Clinicopathological Conference

A Case of Adult Coeliac Disease with Addison's Disease

PRESENTED AT THE ROYAL POSTGRADUATE MEDICAL SCHOOL

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Clinical History

Professor C. C. BOOTH (1): The patient (C.P.C. No. 315564; P.M. No. 12321) was a married housewife aged 66 years at the time of her death. She remembered having had repeated bouts of diarrhoea as a child, and between the ages of 9 and 13 years she had had recurrent episodes of pleurisy. Between 1931 and 1933 she continued with recurrent episodes of diarrhoea, and then in 1936 developed anaemia for the first time. This was apparently macrocytic, since she was treated with liver extract with an excellent response. In 1940 she developed red, sore spots on her shins which were diagnosed as possibly due to erythema nodosum. Two years later, in 1942, there was a recurrence of anaemia, and she was again treated with liver extract. In 1944 she developed some large lymph nodes on the right side of the neck which were thought to be tuberculous, but she received no definitive treatment. In 1951 she had a radical left mastectomy for cancer of the breast followed by deep *x*-ray therapy. There was no recurrence of this cancer throughout the rest of her life. In 1961 she again developed anaemia after a change in her treatment from liver extract to vitamin B_{12}. This recurrence of anaemia despite receiving vitamin B_{12} suggested that she was suffering from folic acid deficiency. Her treatment was changed back to liver extract and the anaemia again responded satisfactorily.

Despite this, her diarrhoea continued, and in 1962 she was having recurrent and troublesome bouts of diarrhoea, the motions being loose and watery and up to six or seven times per day. At this time she said that the diarrhoea was only relieved by eating "crab meat." By now she had begun to lose weight, and she lost 28 lbs (12·5 kg.) during that year. In March 1966 she developed cystitis: Investigation of the urinary tract including cystoscopy and an intravenous pyelogram were normal. At sigmoidoscopy, carried out because of her diarrhoea, the rectal mucosa was seen to bleed easily but was otherwise normal. Soon after she began to complain of pins and needles in her fingers, and her loss of weight continued. Her diarrhoea was persistently troublesome during the next three months—up to three or four motions daily—and in June of 1966 she was referred to Hammersmith Hospital for further investigation and treatment.

On examination she was a rather thin middle-aged lady who was otherwise well. There was a well-healed left radical mastectomy scar and no lymph nodes were felt in either axilla. Trousseau's and Chvostek's signs were positive. The pulse was regular, the blood pressure was 110/60, and the heart normal. The chest was normal. In the abdomen there were no masses to be felt, and the liver and spleen were not palpable. The central nervous system was normal.

Investigations

Intestinal anatomy.—A barium follow through showed a small hiatus hernia of the sliding type. There was considerable flocculation and dilatation of the bowel, the appearances being characteristic of steatorrhoea. A jejunal biopsy was carried out and this showed a completely flat jejunal mucosa (Fig. 1.)

Intestinal function.—A glucose tolerance test was normal, the blood glucose rising from a fasting level of 75 mg./100 ml. to 130 1½ hours after 50 g. of oral glucose. Xylose excretion was reduced, only 2·1 g. being excreted in the urine in five hours after a 25 g. test dose (normal >5 g.) Faecal fat excretion averaged 13·3 g. per day during a six-day balance period (normal range <6 g. per day). Vitamin B_{12} absorption was also subnormal; even when a test dose of B_{12} was given with intrinsic factor only 0·3% of the test dose was excreted in the urine during 24 hours (normal range >10%).

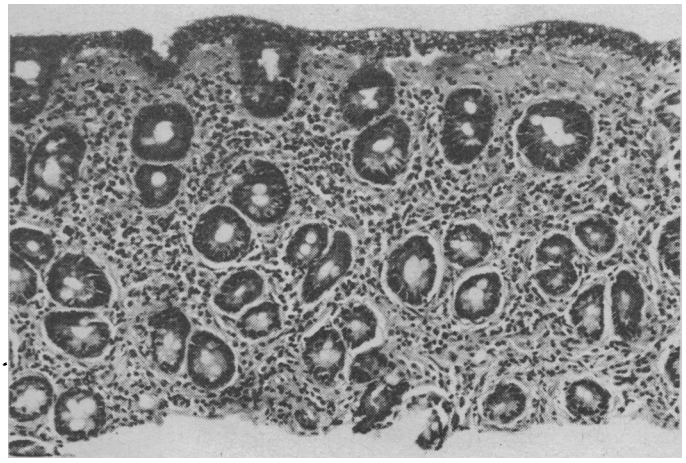

FIG. 1.—Jejunal biopsy before treatment showing flat mucosa with short abnormal superficial cells (H. & E. ×126.)

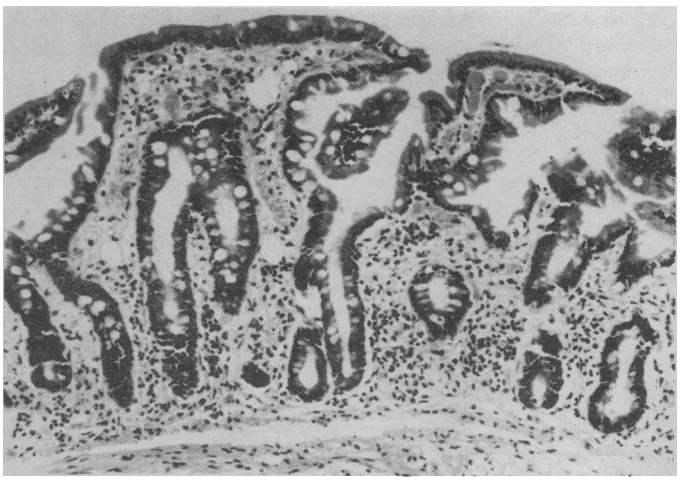

FIG. 2.—Jejunal biopsy after gluten free diet for 17 months and steroids. There is marked improvement of villous architecture and the surface cells show increased height. (H. & E. ×126.)

Nutritional deficiencies.—Haematological findings showed haemoglobin 13·1 g./100 ml., R.B.C. 4·2 × 10^6/c.mm. and W.B.C. 12,000/c.mm. Platelets were 279,000/c.mm. The serum iron was 95 ng./100 ml. and the marrow was normo-

blastic, presumably as a result of previous treatment with liver extract. The prothrombin time was considerably prolonged at 27 seconds but fell to 18 seconds six days after treatment with 10 mg. of Vitamin K.

Bone radiographs showed evidence of very thin bones, and the appearances of the fingers suggested hyperparathyroidism. The serum calcium was 4·2 mN. falling to 3·7 and 3·8 mN. during the first week after admission. The phosphate was 1·7 mN. and the serum magnesium 1·0 mN. The alkaline phosphatase level was normal, being 12 K.A. units. A bone biopsy showed evidence of osteomalacia, and the serum vitamin D level measured by the rachitic rat bioassay technique showed that there was no measurable vitamin D in the plasma. The phosphate excretion index was markedly raised at + 0·174 and + 0·129 (normal range ± ·09). The plasma proteins showed a low serum albumin (2·5 g./100 ml.) and a normal serum globulin. The immunoglobulins were as follows: γG 1,050 mg./100 ml. (normal range 600 to 1,600) γA 280 (normal range 50 to 450) and γM 20 (normal range 50 to 150), the results showing deficiency of γM globulin.

Electrolytes showed sodium 142, potassium 3·8, chloride 106 and bicarbonate 22 m.Eq./1. The blood urea was normal, being 27 mg./100 ml.

Calcium absorption and excretion by the gut.—This was measured by a combined external balance and calcium isotope technique. The external balance was −12·4 m.Eq./day, and the net absorption −11·5 m.Eq./day; both values are abnormally low. The intravenous ^{47}Ca test showed the endogenous faecal calcium to be 18·6 m.Eq./day; this is about twice the upper limit of normal. Adding this value to the net absorption figure of the balance, the true diet calcium absorption of 7·1 m.Eq./day is obtained; this is mid-normal. When studied after eight months on gluten-free diet the endogenous faecal calcium had fallen to normal. These tests were interpreted as showing that the negative calcium balance was due to an abnormal "leak" of body calcium into the gut, while the absorption of calcium from the diet was normal.

Initial Diagnosis

The diagnosis was, therefore, adult coeliac disease causing malabsorption. There was osteomalacia due to vitamin D deficiency and evidence of secondary hyperparathyroidism. She was first treated with codeine phosphate as symptomatic treatment for the diarrhoea, and she was given a strict gluten-free diet. By 5 August 1966 she was very much improved and her weight was increasing. In November 1966, however, she developed a rash for the first time, macular blotches appearing over the neck and legs. But in January 1967 her weight had increased by 16 lb. (7·5 kg.), she had no diarrhoea, and she was, in fact, very well. On 5 March she was readmitted to Hammersmith Hospital feeling fit and well except for the rash. She now had a scaly, red-purplish rash in patches all over the trunk and thighs. The diagnoses offered at this time were either nodular vasculitis or possibly a drug reaction. A bone biopsy showed considerable healing of the osteomalacia. The γM level in the blood had risen to 50 mg./100 ml., but the xylose excretion was still abnormal at only 2·2 g. Calcium and phosphate had risen to normal levels. A jejunal biopsy showed only dubious improvement, however, and estimation of the faecal fat showed persisting steatorrhoea (8 g./day). The gluten-free diet was continued.

In May 1967 she was readmitted for follow-up. Despite a satisfactory clinical response to the gluten-free diet, her xylose excretion was still abnormal (1·4 g.), the faecal fat was still elevated 11·5 g./day, and the Schilling test 0·4%. The rash also persisted. The level of vitamin D was measured during this admission, and it had risen to the normal range, being 1 I.U./ml. In August 1967 she was still on a strict gluten-free diet, but by now her weight had begun to fall, and she had lost 14 lb. (6·4 kg.) during the previous month. The rash had become more extensive and was covering both the trunk and the limbs.

Addisonian Crisis

In September 1967 she suddenly became unwell, with an episode of severe vomiting and diarrhoea. She was readmitted to Guildford Hospital, where the clinical findings suggested an acute Addisonian crisis. The blood pressure was found to be 70/50 mm. Hg and she had a serum sodium level of 118 and a potassium level of 6·8 mN. A diagnosis of idiopathic Addison's disease was made, and she was treated with intravenous fluids and prednisone 30 mg. daily. The response to this treatment was satisfactory, and she was sent home on a gluten-free diet.

In October 1967, however, she was readmitted with fever. At this time the rash was shown to be ulcerating and it was concluded that she was suffering from a septicaemia. She was treated with ampicillin and the prednisone was increased to 80 mg. daily to cover the inter-current infection. Her condition did not improve, and on 30 October she was transferred to Hammersmith Hospital. At this time she was found to have an indurated and ulcerated rash on the right forearm, back, and chest. The blood pressure was 135/75 mm. Hg; the haemoglobin was 12 g./100 ml. The serum sodium was 140 m.Eq./1. The serum cortisol was 5·5 μg./100 ml. and there was no significant rise after five days of ACTH. A skin biopsy was taken and this suggested an allergic vasculitis. The possibility of a skin reticulosis was, however, also raised. Liver function was now shown to be grossly abnormal, even though there were no signs of liver dysfunction clinically and in particular the liver was not palpable. The bilirubin was 1·4 mg./100 ml. The alkaline phosphatase had risen 17 K.A. units and the isocitric dehydrogenase was 25 i.u. A liver biopsy was done, and this merely showed polymorphonuclear infiltration.

On 10 November the patient's condition suddenly deteriorated with the onset of generalized abdominal pain and marked abdominal rigidity. A diagnosis of a ruptured viscus was made, either a perforated gastric ulcer or possibly a perforation of the small bowel through a lymphomatous deposit in the small intestine. She was now desperately ill, not fit enough for gastrointestinal surgery. She was resuscitated with intravenous saline and hydrocortisone, but she developed an episode of pulmonary oedema from which there was progressive deterioration until her death on 11 November.

Clinical Diagnosis

(1) Adult coeliac disease.
(2) Treated osteomalacia.
(3) Idiopathic Addison's disease.
(4) Rash? allergic? associated with lymphoma.

She was thought also to have a perforated gastric ulcer or else perforation of a lymphomatous plaque in the small intestine. The question of hepatic sepsis was also considered.

Post-mortem Findings

Dr. D. EVANS (2): Three jejunal biopsies were taken. The first of these, pre-treatment, showed subtotal villous atrophy (Fig. 1). After withdrawal of gluten a second biopsy showed little improvement. A third biopsy (Fig. 2), taken during steroid therapy in her final illness, showed partial villous atrophy with improved cell height.

Biopsy of a section of skin showed "allergic" vasculitis with fewer polymorphs in the exudate than usual. The liver biopsy showed polymorphs in the portal tract, owing to intra-abdominal sepsis or cholangitis.

At necropsy, the body was that of a small woman (43 kg.) with a healed mastectomy scar and an oedematous right arm.

The skin showed discrete indurated plaques on the trunk, neck, and limbs, some ulcerated, and some of the ulcers showing healing. Microscopically there was a vasculitis (Fig. 3) with some vessels occluded by thrombus and showing mural fibrin but preserved elastic laminae. The cardiovascular system was normal; but there was mild pulmonary oedema. There was no gastric atrophy. Two large acute gastric ulcers were present: 2·4 cm. diameter on anterior wall and 3·5 cm. diameter on posterior wall near the lesser curve, the latter showing a small perforation into the lesser sac, with surrounding fibrinous adhesions and generalized purulent peritonitis.

Microscopically, the gastric mucosa contained specialized cells. The ulcers were acute, and both the ulcer surface and peritoneal exudate contained a yeast.

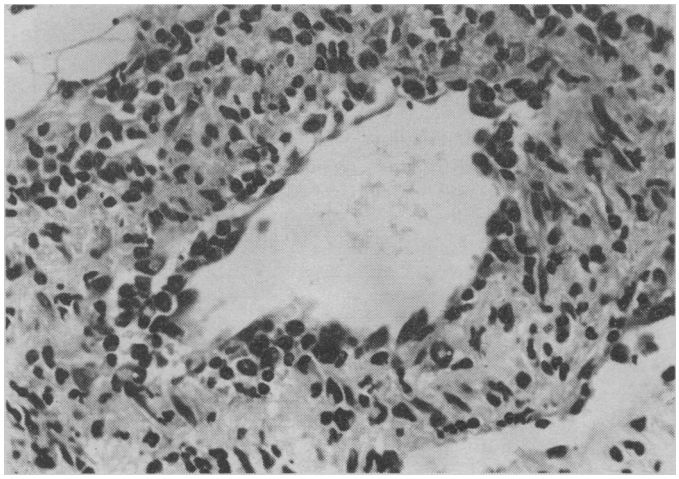

FIG. 3.—Infiltration of wall of skin vessel by mixed inflammatory infiltrate. Polymorphs are less frequent than usual in cases of vasculitis. (H. & E. ×308.)

FIG. 4.—Low-power view of adrenal to show gross atrophy, capsular fibrosis and infiltration with inflammatory cells. (H. & E. ×84.)

The small intestine showed loss of mucosal folds in the proximal 20 cm. of jejunum: microscopically there was partial villous atrophy. In the distal jejunum and ileum villi were present. The liver weighed 1,203 g. and was markedly autolysed. There were several yellowish infarcts, predominately subcapsular. The spleen was soft and microscopically normal. The adrenals together weighed only 1·1 g. (Fig. 4). Microscopically there was marked capsular thickening and gross loss of cortical cells (Fig. 5), with a dense infiltrate of lymphocytes, plasma cells, mononuclears, and some megakaryocytes. There were some enlarged nuclei and occasional mitoses in surviving adrenal cortical cells. The pituitary showed Crooke's hyaline change in the basophils. Four normal size parathyroids were found with normal amounts of fat microscopically. The tenth thoracic vertebrae was collapsed, but microscopically there was no evidence of osteoporosis in rib, sternum, vertebrae, or iliac crest, and no osteomalacia in undecalcified sections. The collapsed vertebrae showed a Schmorl's node.

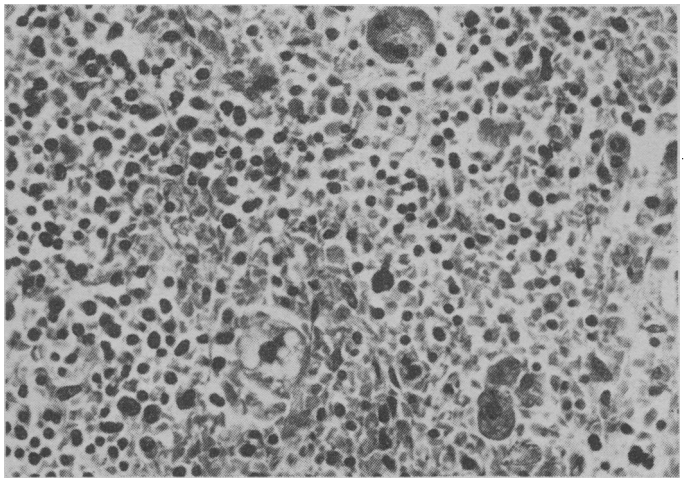

FIG. 5.—Adrenal cortex showing loss of cortical cells and marked mixed chronic inflammatory infiltrate. (H. & E. ×308.)

Pathologist's Diagnosis

(1) Adult coeliac disease.
(2) Idiopathic Addison's disease.
(3) Iatrogenic Cushing's syndrome.
(4) "Allergic" vasculitis.
(5) Perforated acute gastric erosion. } with yeasts present.
(6) Peritonitis. }
(7) Pulmonary oedema.

Discussion

Professor BOOTH: Perhaps I could lead off by saying what we think adult coeliac disease is. Two main aetiologies have been offered. The first hypothesis suggests that it may be due to the lack of a peptidase of some sort in the intestinal mucosal cell, allowing the entry of a toxic peptide derived from the digestion of gluten. This peptide is thought possibly to cause cellular damage by rupturing the lysosomal membrane of the cell. Variable deficiency of this peptidase might, therefore, give rise to variable degrees of abnormality of the gut mucosa. This idea can be tested by taking peptides derived by digesting gluten and mixing them with the intestinal mucosal cells and seeing what amino-acids are released. In fact very much less proline and glutamic acid (the main amino-acid in gluten) are released by the untreated coeliac mucosa than by normal mucosal homogenate, suggesting that there is deficiency of peptides in the mucosa.

This is clearly secondary, however, to the mucosal damage—because after treatment with a gluten-free diet the mucosa returns to normal and the amounts of amino-acids released from gluten peptides also become normal. Such evidence suggests that the defective peptidase hypothesis for the aetiology of coeliac disease is not true.

Well now, what else could it be? There are certain interesting abnormalities of immunity in this condition. Dr. Hobbs has shown that about 60% of untreated patients will show a low level of immune globulin M. We do not know the cause, but Dr. Brown and Dr. Hobbs have measured the synthesis rates of the Ig M just to be sure that its low level is not due to loss into the gut. The results indicate that there is a defect of synthesis of Ig M in coeliac disease, but again it

is probably secondary, since in most cases it returns to normal after treatment with a gluten-free diet. Normally the immunocytes of the small intestine produce IgA predominantly. In untreated coeliac disease, on the other hand, there is a striking infiltration of the gut mucosa with cells producing IgM. One does not know why this should occur, but it suggests the possibility that the intestinal abnormality may be due to an immunological reaction of some sort. When we see a patient who has a gut sensitivity developing a skin lesion of an allergic type as in the patient shown this morning, one just wonders whether this does not represent a sensitivity of the same sort. Having said that, may I pass the discussion on to Dr. Jack Hobbs?

Immunological Studies

Dr. J. HOBBS (3): This patient makes the immunological mystery of coeliac disease[1] even more mysterious. She did have IgM deficiency, but it responded to a gluten-free diet and became normal. In November 1966 she doubled her IgA level at the time she developed the first skin lesions. This is not very specific—most skin lesions of a widespread nature increase the serum level of IgA. The first rash does not seem to be the same as the subsequent one, which was a nodular vasculitis. The sera taken at this time showed a cryoprecipitate at 4° C. which contained IgM, IgG and some IgA—typical of mixed cryoglobulinaemia.[2] The precipitate redissolved in the warm, when it was strongly positive for rheumatoid factor, so the IgM component was probably an autoantibody against the IgG in the precipitate.

Characteristically, lesions are found in the skin and not in the internal organs in mixed cryoglobulinaemia. Immune complexes occur in the circulation, usually of an IgM antibody against IgG or IgA, and these lodge preferentially (affected by temperature) in the small arteries of the skin. Complement activation seems to follow, and this leads to the vasculitis.

The other thing that was curious about this patient's immunological findings was that besides making autoantibodies to her own IgG-globulin she had idiopathic Addison's disease with marked lymphoid infiltration. Dr. W. J. Irvine, at Edinburgh, did not find any serum antibodies by immunofluorescence to adrenal, gonads, thyroid, gastric parietal cells, or mitochondria. Negative results are found in some 20% of women with idiopathic Addison's disease. Most such patients show cellular hypersensitivity to the adrenal[3], and while this was not sought in our patient, the post-mortem histological appearances strongly suggest she had autoimmune adrenalitis.

Professor BOOTH: The finding of idiopathic Addison's disease raises the possible association of a so-called autoimmune phenomenon with an immunological condition in the intestine.

Dr. G. R. THOMPSON (4): So this patient developed two probable autoimmune diseases. Why?

Dr. HOBBS: The underlying problem for patients with coeliac disease may be that, using their normal immunological mechanisms at the jejunal level, they cannot cope with whatever is produced from gluten—a localized dysgammaglobulinaemia of the small intestine. So the untreated patient has to compensate by increasing other forms of immunity such as the IgM response seen in this patient's jejunum. Patients with dysgammaglobulinaemia—who are forced to compensate by using cellular or other mechanisms of immunity—run the risk of spilling over to autoimmune reaction. Autoimmune disease is a common complication that occurs in something like 20% of the patients with dysgammaglobulinaemia[4]. That may be one of the reasons why she has gone on to get two odd diseases. We have now seen two other patients with coeliac disease who have had mixed cryoglobulinaemia and vasculitis and have heard of four others who have developed idiopathic Addison's disease, so these associations may be significant.

Stomach Lesions

Dr. BRIAN CAMPBELL (5): I wonder if we may not possibly add a third autoimmune disease to Dr. Hobbs's list. The ileum looked very normal, yet some five months before she died the Schilling test was reported as 0·4%—a surprisingly low level in any case for a patient with malabsorption. I wonder, firstly, if this dose was given with intrinsic factor; and secondly, if the nursing staff gave the flushing dose of B_{12}; and thirdly, if perhaps Dr. Evans could tell us more about the rest of the gastric histology at autopsy.

Dr. EVANS: Despite marked autolysis it is possible to say that the patient had not got gastric atrophy.

Professor BOOTH: And the test dose was given with intrinsic factor and with the flushing dose. So there was malabsorption of B_{12}, of an unusually severe degree for a patient with adult coeliac disease.

Dr. CAMPBELL: Particularly with an ileum that histologically looks convincingly normal.

Professor BOOTH: That was at necropsy, and the absorption test was carried out nearly a year before. There might have been some difference during that period.

Adrenal Hypofunction

Dr. THOMPSON: Is not adrenal hypofunction well recognized as a complication in coeliac disease and doesn't it sometimes improve with gluten-free diet? Does one have to invoke immunological mechanisms?

Dr. C. W. BURKE (6): "Pseudo hypoadrenalism" is commonly described both in coeliac disease and in tuberculosis. By this is usually meant low urinary steroid excretion but a normal response to stimulation tests—a normal adrenal reserve. There is no good evidence of functional cortisol lack in this situation. The urinary steroid may not be there, but otherwise adrenal function and reserve are normal. A low plasma cortisol may be due to deficiency of corticosteroid-binding globulin, but the unbound cortisol—the effective bit— is normal in coeliac disease. Also the A.C.T.H. response is still normal.

In this case the hypoadrenalism was definitely diagnosed as primary after a stimulation test with A.C.T.H. Five days is enough to bring up the levels even in most who have been treated with steroids.

Dr. THOMPSON: This lady was undoubtedly vitamin D deficient. In experiments on animals it has been shown that absence of vitamin D interferes with the active transport of calcium, which occurs mainly in the upper small intestine. I find it rather difficult to understand how this patient could selectively malabsorb or perhaps leak endogenous calcium and yet absorb dietary calcium practically normally. Was there any possible technical reason for this?

Calcium Studies

Dr. G. F. JOPLIN (7): Our value for the endogenous faecal calcium is difficult to dispute. It is measured by three independent sets of laboratory data, all of which agreed in her case, as indeed they did in the other patients in the series. The enigma is your first point; how does it come about that her true absorption was so normal with the undetectable level of vitamin D? Here one can only speculate, but I imagine that there are two factors: one is that she showed clear evidence of secondary hyperparathyroidism, which, presumably, can compensate for a relatively low vitamin D

level; the second point is that it may well be that the vitamin D level in these particular patients does not really fall down to zero, and we are probably therefore not studying patients in the presence of complete vitamin D deficiency at all. Quite possibly such patients would need to be untreated for a very long period of time before complete D deficiency develops.

Dr. THOMPSON: You mean that you think she had enough vitamin D deficiency to get osteomalacia but not to interfere with her dietary absorption of calcium?

Dr. JOPLIN: Yes. The important point is the high level of parathyroid hormone. For instance, there is a precedent for this proposition in renal failure, where there really is calcium malabsorption; when the patient eventually gets to the stage of tertiary hyperparathyroidism calcium absorption can be quite normal. I suspect that that is what happened in today's case.

Professor BOOTH: That again is speculation at this stage.

Dr. D. GOMPERZ (8): Could I come back to this idea of exogenous and endogenous calcium absorption. Dr. Joplin, can you make a case for two different calcium pools in the small intestine?

Dr. JOPLIN: Here we really have to confess ignorance, because we don't even know from the gastroenterologists the anatomical level at which calcium is normally secreted into the gut.

Effect of Fat

Dr. HOBBS: Did you give the tracer that is marking the calcium on an empty stomach in the absence of fat?

Dr. JOPLIN: In this particular study the endogenous calcium loss is obtained by the cumulative faecal excretion of intravenously administered isotope in a patient maintained on a constant diet, so this is information gleaned over a period of say 10 days. No oral isotope is used.

Dr. R. H. DOWLING (9): In coeliac disease one may see either tetany or osteomalacia but it is unusual to find both these conditions at the same time. It has been suggested that the clinical presentation of altered calcium metabolism is related to the speed of onset of coeliac disease and to the time necessary to develop secondary hyperparathyroidism. Could I ask Dr. Joplin to comment?

Dr. JOPLIN: Your suggestion is probably right. There may have been insufficient time for the secondary hyperparathyroidism to catch up, because though she did have a degree of hyperparathyroidism it was not quite enough to keep the calcium level normal throughout the acute stage.

Professor BOOTH: Another factor is magnesium deficiency. The parathyroids are said not to work in magnesium deficiency, and she had a low serum magnesium level.

Dr. C. PALLIS (10): I would like to ask two questions. The serum vitamin D level was said to be very low. How reliable an observation is this? To the uninitiated the procedure sounded so incredibly complicated as to throw doubt on its reliability: rendering rats rickety, then feeding them some of the patient's serum and quantitating subsequent changes in their bones. How is the degree of rachitic change in the bones of these rats estimated? Is the same bone biopsied before and after a particular rat has been fed serum? Or is the assessment radiological?

Dr. G. NEALE (11): We used the standard bioassay for vitamin D. Dr. Pallis is absolutely right—it is incredibly tedious and not very accurate. The sensitivity of the assay is limited. One cannot say more than that the serum of this patient failed to heal the bones of rachitic rats, and that she had less than 0·4 international units of vitamin D per ml. of plasma.

Dr. PALLIS: You feed the serum to lots of rats?

Dr. NEALE: Yes. One feeds one group of rats with serum and two with known quantities of vitamin D. The degree of healing of the rachitic bones of the first group of rats is compared with the result of the other two groups.

Dr. PALLIS: Dr. Joplin showed a diagram illustrating the relative proportions of osteoid, partially calcified bone, and normally calcified bone in biopsy specimens from different bones of this patient obtained before and after treatment. It seems to me that inaccuracies due to sampling must arise here. How can you ensure that the samples come from portions of bone in which the relative widths of the seams were originally the same? Cannot this vary very widely?

Bone Biopsies

Dr. JOPLIN: Fortunately this is not so in osteomalacia. If you were making the same objection to the rating of osteoporosis from small bone biopsies everyone would go along with you. But for some curious reason in osteomalacia it scarcely matters if the biopsy is taken from a rib or an iliac crest; the answer comes up remarkably the same. Site variations are very small in osteomalacia.

Professor BOOTH: In this patient, then, the bones healed and the vitamin D level increased on a gluten-free diet alone without vitamin D being given. It is important that when this complication occurs in coeliac disease a gluten-free diet is given. If only vitamin D and calcium is given the healing of the bone is often slow until the gluten-free diet is given. The gluten-free diet appears to be more important than the vitamin D or the calcium.

Professor GOODWIN: Could I come back to the problem of pulmonary oedema in the presence of an absolutely normal heart? Presumably it was due to one of three causes: either the fluid overload, aspiration of vomit, or to a very low serum albumen. I would like to know which of these three, either singly or in combination, you think was the cause, because this must have been one of the reasons for not treating her surgically.

Professor RUSSELL FRASER (12): What about bleeding too?

Professor GOODWIN: Bleeding, as a cause of pulmonary oedema?

Professor RUSSELL FRASER: By a drop in the blood pressure.

Professor GOODWIN: I do not think so. The pressure in the pulmonary veins has to be high enough to force fluid into the alveoli, unless there is some toxic effect or irritant effect on alveolar walls, An "allergic" type of pulmonary oedema sometimes occurs, and, of course it can be due to inhalation of irritant substances. The most common irritant effect is from the inhalation of gastric juice. I should not have thought that bleeding from the gut or from anywhere else would cause pulmonary oedema.

Dr. NEALE: The serum albumen was 2·5 to 2·8 g./100 ml., and I do not think this somewhat low level was the cause of pulmonary oedema in this desperately sick patient. I cannot explain it, though one does find pulmonary oedema terminally in many patients. I would like to ask about the treatment of this patient's Addison's disease with 30 mg. prednisone a day?

Dr. JOPLIN: That would not be the standard treatment of a straightforward Addison's disease at all. I imagine that she was treated in the standard way at one stage during her life with cortisone plus or minus cludrocortisone.

Dr. HOBBS: It is worth mentioning that up till March 1967 her electrolytes balanced, and she had no troubles at all. Six months later she was in Addisonian crisis. It is a quite remarkable deterioration.

Professor BOOTH: In summary then, this was a patient with a treatable condition of the intestine who responded reasonably well. She then developed Addison's disease of possibly autoimmune type, which may or may not have been related. This was then treated with excessive steroids and she perforated a gastric ulcer. I suppose the excessive presence of steroids is borne out by the presence of the Cushing's changes that Dr. Evans showed us.

Dr. EVANS: Could I just return for a moment to the association between the Addison's disease and the steatorrhoea.

This is not apparently the first case in which this has been documented. There are two cases written up by Goudie *et al.*[5] at the beginning of the year of patients with steroid-treated idiopathic steatorrhoea with antibodies against adrenal cortex.

APPOINTMENTS OF SPEAKERS

(1) Professor C. C. Booth, Professor of Medicine, Royal Postgraduate Medical School.
(2) Dr. D. Evans, Lecturer in Morbid Anatomy, Royal Postgraduate Medical School.
(3) Dr. J. R. Hobbs, Lecturer, Chemical Pathology, Royal Postgraduate Medical School.
(4) Dr. G. R. Thompson, Lecturer, Royal Postgraduate Medical School.
(5) Dr. Brian Campbell.
(6) Dr. C. W. Burke, Clinical Endocrinologist, Royal Postgraduate Medical School.
(7) Dr. G. F. Joplin, Lecturer, Royal Postgraduate Medical School.
(8) Dr. D. Gomperz, Lecturer, Royal Postgraduate Medical School.
(9) Dr. R. H. Dowling, Department of Medicine, Royal Postgraduate Medical School.
(10) Dr. C. Pallis, Consultant Neurologist, Royal Postgraduate Medical School.
(11) Dr. G. Neale, Lecturer, Royal Postgraduate Medical School.
(12) Professor Russell Fraser, Professor of Clinical Endocrinology, Royal Postgraduate Medical School.

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ANY QUESTIONS?

We publish below a selection of questions and answers of general interest.

Ichthyosis and Vaccination

Q.—*Is ichthyosis in a child a contraindication to vaccination against smallpox? There is no family history of eczema.*

A.—There is no contraindication to vaccination of patients suffering from ichthyosis provided this is not associated with an atopic eczema. Indeed, the latter is the only dermatological contraindication for vaccination. Naturally, it is wise not to vaccinate small children or even adults with any condition associated with itching, because of the risk of accidental vaccination at several sites including the face.

Differential Diagnosis of Pregnancy

Q.—*What is the rationale of the administration of Tab. Amenorone Forte to differentiate early pregnancy from amenorrhoea from some other cause? Is it possible to produce abortion by the administration of these tablets in early pregnancy or in late pregnancy?*

A.—Tab. Amenorone Forte contains ethynyl oestradiol and ethisterone—an oestrogen and a progestagen. Administration of such a combination for a few days to a woman with secondary amenorrhoea of short duration usually gives rise to withdrawal bleeding a few days later. Nevertheless, if the amenorrhoea is due to pregnancy the endogenous oestrogen and progesterone levels are already raised, and so this preparation does not cause bleeding. A negative response—no bleeding—is therefore indicative of pregnancy. Nevertheless, false-negatives—i.e., no bleeding when there is no pregnancy—are not uncommon, the more so the longer the duration of secondary amenorrhoea. False-positives—bleeding even though the patient is pregnant—may occur, but are uncommon. Clearly the test cannot be used in women suspected of being pregnant but with abnormal bleeding (for example, in threatened abortion or ectopic pregnancy).

There is no evidence that administration of these tablets can produce abortion either in early or in late pregnancy.

Antibody Response in Tetanus

Q.—*Are there any serological tests that will show that a person has or has had tetanus?*

A.—There are no serological tests that will show whether a person has or has had tetanus. The minimum amount of *Clostridium tetani* toxin required to produce an antibody response in man greatly exceeds the lethal amount.

Androgens and Prostatic Cancer

Q.—*Is the administration of testosterone to normal persons or to a patient with non-malignant prostatic hypertrophy likely to induce malignancy?*

A.—There is no evidence to suggest that the administration of testosterone to men with entirely normal prostates or prostates showing benign hypertrophy can induce malignancy. It is well known that testosterone can aggravate established prostatic metastases,[1] but more important is the effects of androgens on latent prostatic cancer. Necropsy studies have shown small latent foci of carcinoma in the prostates of 14-46% of males over the age of 50 years.[2 3] Many of these foci are demonstrable only on serial sectioning of the gland, and thus a clinical trial to show the effects of testosterone on latent carcinoma would be impracticable.

A retrospective study by Lesser, Vose, and Dixey[4] compared two groups of 100 men over 45 years old. One group was a control and the other group received weekly injections of 25-75 mg. of testosterone proprionate for up to four years. There were more prostates showing benign hypertrophy and palpable irregularities in the control group than in the study group. There was only one patient with a carcinoma, and he was an 80-year-old in the study group, whose cancer was found seven years after the cessation of testosterone treatment.

A panel of urologists[5] concluded that they had not seen a case of androgen-induced carcinoma of the prostate and that there was no appreciable risk in giving testosterone to elderly men, provided that established prostatic cancer can be excluded.

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Energetic Games after Nephrectomy

Q.—*Should a boy aged 10 who had a nephrectomy at the age of 18 months for hydronephrosis be encouraged to lead a completely normal life, including playing energetic games, or should the risk of trauma to the remaining kidney be guarded against? The remaining kidney and ureter are normal.*

A.—Although possession of only one kidney is compatible with a normal expectancy of life,[1-4] it is only common sense to avoid those situations where the other kidney might be ruptured. For this reason it is usual to advise avoiding rough games (American "body contact sports"), such as Rugby football. There is no reason why swimming, running, and most athletic activities need not be encouraged.

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