins 1955) and the reticulocyte count can then be followed if necessary. If there is no fall in serum iron folic acid can be given. Folic acid is dangerous in pernicious anæmia as it may precipitate a severe neuropathy due to the dwindling reserves of vitamin B_{12} being used for the formation of blood, but this risk does not seem to be present in idiopathic steatorrhœa even when a B_{12} deficiency exists as well.

There are, then, two main groups, pernicious anæmia and idiopathic steatorrhœa. But is each a single entity with a single cause, or will the future show a breakdown of each group with different ætiologies? I suspect the latter. It is not known why some cases of idiopathic steatorrhœa fail to respond to withdrawal of gluten although the clinical picture, jejunal mucosa and autopsy appearances are identical with others which do. We are, at present, studying a man aged 31 with gout who also had a megaloblastic anæmia due to folic acid deficiency. A jejunal biopsy showed blunting of the villi with changes in the epithelial cells; the nuclei of these were swollen in some, and in others there were particles resembling nuclear remnants. The appearances were similar to those produced in the intestinal mucosa of rats by Leblond & Stevens (1948). These workers used colchicine to arrest mitosis in order to estimate 'turnover time' of the intestinal epithelium. My patient had been taking colchicine daily for at

least ten years and it is possible that the changes were also due to this drug, and that the megaloblastic anæmia had followed the damage to the jejunal mucosa. Further work has been planned in the hope of proving this hypothesis.

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Effects of Malabsorption Syndrome on Calcium Metabolism

by B E C Nordin MD MRCP PhD (*Glasgow*)

The malabsorption syndrome causes specific secondary effects on the endocrine glands, on the hæmopoietic system and on calcium metabolism. The secondary effects on calcium metabolism take the form of osteoporosis (i.e. reduced bone mass), osteomalacia (i.e. inadequate calcification of bone) or tetany or any combination of these three. Some idea of the relative incidence of these complications may be obtained from Table 1 which shows that 11 out of 21 cases of steatorrhœa, mostly of the 'idiopathic' variety, were found to be suffering from complications involving calcium metabolism, mainly spinal osteoporosis. Conversely the screening of 56 cases of osteoporosis and 14 of osteomalacia disclosed 8 cases of steatorrhœa among the former and 11 cases of steatorrhœa among the latter (Table 2). It would appear from these data that osteoporosis is a relatively common complication of steatorrhœa, and that steatorrhœa is in turn the commonest cause of osteomalacia in this country at the present time.

Table 1
Disorders of calcium metabolism in 21 cases of steatorrhœa

Osteoporosis	6
Osteomalacia	3
Osteoporosis & osteomalacia	1
Osteoporosis & tetany	1
No abnormality	10

Table 2
Steatorrhœa in 70 cases of metabolic bone disease

	Osteoporosis	*Osteomalacia*
Steatorrhœa	8	11
No steatorrhœa	48	3
Total	56	14

Investigation and Diagnosis

The investigation of calcium metabolism in a case of steatorrhœa requires in the first instance X-rays of the hands, femur and lumbar spine and certain biochemical tests on the blood and urine. These procedures can be performed on outpatients and will usually provide most of the necessary information. Further investigation in hospital, which may be necessary in difficult cases or because of the patient's clinical condition, consists in carrying out the four-hour retention test, iliac crest biopsy and possibly a calcium balance. These procedures will be considered in turn.

Bone X-rays: The bone X-ray procedure described by Barnett & Nordin (1960) involves standard measurements on X-rays of the hands and femur and on a lateral view of the lumbar spine. Reduction in the thickness of the cortex of the femur or metacarpals is indicative of peripheral osteoporosis. Biconcavity of the lumbar vertebral bodies (which is best determined on a lateral tomogram of the lumbar spine) is usually associated with accentuated vertical trabeculation of the vertebræ and indicates spinal osteoporosis. These two forms of osteoporosis may co-exist. We do not at present understand the clinical significance or pathogenesis of peripheral osteoporosis and all the cases of osteoporosis which we have so far discovered in association with steatorrhœa have been spinal or mixed.

The radiological features of osteomalacia are rather different. The pathognomonic feature is the pseudo-fracture or Looser zone which may be seen in the cortex of a long bone or in the pelvis. Alternatively there may be cancellization of the cortex, i.e. the femoral cortex is as thick as usual but less homogeneous, as though there was patchy failure of mineralization within the compact bone. The spine X-rays may be relatively normal or there may be a curious haziness of the vertebral bodies which looks like a technical artifact but which is probably a genuine feature of the condition. The radiological features of osteoporosis may be present in addition, signifying that the two conditions are present at the same time.

Biochemistry: The first step in the biochemical investigation of these cases is to obtain a random urine sample together with a blood sample preferably obtained near the midpoint of this urine collection. Calcium, inorganic phosphate and creatinine are measured in the plasma and urine and the alkaline phosphatase in the plasma. This procedure permits the measurement not only of

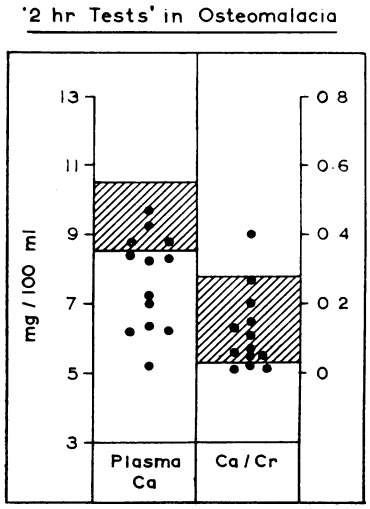

Fig 1 *Plasma calcium and urinary calcium/creatinine ratio in 13 cases of osteomalacia. The shaded area shows the normal range*

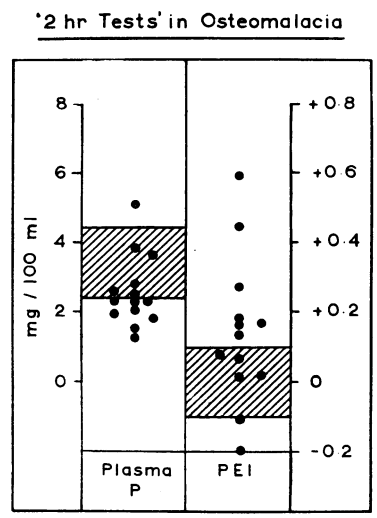

Fig 2 *Plasma phosphorus and phosphate excretion index (P.E.I.) in 13 cases of osteomalacia*

the plasma levels of calcium, phosphorus and alkaline phosphatase but also of the urinary calcium/creatinine ratio and the phosphate/creatinine clearance ratio. In simple osteoporosis all these values are normal with the possible exception of the urinary calcium/creatinine ratio which may be low, normal or high.

Table 3
Biochemical data in osteomalacia

	Ca	*P*	$[Ca]^3 \times [P]^2$		*Phosphate excretion index*	*Alkaline phosphatase*
Normal range in adults	*(mg%)* (9·0–10·5)	*(mg%)* (2·5–4·5)	(4,600–20,000)	*Ca/Cr* (0·03–0·28)	(–0·09–+0·09)	*(K-A units)* (10–14)
Steatorrhœa						
TH	6·2	2·8	1,880	0·07	+0·09	65
IF	7·2	2·6	2,600	0·01	+0·17	11
ED	8·8	2·5	4,250	0·13	+0·18	26
JB	6·2	2·0	960	0·14	+0·02	11
IW●	6·3	3·9	3,800	0·07	−0·10	44
JN●	8·4	3·8	10,200	0·10	+0·02	20
JM	8·4	1·6	1,600	0·05	+0·14	20
BS	5·2	1·4	260	0·02	+0·30	14
MH	7·0	1·9	1,240	0·20	+0·60	50
MM	8·4	2·4	3,450	0·27	+0·08	24
No steatorrhœa						
AB●	9·7	6·2	26,500	0·01	−0·20	49
MW	9·2	2·1	4,400	0·06	+0·45	13
RN	8·8	2·4	3,250	0·27	+0·08	24

●adolescent

The biochemical results obtained in 13 cases of osteomalacia (10 associated with steatorrhœa) are shown in Figs 1 & 2 and Table 3. In the typical case of osteomalacia there is a reduction in the plasma levels of calcium and particularly of phosphate, and an abnormally low product $[Ca]^3 \times [P]^2$ (Nordin 1960). The urinary calcium/creatinine ratio may be low but is more frequently normal; the only case in this series in which it was actually raised was one of biliary cirrhosis with steatorrhœa in which the plasma citrate level was raised; this may explain the hypercalciuria. The phosphate excretion index (P.E.I.) (Nordin & Fraser 1960) is raised and can be restored to normal by the intravenous infusion of calcium (Nordin & Fraser 1954). The plasma alkaline phosphatase is raised. Table 3 shows that certain cases did not fulfil all these criteria, particularly cases I W, J N and A B. These were all adolescents with rickets, two of them associated with steatorrhœa and one with dietary vitamin-D deficiency.

The four-hour retention test: If the preliminary investigation does not establish the diagnosis beyond all reasonable doubt, or if the patient is in hospital for other reasons, the four-hour calcium retention test (Finlay *et al.* 1956) provides very reliable information. It is simple to perform and invariably gives a high calcium retention figure in osteomalacia. It may be possible to diagnose osteomalacia with this technique at an earlier stage than is possible with the other procedures.

Iliac crest biopsy: It is rare for iliac crest biopsy to be an essential investigation, but it is frequently highly desirable. Comparison of the amount of bone in a standard biopsy sample with a 9-point scale enables the diagnosis of osteoporosis to be made with some degree of confidence (Beck & Nordin 1960). In cases of steatorrhœa two samples should be obtained and one of them cut without decalcification for assessment of the osteoid borders the enlargement of which is the diagnostic characteristic of osteomalacic bone.

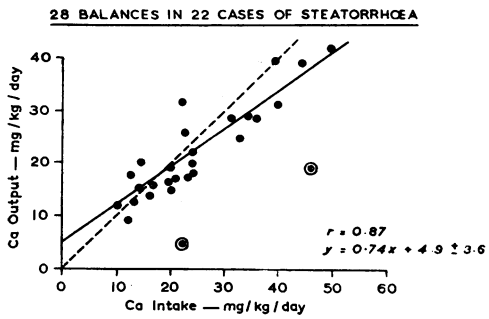

Fig 3 *Relation between calcium intake and ouput in 28 balances in 22 cases of steatorrhœa. (Note: circled values not included in statistical analysis)*

Calcium balance: The purpose of a calcium balance is to provide information about the patient's ability to absorb calcium. It is a lengthy and costly procedure but until some satisfactory isotopic technique has been perfected it is the only available method. Fig 3 shows the result of 28 calcium balances in 22 cases of steatorrhœa. At all levels of intake cases of steatorrhœa tend to be in slightly more negative or less positive calcium balance than normal subjects on the same intake. This is entirely due to the difference in fæcal calcium, which tends to be slightly higher in cases of steatorrhœa than in normal subjects. However, the slope of the regression of output on intake is parallel with that of normal subjects, indicating that some degree of positive balance can be achieved in steatorrhœa if the calcium intake is high enough. No consistent difference has been observed between the calcium absorption of cases of steatorrhœa with osteoporosis and those with osteomalacia, although it is true that the osteomalacia group do include the cases with the highest fæcal calcium output. The mean calcium requirement of the cases shown in Fig. 3 (i.e. the value of intake at which intake and output are equal) is 18·9 mg/kg as compared with the normal mean requirement of 9·3 mg/kg.

Pathogenesis

(*a*) *The cause of the osteoporosis:* The association of osteoporosis and steatorrhœa is entirely compatible with the hypothesis that spinal osteoporosis is due to prolonged negative calcium balance (Nordin 1960). If calcium balance is a function of the relationship between intake, absorption and excretion then malabsorption of calcium would tend to produce negative calcium balance. This negative balance may result from a very high fæcal calcium, explained by the trapping of digestive juice calcium in the gut, or it may be the result of persistent normocalciuria in the face of an inadequate calcium absorption. The great majority of our cases of osteoporosis with steatorrhœa have a normal urinary calcium excretion and not the low urine calcium which would be required if they were to remain in calcium balance in the face of inadequate calcium absorption.

The cause of the malabsorption of calcium in steatorrhœa is uncertain but it has at various times been attributed to vitamin-D deficiency and to the formation of insoluble calcium soaps. Nassim *et al.* (1959) however, have shown convincingly, that the malabsorption of calcium in steatorrhœa with osteomalacia cannot be corrected even by parenteral vitamin-D but responds to a gluten-free diet and we have found the same to be true in steatorrhœa with osteoporosis. The malabsorption of calcium does not therefore appear to be due to vitamin-D deficiency.

If the malabsorption of calcium were due to calcium soap formation one might expect to find some quantitative relationship between the amount of fat and the proportion of ingested calcium excreted in the fæces. Fig 4 shows that there was little or no relationship between these two measurements in 146 balance periods on 17 cases of steatorrhœa with osteomalacia and/or osteoporosis. This does not appear to support the idea that calcium malabsorption is due to calcium soap formation.

It is more probable that the malabsorption of calcium in steatorrhœa is a direct reflection of the alimentary disorder which is also responsible for the malabsorption of fat. When this basic disorder is corrected (as with a gluten-free diet in

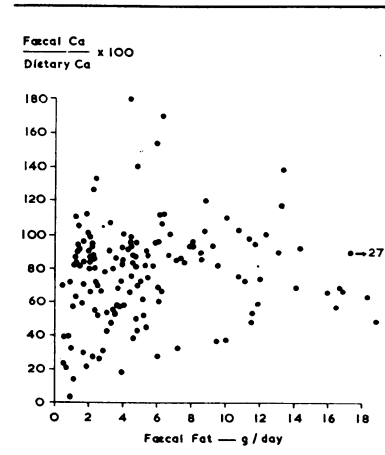

Fig 4 *Relation between fæcal fat and fæcal calcium (expressed as a percentage of dietary calcium) in 17 cases of steatorrhœa*

idiopathic steatorrhœa) calcium absorption improves together with the absorption of other minerals and vitamins.

(*b*) *The cause of the osteomalaica:* The osteomalacia of steatorrhœa is probably due to vitamin-D deficiency rather than to malabsorption of calcium. It is well established that vitamin D acts directly on the skeleton to sustain the plasma calcium concentration and that this effect on plasma calcium is quite independent of the effect of vitamin D upon calcium absorption (Carlsson & Lindquist 1955, Nordin 1960). Deficiency of vitamin D therefore leads to a fall in plasma calcium which usually stimulates the parathyroid glands and so causes hypophosphatæmia and a raised phosphate clearance, which is reflected in a high P.E.I. Occasionally, however, the parathyroid glands fail to respond – reflecting perhaps the general impairment of endocrine function in steatorrhœa (Mickerson 1960) – and this leads to tetany. Tetany and osteomalacia may co-exist if the rise in plasma phosphate in these cases is insufficient to offset the effect of the reduced plasma calcium on the $[Ca]^3 \times [P]^2$ product (Nordin 1960).

In the light of these general observations the various abnormalities and disturbances of calcium metabolism which occur in steatorrhœa can be explained in the following way. Simple malabsorption of calcium produces negative calcium balance and osteoporosis. Vitamin-D deficiency leads to abnormalities in the plasma biochemistry and consequently to osteomalacia and/or tetany. The combination of malabsorption of calcium with abnormal biochemistry produces the combined syndrome of osteoporosis and osteomalacia which is not uncommonly seen in malabsorption states.

Therapy

This explanation is supported by the fact that vitamin-D therapy given in the form of ultraviolet light corrects the biochemical disorder of osteomalacia without having any demonstrable effect upon calcium absorption (Nordin 1960). One month of ultraviolet light therapy restores the $[Ca]^3 \times [P]^2$ product to normal. We have seen complete radiological healing of rickets within two or three months and very considerable improvement in the state of the femoral cortex after a rather longer period. The beneficial effect of a course of ultra-violet light appears to last about one year in uncontrolled steatorrhœa, but if the steatorrhœa can be controlled with a gluten-free diet or by other means it is probable that small oral doses of vitamin D can then be given as maintenance therapy.

We are not sure how the osteoporosis should be treated. The balance data suggest that some improvement in calcium balance can be obtained by feeding calcium supplements, but this improvement is not nearly so impressive as the improvement in calcium balance obtained with calcium supplements in osteoporosis without steatorrhœa. In the present state of knowledge it is probably advisable to give calcium supplements in a dose of about 1 g of calcium daily above the patients' ordinary diet. This can conveniently be given as calcium glycerophosphate 6 g daily.

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