Clinico-pathological Conference

STEATORRHOEA

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DR. S. D. BANDARKER: Mr. Chairman, ladies and gentlemen, the patient I am going to present this morning is a 65-year-old lady who was seen in November, 1960, with diarrhoea of three years duration and backache and weight loss of one and a half years' duration. The diarrhoea was incapacitating; she had 6 to 8 pale, bulky and four-smelling stools per day. For about four weeks before admission she had a cough with purulent spit.

There was nothing relevant in her past history; in particular she had never suffered from diarrhoea in earlier years, nor was there any history of gastrointestinal surgery. She had no children, and her periods stopped at the age of 40.

On examination she was very ill. The skin and mucosæ were pale and she had clubbing of the fingers. There were persistent râles and rhonchi at both lung bases and over the right middle lobe. Examination of the alimentary, cardio-vascular and central nervous systems did not reveal any abnormality.

She was transferred to the metabolic ward and investigated further under conditions of continuous balance. The faecal fat during the first week of her stay in the ward was 11.8 g. per day—a grossly abnormal figure. Radio-active fat absorption tests and jejunal biopsy were carried out—Dr. Cartwright will speak about these later on. Blood examination revealed the following: Hb.—7.8 g./100 ml.; MCHC—27.5%; bone marrow—normoblastic; serum B_{12} —148 μ g per ml.; ESR—87 mm. at one hour. X-ray of the chest showed middle lobe consolidation. Her sputum contained pneumococci and *B. proteus* which responded very well to appropriate antibiotic therapy.

X-ray of her bones showed marked osteoporosis. Fig. 1 is a lateral tomogram of the lumbar spine and shows bi-concavity of the vertebral bodies and marked accentuation of the vertical trabeculae.

FIG. 1.—Lateral tomogram of the lumbar spine showing bi-concavity of the vertebral bodies and marked accentuation of the vertical trabeculae.

Fig. 2 shows marked thinning of the cortical bone of the femoral shaft which is also cancellized. The osteoporosis is, therefore, generalized. Her serum calcium was 5.2 mg./100 ml. and the serum phosphate 1.4 mg./100 ml.—both grossly abnormal figures. These figures indicate the presence of osteomalacia despite an alkaline phosphatase of 10 King-Armstrong units. The phosphate excre-

FIG. 2.—Femoral shaft showing marked thinning and cancellization of the cortical bone.

tion index was $+0.28$ —a high figure indicative of excessive phosphate leak through the kidneys due to secondary hyperparathyroidism. Her four-hour retention of calcium was 75%; in our experience this is also a high figure and further indicates the presence of osteomalacia. An iliac crest biopsy was carried out and showed severe osteoporosis and minimal osteomalacia (i.e. she had very thin bone trabeculae but they were well calcified except for occasional slightly excessive osteoid margins).

Progress

During her first week in hospital the patient's condition continued to deteriorate, so that at the end of the week we had to start treatment with a gluten-free diet in order to control her diarrhoea. Ultra-violet light therapy was started at the same time in order to treat her osteomalacia. On this therapy her serum calcium rose from 5.2 to 8.5 mg./100 ml. and her serum phosphorus rose from 1.4 to 4.1 mg./100 ml. The phosphate excretion index fell to within normal limits (Fig. 3). These data indicate that as her plasma calcium rose the excessive parathyroid activity diminished so that the excessive phosphate leak into the urine was controlled, allowing the plasma phosphorus to rise. It might be argued that this was the result of

a positive calcium and phosphorus balance rather than the ultra-violet light. However, Fig. 4 shows that the product of calcium and phosphorus, which was at the low level of 8, rose above the critical level of 20 before the calcium and phosphorus balance had become positive. The rise in the plasma levels of calcium and phosphorus must therefore be independent of the improved absorptive function of the gastrointestinal tract and rather the result of the action of the ultra-violet light therapy on the skeleton.

In view of her anaemia she was treated with parenteral iron and the haemoglobin rose from 7.8 to 12.5 g./100 ml. During her stay in the ward she showed a continuous and progressive improvement and is now feeling very much stronger and better and has one normal formed movement per day.

At this point the patient was presented.

Fat Metabolism

PROFESSOR ILLINGWORTH: Dr. Cartwright, now that Dr. Bandarkar has presented this interesting patient can you tell us about the investigations of the faecal fat by isotope methods?

DR. E. J. CARTWRIGHT: I was very glad to have the opportunity of investigating fat absorption in this patient by a double tracer technique. In this method an iodinated fat and a brominated fatty acid are given at the same time by mouth. The relative proportion of each in the blood at the end of four hours is found. Fig. 5 shows the result in controls, in the steatorrhoea of pancreatic deficiency, and in idiopathic steatorrhoea. In the control groups, there is good absorption of both, and the ratio of fatty acid to fat is 1.5 (range 1.0 to 2.0). In idiopathic steatorrhoea the absorption of both is poor due to abnormality of the small intestine, but the ratio remains within the normal range, though the blood levels are low. In pancreatic dysfunction the fat cannot be split due to deficiency of enzymes so that we get very poor fat absorption, but the gut wall is normal so that the fatty acid is absorbed normally, and the mean ratio is therefore high, say 4.7.

This patient was already on treatment at the time she was tested and the ratio of the fatty acid to fat was normal at 1.22. The blood level of iodinated fat was found to be 2.8% dose per litre of plasma, which was lower than the control group, who showed a mean blood level of 3.3%, but higher than the mean of 1.4% for the group with idiopathic steatorrhoea. I think this must be attributed to the fact that she was on a gluten-free diet and already improving at the time. The thyroid is blocked with perchlorate before giving this dose, so thyroid function is irrelevant. Her faecal fat at the same time was 2.98 g. per day and

FIG. 4.—Showing phosphorus and calcium balances and the calcium and phosphorus products. The intake is measured upwards from the base line and the output downwards from the top of the intake line. Faecal excretion is solid black and urinary excretion dotted.

FIG. 3.—Chart showing the rise in serum Ca and serum P following ultra-violet light therapy, associated with a fall in the phosphate excretion index.

^{131}I TRIOLEIN & ^{82}Br OLEIC ACID ABSORPTION TEST

FIG. 5.—Showing the absorption of ^{131}I Triolein and ^{82}Br oleic acid in controls, obstructive jaundice, pancreatic dysfunction and idiopathic steatorrhoea. The ratio of the two at the four-hour period is taken for comparison.

the faecal excretion of iodinated triolein was less than 1% of the dose. Both these figures are within the normal range and suggest that fat absorption had returned to normal.

In addition, much more recently, I did a jejunal biopsy with the Crosby capsule. This showed almost complete absence of villi and heavy cellular infiltration in the sub-mucosa (Fig. 6), despite the fact that it was done at a time when the patient had been on a gluten-free diet for a couple of months, and despite a normal fat absorption, haematological response and clinical response. We believe that these changes have been present since early childhood, as has been shown in children with coeliac disease. Yet until she is 65 she seems to have remained pretty well except for a little diarrhoea.

DR. B. LENNOX: There were a lot of glands in the sub-mucosa in one part of your biopsy. Surely this means it must be from the duodenum. Of course, it is still a very abnormal mucosa.

DR. CARTWRIGHT: These changes are present from the duodenum downwards. So a duodenal

biopsy is representative of changes in the small bowel.

DR. B. E. C. NORDIN: I think you would agree, wouldn't you, Dr. Cartwright, that with the combination of the response to the gluten-free diet, the biopsy, and your radio-fat test, there is no doubt that this is a case of idiopathic steatorrhoea?

DR. CARTWRIGHT: No doubt at all. The biopsy is diagnostic.

DR. NORDIN: And even without that would a response to a gluten-free diet as dramatic as this also be sufficient?

DR. CARTWRIGHT: No. Many patients remit spontaneously in hospital or with rest in bed.

PROFESSOR ILLINGWORTH: Have you any information as to how the gluten-free diet acts?

DR. CARTWRIGHT: Basically, we do not know. Some patients may have an allergy to gluten but even those who do not may respond temporarily. Another point is that it is a constipating diet by itself.

DR. NORDIN. I wouldn't have said that the latter is the explanation.

FIG. 6.—Jejunal biopsy showing complete absence of villi and having cellular infiltration in the sub-mucosa.

DR. LENNOX: Would you expect to see any difference between this biopsy and the biopsy of someone who was actually taking gluten? Is there an active inflammation which interferes with absorption apart from the deficiency of the epithelium?

DR. CARTWRIGHT: Shiner (1959) has done biopsies before and after four years of a gluten-free diet, and the changes are identical. The atrophy, the complete absence of villi and the cellular infiltration remain constant.

PROFESSOR ILLINGWORTH: You mean that no change is produced by the gluten-free diet?

DR. CARTWRIGHT: None whatever, in spite of the clinical improvement and the well-being of the patient.

DR. NORDIN: But isn't it a fact, Dr. Cartwright, that there is a reduction in mucus secretion? The barium clumping which is seen on intestinal follow-through, and is believed to be due to excessive mucus, disappears.

DR. CARTWRIGHT: Perhaps. Certainly the intestinal dilatation is less and the discomfort less.

Calcium Metabolism

PROFESSOR ILLINGWORTH: Would Dr. Nordin like to say something about the complications of malabsorption?

DR. NORDIN: I think, sir, that we are all agreed that this is a case of idiopathic steatorrhœa. The complications of this condition, as of any malabsorption syndrome, appear to fall into three main groups. There is malabsorption of hæmatinic substances, about which Dr. Adams and Dr. Goldberg will be speaking. There is malabsorption

of calcium and/or vitamin D. Thirdly, there are secondary effects on the endocrine system, about which I will say a word later.

As far as calcium metabolism is concerned, these people can develop osteoporosis, osteomalacia or tetany; and you can get any permutation or combination of these three. The simplest way to look at this, though not necessarily the correct way, is to say that these patients may suffer from malabsorption of calcium or vitamin D or both and that there may or may not be a consequent parathyroid response. If they suffer from simple malabsorption of calcium (and there is good evidence that patients with steatorrhœa as a group have a higher fæcal calcium than normal people at all intake levels), then they will go into negative calcium balance unless their intake is very high, and it is at least probable, if not certain, that a negative calcium balance in the long run produces osteoporosis. That is certainly part of this patient's bone disease, though it is not the whole story.

If, in addition, such patients develop a vitamin D deficiency, then the plasma calcium will fall because of the loss of the action of the vitamin on the skeleton. Two things can then happen. First, if the parathyroids respond to this stimulus the plasma calcium is maintained at a tolerable level, usually about 7 or 8 mg./100 ml., but the phosphorus level is depressed by the phosphaturia of secondary hyperparathyroidism, and you get a high phosphorus excretion index. Because the level of calcium is slightly low and the level of phosphorus very low, there is a low calcium-phosphorus product, and from then on such new bone as is formed fails to calcify and there is a

progressive fall in the mineralization of the skeleton. Second, if the parathyroid glands do not respond to this stimulus, the calcium drops catastrophically and you get tetany.

This patient shows an intermediate picture. In the first place, the bone biopsy shows very definite osteoporosis and corresponds with No. 4 in our biopsy scale (Beck and Nordin, 1960). This is compatible with the X-ray findings. On the other hand, the evidence for osteomalacia is minimal. Presumably the histological changes of osteomalacia are minimal despite severe biochemical osteomalacia because she is an old lady who is not forming bone at a rapid rate and simply has not laid down enough osteoid to produce the picture of florid osteomalacia. I imagine that the alkaline phosphatase level is not raised for the same reason.

Iron Metabolism

DR. A. GOLDBERG: From the results of the blood examinations we have just been shown this patient would seem to have an iron-deficiency anaemia with a haemoglobin of 7.8 g./100 ml. and a low MCHC. Her bone marrow is normoblastic, not megaloblastic, and her serum B_{12} 148 $\mu\text{g.}/\text{ml.}$, which is at the lower limit of the normal range. In idiopathic steatorrhoea there is evidence of a defect in the absorption of three major haematinics: (1) iron, (2) folic acid, (3) vitamin B_{12} . This lady has evidence of malabsorption of two of these factors. She has responded to parenteral iron, which is usually necessary in an iron deficiency of any great severity.

Though in this particular patient, of course, the steatorrhoea was florid, the haematological complications may be the presenting clinical features. You may be presented with a patient who has an iron-deficiency anaemia or a macrocytic anaemia in whom the steatorrhoea is latent and can only be detected by faecal fat estimation or by the other tests such as Dr. Cartwright has mentioned. It is now known that a good proportion, perhaps 30%, of these people have a defect in the absorption of vitamin B_{12} . If it is necessary to give folic acid permanently, then it is essential to give vitamin B_{12} in addition in the same dosage as in pernicious anaemia, lest folic acid alone precipitate subacute combined degeneration of the cord. Although it is usually necessary to give iron parenterally at the beginning one should not underestimate the patient's ability to absorb some iron if given orally. This will diminish the requirements for parenteral iron. In some cases there is a diminution in the number of stools and even of the steatorrhoea itself after the administration of folic acid, with improvement in the anaemia. This is not common, but it is sometimes not necessary to give a gluten-

free diet in such cases, particularly where the steatorrhoea is latent.

DR. J. RENWICK: Could this improvement in the diarrhoea be related to a change in the flora of the intestine, consequent upon the change of the folic acid content of the intestine? I wonder if anybody knows what proportion of the symptoms of idiopathic steatorrhoea are due to change in bacterial flora.

DR. GOLDBERG: I am afraid that I cannot answer that one. I would have thought that the improvement in haemoglobin was another factor which would improve the function of the intestine. There is a great deal of controversy about the intestinal flora in idiopathic steatorrhoea and also in some other conditions like intestinal loops and diverticula.

DR. CARTWRIGHT: Charlotte Anderson (Anderson and Langford, 1958) sampled the small gut in children with coeliac disease and found the same organisms as in normals. She concluded that infection of the small gut was not a potent factor in producing symptoms.

DR. NORDIN: I am extremely sceptical about folic acid having any effect on the diarrhoea of idiopathic steatorrhoea. Surely this is a diagnostic, pathognomonic sign of tropical sprue? I would like to see some very well-documented cases of idiopathic non-tropical sprue responding to folic acid before I would accept them.

DR. GOLDBERG: I think there is no doubt that occasionally the diarrhoea decreases, although the fatty stools remain.

PROFESSOR ILLINGWORTH: Do you attribute iron deficiency directly to the histological changes in the upper part of the intestine or to the diarrhoea?

DR. GOLDBERG: I think to both factors. Badenoch and Callender (1954), using radio-iron, have shown that in the majority of these patients there is malabsorption. They do not absorb iron even when they are grossly anaemic, a state which should stimulate iron absorption. With the gluten-free diet there is an increase in the absorption of iron, confirmed by radio-iron studies.

DR. D. KOUTRAS: In what form was the parenteral iron given?

DR. NORDIN: Imferon.

DR. J. F. ADAMS: Professor Wayne says we can use that now?

DR. LENNOX: Could we ask Professor Wayne to settle this matter of imferon? Are clinicians as well as pathologists agreed firmly that parenteral iron is safe?

PROFESSOR E. J. WAYNE: Well, of course, no one can settle that it is safe. It produces sarcomata in rats, and once an experimentalist has produced sarcoma in any species of animal by injecting any substance, then I suppose no one can say that that

substance is completely safe. The rat is the only animal in which imferon sarcomata have been produced, but many other substances when injected into rats produced sarcomata, and there is no evidence that it has happened in the human. There have been one or two cases where secondary carcinoma has developed at the site of an injection of imferon, but this is known to occur at injection sites generally. There was a Vancouver case which was alleged to be a sarcoma, but Professor R. A. Willis has seen the slides and thinks that it is non-malignant (Goldberg, 1960). The evidence is, therefore, indecisive and amounts to a straight matter of opinion. I believe that even if a very occasional sarcoma was seen—and in the million of injections in humans it has never been seen yet—the injection of iron parenterally is so valuable in cases like those we have heard about today that we should continue with it.

DR. B. R. KNOWLES: I understand that the rise in the level of hæmoglobin in this patient was slower than one would expect with parenteral iron. Does Dr. Goldberg feel, in spite of the low though normal serum B_{12} and normal bone marrow, that B_{12} deficiency was playing any part in this anæmia?

DR. GOLDBERG: I think there are two points here. You suggest that parenteral iron gives a more rapid increase in the hæmoglobin than oral iron. Normally, of course, this is not so. If oral iron is absorbed properly, the hæmoglobin will come up to the same level in the same time. In retrospect, the rise in this patient was a little slow, and the fact that she had a low serum albumin shows that there must have been some defect in the absorption of protein factors which would make her hæmoglobin synthesis poorer than it should be.

The second point you raised concerned vitamin B_{12} deficiency and this is very difficult to answer. There was no evidence of a megaloblastic or even a macro-normoblastic bone marrow, and presumably there was sufficient folic acid and sufficient B_{12} in her bone marrow to prevent this happening at her low rate of hæmoglobin formation. On the other hand, once she had been given iron, blood formation was stimulated and there was probably an increased requirement of B_{12} . I think in this particular woman it would be of value to give B_{12} injections in addition to iron.

DR. NORDIN: We have had two patients with steatorrhœa and pure iron-deficiency anæmia treated with parenteral iron, both of whom presented a year later with megaloblastic anæmia and had to be treated with B_{12} and folic acid.

PROFESSOR WAYNE: I think that, in general, it is wise to give vitamin B_{12} supplements to patients with the steatorrhœa syndrome.

DR. ADAMS: Even five years ago the teaching

was that you should never give B_{12} and folic acid at the same time to the same patient. Now opinion is almost unanimous that you should give patients with idiopathic steatorrhœa both. It has been reported that nearly all of them fail to absorb folic acid and about a third of them fail to absorb B_{12} . Usually, however, a single absorption test with radioactive B_{12} has been relied on. I have tested the absorption of radioactive vitamin B_{12} in one patient with steatorrhœa on 12 separate occasions at weekly intervals and four of these tests were normal and eight abnormal, so that I am unwilling to accept the statement that a patient does or does not absorb B_{12} on the result of a single test. I think this is the case with many of these tests—we do not know enough about the reliability or the reproducibility of the test in the same patient. The same thing applies to xylose absorption.

I am not surprised that her marrow was normal with this serum B_{12} level. If you had found a megaloblastic marrow with this serum B_{12} level I think you would have been justified in assuming that it was due to folic acid deficiency.

There are one or two points of interest about the vitamin B_{12} level of $148 \mu\text{g./ml.}$ It is an interesting level which we do not see very frequently. Strictly speaking, it is normal. The normal range by the method is from 140 to about 900; the abnormal range is below 80 and the borderline range is 80 to 140. When the assay was originally applied by Mollin and Ross (1953), a series of patients with pernicious anæmia were tested against a series of hospital normals. All the former were below 100 and all the normals were above 150. The dividing line was taken at 100 plus or minus 20%, which was the error of the assay. The upper limit has since been pushed up to 140, but, in fact, in our experience normal levels under 200 are very rare. In a consecutive series of 97 hospital normals which I examined recently only two had levels below 200. One had a level of 120; this man, who came to hospital with a myocardial infarct, was investigated further and found to have P.A. The second one, with 170, was not investigated further. So that the figures of 148 rouses suspicion, although 'officially' it is not abnormal. It is a figure which we quite commonly see in idiopathic steatorrhœa, where we do not see levels below 80 unless with florid megaloblastic anæmia in relapse. This might be due to folic acid deficiency as well as B_{12} deficiency. Another thing I have never understood is that one quite often finds this kind of level in post-gastrectomy megaloblastic anæmia whether or not they have steatorrhœa.

Endocrine Abnormalities

DR. NORDIN: I would like to say a word now about the secondary effects of the endocrine

system. It is now established that a fair proportion of these patients develop some degree of pituitary insufficiency. This is certainly very obvious in the children, the coeliacs who fail to grow; but it has also been demonstrated in adults, and we have in fact looked into this patient's pituitary function. The FSH was greater than 20 but less than 40 mouse units per day, which is a low result suggesting pituitary insufficiency. This impression was confirmed by 24 hour ketosteroids of 4.1 mg. and ketogenic steroids of 2.1 mg., both of which are low. The serum PBI was 1.4 μ g./100 ml. and this low level failed to rise after the injection of TSH on successive days, which suggests a degree of thyroid deficiency as well.

DR. S. KRAMER: May I ask if anything is known as to the cause of the endocrine disturbances?

DR. NORDIN: Well, you are entitled to ask, but nobody knows the answer! I think it is fair to say that general malnutrition is the most reasonable answer available in our present state of knowledge. So little is known about the precursors of the various pituitary hormones that no one can say what specific malabsorption would be required to inhibit the anterior pituitary. In anorexia nervosa you can reproduce pituitary insufficiency simply from starvation. Since malabsorption is a form of starvation I think this is a fair analogy.

MR. A. P. M. FORREST: There have been some recent cases where pigmentation has been a pro-

minent feature. This would be against primary pituitary insufficiency but would rather suggest that there was adrenal failure due to malnutrition.

DR. NORDIN: This is perfectly fair. In fact, pigmentation is one of the classical signs of steatorrhœa. However, this description antedates modern hormonal techniques. The fact that someone is pigmented cannot be taken, *per se*, as evidence of adrenal insufficiency. As far as the evidence goes it is the pituitary that is involved primarily in steatorrhœa, and the adrenals, the thyroid and the gonads secondarily.

MR. FORREST: If someone is pigmented *and* has symptoms of adrenal hypofunction, isn't this pretty good evidence that the pituitary is not inhibited?

DR. NORDIN: Only if you assume that the pigmentation is due to the secretion of melanophore-stimulating hormone and unless you assay this you cannot be certain. There are many other causes of pigmentation and if you have a low FSH and a positive TSH test and gonadal insufficiency as well as adrenal insufficiency, then the case is one of pituitary insufficiency, regardless of pigmentation.

DR. GOLDBERG: One shouldn't forget this general point. Iron deficiency in the adolescent if it is severe enough will delay the onset of puberty. B₁₂ is an essential substance for the metabolism of most tissues. Either of these factors may affect pituitary function.

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