Clinicopathological Conference

A Case of Adult Coeliac Disease Resistant to Treatment

DEMONSTRATED AT THE ROYAL POSTGRADUATE MEDICAL SCHOOL

Clinical History

Dr. G. Neale (1)*: The patient (Case No. 316260; P.M. 12193) was 50 years old at the time of his death in 1967. His early medical history was unremarkable. In 1953 he became progressively unwell with loss of weight, vague abdominal pains, and later some diarrhoea. He was admitted to Chelmsford Hospital, where he was found to have a megaloblastic anaemia (haemoglobin 7 g./100 ml.), free gastric acid, and steatorrhoea. The provisional diagnosis of idiopathic steatorrhoea was justified by a good response to treatment with a gluten-free diet and folic acid. He was obsessive about his diet, though whenever he was mentally stressed he tended to get abdominal upsets with pain or diarrhoea. In 1963 a jejunal biopsy taken at Chelmsford showed partial villous atrophy, which confirmed the diagnosis of idiopathic steatorrhoea.

In 1965 the patient developed a gastric ulcer, which was treated with antacids, including the proprietary preparation Nulacin. His ulcer healed rapidly, but the diarrhoea recurred and he again started to lose weight. He was readmitted to Chelmsford Hospital and his progress is shown in Fig. 1. In hospital he was shown to have steatorrhoea (15 g./day), which was thought possibly to be due to Nulacin, since this preparation has a base of wheat flour. Nevertheless, despite the most careful gluten-free diet thereafter, the patient's condition deteriorated with rapid loss of weight from 63 to 50 kg. In June 1966 he was referred to Professor C. C. Booth for further investigation.

Radiological Examination

A barium meal and follow-through examination showed a grossly abnormal small bowel (Fig. 2). The proximal and mid jejenum were markedly and uniformly reduced in calibre with little or no mucosal pattern. The distal small bowel was somewhat dilated and its mucosal pattern not normally prominent. There were fluid levels in the erect position and some flocculation of the barium. A tubular and rather featureless jejenum seems to be a feature of some patients with a clinically severe enteropathy.

Jejunal biopsy showed subtotal villous atrophy with very low disaccharidase activities (lactase 0, maltase 5.6, and sucrase 2.8 units). Normal values: lactase >2.5, sucrase >3.0, maltase >6.0 μmoles of substrate hydrolysed/g. wet mucosa/min. at 37° C.). The small bowel was intubated and fluid obtained from the jejenum grew only 104 staphylococci/ml. Following a Lundh test meal the tryptase content of jejunal fluid rose to 10 units/ml. This excluded severe pancreatic deficiency.

On admission to Hammersmith Hospital the patient was thin but showed no symptoms, signs, or biochemical evidence of specific nutritional deficiencies. Investigations showed: haemoglobin 13.2 g./100 ml., white blood count 9,000/cu. mm., blood film normal; serum iron 80 μg./100 ml., B12 900 μg./ml.; folic acid 6.9 μg./ml.; plasma urea 30 mg./100 ml., sodium 139, potassium 3.9, chloride 95, bicarbonate 26, calcium 4.9, and phosphate 2.2 mN; serum bilirubin 0.6 mg./100 ml.

* List of speakers' appointments at p. 684.
Clinicopathological Conference

**Fig. 5.** A jejunal biopsy taken in 1963 showing severe partial villous atrophy. (H. and E. ×108.)

**Fig. 6.** Jejunum at necropsy showing subtotal villous atrophy, with the presence of Paneth cells (arrowed). (Phloxine-tartrazine. ×432.)

**Fig. 7.** Ileum showing acute ulceration in an area of subtotal villous atrophy. (H. and E. ×108.)
Clinicopathological Conference

Fig. 8.—Section of deltoid muscle showing neurogenic atrophy of groups of motor units. (H. and E. ×108.)

Fig. 9.—Acute necrotizing arteritis in skin biopsy. (H. and E. ×108.)

Fig. 10.—Artery from quadriceps showing old occlusion and destruction of elastic lamina. (H. and E. ×108.)
Treatment

Initially milk and milk products, as well as gluten, were excluded from the patient’s diet. This was done because of the absence of demonstrable lactase activity in the intestinal mucosa, and because some children with coeliac disease appear to respond to milk restriction when gluten-free diets are not immediately successful in controlling their disease. There was some improvement in the diarrhoea, but the steatorrhoea persisted unchanged. In August 1966 Professor R. B. Welbourn performed a laparotomy and the results of which excluded the possibility of an associated malignant disease. No abnormality was found apart from a very thin-walled small intestine. After operation the patient was treated with prednisone (Fig. 1), but again there was no improvement, and in November 1967 signs of hypoproteinaemia oedema appeared.

Study of the patient’s protein metabolism showed the following results: plasma albumin concentration 1.7 g./day (normal 4.1–5.8); intravenous albumin pool 1.2 g./kg. (normal 1.6–2.4); fractional albumin synthesis rate 14.4% of i.v. pool/day (normal 9.1–12.1); absolute albumin synthesis rate 7.4 g./day (normal 10.5–17.1)—177 mg./kg./day (normal 136–257); urea synthesis rate 506 mg./kg./day (normal 367–802); plasma urea 33 mg./100 ml.; urea pool 224 mg./kg. (normal 196–334); 14C-pviniyl pyridoline excretion 1.2% (normal 0.5–1.5); and the fasting plasma amino-acids were much reduced (Fig. 3). The studies were performed by Dr. E. A. Jones.

At this stage the patient was severely malnourished, so he was treated subsequently with intravenous albumin, amino-acids, ethanol, and sugar solutions. For one month he took no protein by mouth but this did not lead to any improvement in absorption. His weight slowly increased (Fig. 1) and by May 1967 following one month’s treatment with A.C.T.H. there seemed to be some slight improvement in bowel function (faecal fat excretion 30 g. of a 50 g. diet; xylose excretion 2.2 g. of a 25 g. dose).

Complications

The patient’s progress was, unfortunately, marred by a succession of complications.

Liver disease: After the appearance of hypoproteinaemia there were marked disturbances of liver function (Fig. 4), with elevated levels of bilirubin, alkaline phosphatase, and isocitric dehydrogenase. At first these disturbances seemed to be related to a sepsicaemia associated with intravenous feeding, but the liver function tests then remained abnormal throughout the last six months of his illness.

Lactic acidosis: Shortly after starting intravenous therapy the patient became unwell and markedly acidic. Investi-

Treatment showed plasma sodium 133, chloride 90, bicarbonate 12, and lactate 11 m.M., and urea 10 mg./100 ml. The patient was treated with intravenous sodium bicarbonate, and this episode may have been related to the administration of aminosol-fructose-ethanol intravenously. Subsequently ethanol was not given and there were no further episodes of lactic acidosis.

Skin disease: In November 1966 the patient developed a curious rash. This affected the limbs much more than the trunk and consisted of non-irritating erythematous slightly raised areas 1–2 cm. across, having a somewhat psoriasisform appearance. These lesions did not respond to topical treatment with essential fatty acids but later healed spontaneously, leaving flat pigmented patches.

Neurological disease: In October 1966 the patient complained of weakness in getting up from the sitting position. His girdle muscles appeared to be weak, but the reflexes were normal and there was no sensory disturbance. The patient was receiving vitamin D parenterally and the serum vitamin E level was normal. Steroid myopathy was a possible diagnosis, but an electromyograph was normal.

In May 1967 the patient complained of tingling and numbness in the hands and feet, and an increasing weakness of all his limbs affecting the distal parts more than the proximal. The reflexes were only just obtainable in the arms and were absent in the legs; the plantar responses were feebly flexor. All modalities of sensation were impaired over hands and feet. The clinical diagnosis of a peripheral neuropathy was confirmed by electromyography, which showed evidence of proximal and distal denervation together with changes suggestive of a myopathy. Examination of the cerebrospinal fluid showed: no cells, glucose 72 mg./100 ml., protein 76 mg./100 ml. The neuropathy affected motor function much more than sensation and progressed rapidly over the next two months, finally causing almost total paralysis of all four limbs. The patient had received large doses of parenteral vitamins throughout his illness and measurements of serum levels of B12, folic acid, and vitamin E were normal.

Infections: Prolonged intravenous feeding is often a cause of sepsicaemia. In December 1966 the patient had a staphylococcal sepsicaemia which was successfully treated with antibiotics, but he then had a succession of infections including two episodes of pneumonia and recurrent attacks of sinusitis (Fig. 2). Towards the end of June 1967 he became increasingly
jaundiced without apparent cause, and on 4 July 1967 he complained of chest pain of pleuritic type. Despite the absence of physical signs and the normal appearances of the chest radiograph and electrocardiogram pulmonary embolism with infarction seemed to be the most likely diagnosis. Four days later he had a right-sided Jacksonian fit and then complained of abdominal pain. Abdominal radiographs and the serum amylase were normal, but the urine was shown to contain 40 red cells/high power field. The body temperature rose from normal to 100.6°F (38.1°C) that evening. There were no abnormal physical signs in the chest and the heart sounds were thought to be unchanged. A systolic murmur noted on admission now seemed to be considerably louder and was maximal in the tricuspid area. Although the jugular venous pulse was unremarkable and the heart size unchanged bacterial endocarditis seemed a likely diagnosis. Blood cultures were taken and the patient was treated with methicillin and kanamycin. His general condition deteriorated rapidly and he became oliguric. His serum bilirubin rose to 30 mg./100 ml., his blood urea to 250 mg./100 ml., and his potassium to 7.5 mN, and he died in a coma five days after starting antibiotics. The blood culture grew Staphylococcus aureus sensitive to methicillin, kanamycin, and fucidin; resistant to penicillin, streptomycin, and tetracycline.

**Clinical Diagnosis**

1. Staphylococcal septicaemia (probable bacterial endocarditis and multiple abscesses).
2. Renal and hepatic failure.
3. Severe malnutrition due to idiopathic steatorrhoea.

**Post-mortem Findings**

Dr. D. Evans (2): The body was that of an emaciated man with wasted muscles, multiple superficial venous thromboses, and a psoriasisform rash over both legs.

The 1963 jejunal biopsy had shown partial villous atrophy (Fig. 5). The 1967 biopsy showed subtotal villous atrophy with flattened surface cells and subepithelial hyalinization, and there was an apparent reduction in the number of Paneth cells. The post-mortem biopsy showed subtotal villous atrophy in the jejunum with recent acute superficial ulceration and loss of mucosa. There appeared to be a normal concentration of Paneth cells (Fig. 6).

There was partial villous atrophy in the ileum (Fig. 7) with subepithelial hyalinization and normal numbers of Paneth cells.

The oesophageal wall was of normal thickness and no site of perforation was found. There was no active gastric ulcer. Apart from some superficial fat necrosis the pancreas was normal.

The 1966 liver biopsy had shown fatty infiltration with occasional mitoses indicating regeneration, and mild Kupffer cell haemosiderosis. A diagnosis of recovery from toxic damage was made. The post-mortem biopsy showed pericholangitis.

There was acute infective endocarditis with many 2–3 mm. vegetations on the free edges of the tricuspid valves, and larger vegetations on the chordae tendineae. Vegetations were also found on the pulmonary and aortic valves.

Metastatic abscesses were found in the kidney medulla, the myocardiun, and the spleen, and septic thrombi were found in the pulmonary arteries together with evidence of lung infarction and destruction of the vessel walls.

A severe degree of denervation atrophy was evident in the hamstrings, though this was less severe in the deltoid (Fig. 8). No lesions were found in the large nerves. There was a severe loss of neurones in the small intramuscular nerves, and central chromatolysis of the anterior horn cells indicating axonal damage. No other significant abnormality of the brain or cord was found.

Acute necrotizing arteritis was seen in the blocks of skin taken for histochemical study in February 1967 (Fig. 9), and we found evidence of old healed necrotizing arteritis in the arteries and muscle (Fig. 10), but no arteritis in the parenchymal organs.

The adrenals weighed 6 g., and the thyroid was normal. There was no evidence of osteomalacia, but osteoporosis was present, and there was severe testicular atrophy.

**Pathologist's Diagnosis**

1. Idiopathic steatorrhoea (adult coeliac disease).
2. Infective endocarditis with widespread abscesses.
3. Pericholangitis.
4. Peripheral neuropathy.
5. Old healed necrotizing arteritis.

**Discussion**

Professor C. C. Booth (3): This is a complex problem, and I wonder if before we start the discussion we could state what the problems are. Clearly the primary lesion was in the gut. This has led to severe malabsorption and thus to severe malnutrition. The features of this nutritional problem are hypoproteinaemia, neuromyopathy, skin lesions, a hepatic abnormality, and a necrotizing arteritis.

First we must ask what is the cause of the gut lesion. About 70% of patients with a flat jejunal mucosa respond to a gluten-free diet, and initially the position here was one of coeliac disease with a good response to a gluten-free diet. The question in 1966–7 was why this patient's intestine had suddenly become wrecked and remained so wrecked that he died of his disease. Dr. CREAMER, could you take it from there?

Dr. B. CREAMER (4): When I saw this man last November he presented a picture identical to that of two fatal cases that we had had (out of a total of about 100!), in that he was severely ill, he was hypoproteinaemic, he was non-responsive to treatment, and he appeared to have very few Paneth cells. Did he have a normal pancreas when he came to necropsy?

Dr. EVANS: There was no pancreatitis—just some recent fat necrosis on the surface. He may possibly have had a slight reduction in zymogen granules.

Dr. CREAMER: So he seems to fit very well into this group. Since then I have counted Paneth cells in our group of cases, and we now have eight cases with a low number of Paneth cells, and they form a remarkably homogeneous group.

Dr. E. D. Williams (5): Were you counting the Paneth cells only on intestinal biopsy, or all the way down the intestine, because there seems to be a discrepancy between the biopsy findings in the jejunum and the necropsy findings in the ileum?

Dr. CREAMER: Yes, only the jejunal biopsies, so this is a very localized specimen, though in one fatal case like yours we had surgical biopsies and several tube biopsies, so that in that case the finding was apparently homogeneous. We now have eight cases, and they all seem very much the same—they are all ill, they are all unresponsive, they have all lost a large amount of weight, two or three were cachectic like your man, and they were all hypoproteinaemic. This is very striking. Radiologically they are all exactly like your case, and Dr. Pierce is now so trained that 10 days ago he rushed up to the department with an x-ray film in his hand and said, "There are no Paneth cells," and, by George, he was right. They all look rather similar with this tubular appearance, lacking the broad barring and being rather narrower than one might expect.
Dr. J. R. Hobbs (6): Do any of your eight patients have a pre-existing history of gluten response?

Dr. Creamer: Yes. One was a coeliac as a child, and has a family history of coeliac disease in a daughter. He was responsive earlier. One other patient was responsive earlier and then declined to this state. The other six appeared initially to move into it. So, on this evidence, I think it could be just a phase of ordinary coeliac disease.

Paneth Cells

Professor Booth: I think some people might not know what a Paneth cell does. Could you show us what you think happens in a patient with a flat biopsy?

Dr. Creamer: First of all, Paneth cells are down at the bottom of the crypts, and there are millions of them—if you put them together they add up to about the size of the pancreas—so they form a considerable organ. They are all secreting a protein into the lumen of the gut, almost certainly not an enzyme. Recent experiments on animals suggest that they are almost certainly secreting continuously and not just with meals, so they appear to be putting protein into the gut lumen.

Why does this mucosa go flat? Well, the evidence that we have suggests that there is a very fast cell turnover. The D.N.A. shed into the lumen of the gut is enormously increased. Almost certainly there is an analogy with haemolysis: the cells turn over too fast because of superficial damage, presumably because of their sensitivity to gluten, or perhaps to something else. That is why patients with coeliac disease have a flat mucosa, and in coeliac’s Paneth cells are relatively deficient or completely absent.

Professor Booth: You suggest that this patient had a flat mucosa which was partially improved, as we saw from the jejunal biopsy, by treatment with gluten-free diet; but that he developed a much flatter one and became very sick because he lost the Paneth cells in his jejunum.

Dr. Creamer: Well, in association with it. The only other condition in which these cells are known to disappear is kwashiorkor, where they go with unfailing regularity. In the Ugandan series the cells have come back with treatment. I was very intrigued by the appearance of the ileum at necropy, of which I have no experience at all. The patient had had, of course, a vast amount of parenteral protein, and I just wondered if he couldn’t have almost recovered before he was carried off by septicemia.

Dr. Evans: Though the ileum is more photogenic, Paneth cells also appear to be present in fairly large numbers in the jejunum.

Dr. Creamer: The other features that coincide are the only two neuropathies I have seen. They have occurred in the group of patients that have been hypoproteinaemic, and I have always thought of it as a rather beriberi-like protein-wasting neuropathy. So your findings are an immense surprise.

Dr. Neale: You don’t necessarily mean that the neuropathy was due to vitamin B deficiency?

Dr. Creamer: No, the neuropathy is thought to be due to deficiency of nutritional protein rather than thiamine.

Professor Booth: I think the evidence in this patient suggests that whatever was wrecking his mucosa at this stage was not related to the Paneth cell population. He had got Paneth cells, and yet his mucosa was abnormal and he was dying as a result of malnutrition. Does this not suggest the possibility that the Paneth cell failure is simply a reflection of the basic abnormality of the gut rather than a primary phenomenon?

Dr. Creamer: This is an open question. Clearly these patients with gross radiological abnormalities have a very severe and extensive mucosal lesion. Against that, if you count Paneth cells and plot them in normals and coeliacs all the coeliacs have relatively less, because in normal people the longer the crypt the more Paneth cells.

Professor Booth: The other question then is, Was there a sensitivity to gluten in this case, or had the patient developed another sensitivity to something else?

Dr. Creamer: I couldn’t speculate. Clearly the patient was gluten-sensitive in 1952, but I have no idea what was happening later. The only thing that has improved our cases—they have all been gluten-insensitive in this phase—is treatment with corticosteroids. Two died, six have recovered, and of these most became gluten-sensitive again.

Dr. Hobbs: Did the Paneth cells recover?

Dr. Creamer: Oh yes, they all came back.

Professor Booth: So it appears that we are completely at sea over the cause of the gut lesion in this man. This is not like the ordinary coeliac with a response to a gluten-free diet. This is an exception, which in Dr. Creamer’s experience affects about 30% of the patients he sees. I suppose most physicians would have a similar experience.

Dr. Creamer: About 30% don’t respond, but there are other causes of non-response, such as pancreatic atrophy.

Professor Booth: But of some 30% of adult patients who will not respond to a gluten-free diet only a few will be like this, running almost a malignant course resulting in death; and the question we have to ask is what could cause it. Dr. Hatfield, you were this patient’s family physician, would you like to comment on your feelings about this patient?

Psychosomatic Aspects

Dr. F. E. S. Hatfield (7): This case has proved baffling to the physicians, the biochemists, and the pathologists. I would like to suggest that the main reason for this is the inadequacy of the concepts which they are using in their attempted explanations. If we treat a patient as a biochemical machine and exclude any concepts which refer to him as a person, then it seems to me that explanations of his illness must be extremely limited. If we turn our attention to this man’s life picture and what little we know of his inner feelings, this illness becomes much more understandable. Perhaps we should be using more relevant concepts as the basis for our explanations. In this case I know there were major emotional conflicts in all the main areas of his life.

I cannot possibly, in three minutes, describe a man’s life picture, and in any case it would not be fair to publish extensive detail which could be painful to his surviving relatives. I can therefore only touch on a few topics which seem to me to be relevant. The onset of the illness followed the death of his father, an event with which a lot of family feeling was associated. The exacerbation of the illness coincided with the collapse of his work relationship after a long period of devoted service but rising tension and with the marriage of his daughter into a very disturbed family, which he felt to be a disaster. I feel that he died because all that he had lived for had somehow come to nothing.

Professor Booth: Thank you very much. The possibility of a psychogenic influence in coeliac disease has been suggested by Paulley,7 and clearly if the basic abnormality of coeliac disease is due to a genetically determined enzyme defect9 I would find it difficult to believe that psychogenic influences could play much part. It is more likely to be a sensitivity. Do you think that the mucosal lesion was due to an enzyme defect, Dr. Douglas?

Dr. A. P. Douglas (8): No, I don’t. I did not study the patient under discussion today, but I have not found any evidence
of a peptidase defect in other patients with idiopathic steatorrhoea who are in remission.10

Could I ask Dr. Evans if there was any histological evidence of a necrotizing arteritis in the gut which could have produced the clinical picture we saw? In other words, the patient had coeliac disease, responded to gluten withdrawal, and then developed something else on top of it.

Dr. EVANS: I didn't find a necrotizing arteritis in the bowel, and there was no perforated ulcer, which is the classical finding in an arteritis affecting the gut. I am in slight difficulty because of the absence of polyarteritis in parenchymal organs, which is the usual finding when there is muscular involvement.

Dr. DOUGLAS: We did draw attention to one ulcer there.

Dr. EVANS: Yes, but it was a superficial mucosal ulcer. We have seen this previously in patients who have died from idiopathic steatorrhoea. I don't know what causes these ulcers, but I think it would be unjustified to blame an undemonstrated acute arteritis. The other arteries show healed arteritis.

Professor Booth: Coming back to the point that the gut lesion is not due to an arteritis, it may be that the basic abnormality was due to some sensitivity to gluten.

Dr. DOUGLAS: If this was due to a sensitivity to gluten, it is conceivable that even when gluten was eliminated the damage might be so severe that it was self-perpetuating.

Complications

Professor Booth: Passing on now to some of the complications. Hypoproteinaemia, as Dr. Creamer pointed out, seems to be a feature of this sort of patient.

Dr. E. A. JONES (9): The fractional albumin synthesis rate was increased, and this cannot be explained on the basis of malabsorption alone. It indicates that there was probably increased destruction of albumin, almost certainly due to the abnormal loss of plasma proteins into the intestine. In an uncomplicated protein-losing enteropathy plasma proteins which pass into the intestine are digested, and the liberated amino-acids are conserved by reabsorption. The absolute albumin synthesis rate in such a patient tends to be increased. In this particular patient the absolute albumin synthesis rate was within the normal range when expressed in terms of body weight, and low when not expressed in terms of body weight. The fact that this value was not higher is probably a reflection of the inefficient utilization of dietary protein due to the intestinal disease. The determination of the fasting concentrations of the plasma amino-acids is probably one of the best tests for detecting a state of protein deficiency. Almost all the concentrations were appreciably reduced. This pattern is unlike that seen typically in association with dietary protein-calorie malnutrition.11 The concentrations of the amino-acids in the plasma provide no indication of the concentrations of amino-acids at the site of albumin synthesis within the liver cells. Low concentrations in the plasma are not inconsistent with a normal albumin synthesis rate. The low concentrations in the plasma may, however, be consistent with a state of severe protein hypoalbuminemia secondary to intestinal malabsorption. With regard to the urea synthesis rate, patients with dietary protein-calorie malnutrition tend to have diminished urea synthesis, whereas in this malnourished patient it was within normal limits. I would like to suggest two factors which may have been augmenting urea synthesis in this patient. Firstly, there was increased catabolism of plasma proteins in the intestine, and, secondly, there was the deamination of unabsorbed protein, peptides, or amino-acids by the enteric bacterial flora in the colon resulting in the liberation of ammonia, which would subsequently be incorporated into urea.

Professor Booth: Why was the plasma protein level so low if the synthesis rate was apparently normal?

Dr. JONES: The patient was turning over his intravascular albumin pool at an increased rate owing to abnormal loss, but the absolute synthesis rate, though normal, was insufficient to compensate for this; with the result that the pool became depleted, and he developed hypoalbuminaemia.

Professor Booth: Is that all right, Dr. Neale?

Dr. NEALE: Yes. I would like to ask Dr. Jones what interpretation one can give to the fasting plasma amino-acids. The work from South Africa on children's kwashiorkor suggests that fasting plasma amino-acids reflect the dietary protein intake of the patient.12 Immediately the children are given protein the fasting plasma amino-acids return to normal.

Dr. JONES: The timing of the plasma sample in relation to protein intake is most important. For instance, the estimation of the plasma amino-acids may be of no diagnostic value if performed on a child with protein-calorie malnutrition 24 hours after admission to hospital, by which time an adequate protein-containing meal may have been given.

Tests for Protein-losing Enteropathy

Dr. EVANS: I am sorry to be obtuse on this, but are you trying to say there is, in fact, a protein-losing enteropathy here although the 131I P.V.P. test was negative?

Dr. JONES: Yes. I do not think the 131I P.V.P. test is very reliable. The hypoproteinaemia in this patient was probably due to a combination of enteric loss of plasma protein and inadequate synthesis due to malabsorption of nitrogen in a form which could be used for anabolism.

Dr. Hobbs: I would like to return to one point. You thought the phase of lactic acidosis was due to the intravenous feeding. Looking back, in June 1966 the patient had already shown evidence of abnormal liver function; the serum I.C.D. was 26, the 5' nucleotidase 45 i.u., and a bromsulphalein test showed 8% retention at 45 mins. Furthermore, his renal function was suspect; the creatinine clearance was only 50 ml./min., and the urea was running at 42 mg./100 ml. for weeks beforehand. Now, for the three days prior to intravenous feeding this urea steadily came down from 42, 18, 15 to be 10 mg./100 ml. on the morning it started. The bicarbonate had already fallen from 27 to 16 mN, so something had already happened before intravenous feeding started.

Dr. NEALE: Yes. He was now so ill that he had stopped eating. The low blood urea merely reflects the very low protein intake, which was practically nil during that period. The same sort of figures would be found in normal people who stopped eating protein for several days.

Dr. Hobbs: So he was already reaching a crisis before you started your intravenous feeding. I think the lactic acidosis was a reflection of this—he had got into a severe, almost irreversible state, and the fact that you pulled him through was to your credit, because of 26 similar cases of lactic acidosis only three survived. I think the writing was already on the wall before you actually started intravenous feeding. If you hadn't, I think he would have died sooner.

Dr. G. THOMPSON (10): Was not the fatty liver more likely to be due to a protein malnutrition than to alcohol?

Dr. NEALE: I don't think it was alcohol, because the biopsy was taken three weeks after we had stopped Aminosol-fructose-ethanol. We realized that alcohol shouldn't be given to a patient with lactic acidosis. The patient had also had an episode of staphylococcal septicemia before the biopsy was taken.

LIVER IN MALNUTRITION

Professor Booth: Professor Weinbren, would you like to comment on the pathological changes in the liver and their relation to nutrition?
Professor K. Weinbren (11): I agree with Dr. Evans. In this instance I cannot think of any toxic compound or other reason for cells to show mitosis. It is more likely to be a recovery phase. With regard to the inflammatory reaction, I think that it is absolutely right to make the diagnosis of cholangitis or perihepaticitis, and this could well be a result of the septicaemia. All we can say about the liver is that at the stage when we got the first biopsy there was evidence of recovery, and at the end we found the effects of sepsis.

Professor Booth: By “recovery of the lesion” you mean the lesion recovering from the effects of malnutrition?

Professor Weinbren: From the effects of alcohol, probably.

Dr. Neale: Could I follow that up and ask Professor Weinbren about the liver lesion? In patients with severe infection anywhere in the body we may record changes in liver function, and histological examination of the liver will show subacute reactive hepatitis. Are the pericholangiotic changes here a much more severe form of the same pathological process or not?

Professor Weinbren: I don’t think so. The one that we usually record as non-specific does not have this acute inflammatory exudate. This was an acute inflammatory exudate containing mainly polymorphonuclears, and I think this was probably related to the sepsis. Since there was no evidence of purulent intraluminal cholangitis, it is likely to have reflected a general sepsis which had also localized in some foci in the liver.

Neuropathy

Professor Booth: Thank you very much. Then there is the question of the neurological lesions. Dr. Pallis, would you like to take this up?

Dr. C. Pallis (12): The neuropathies complicating coeliac disease have only recently attracted attention, and many physicians may still be unaware of their existence. It might be interesting to consider them in the wider context of the relation of gut disease to disease of the central nervous system.

The association of lesions of the central nervous system (and I emphasize the word central) with disorders of the gastrointestinal tract has been known for a long time. Malabsorption of vitamin B₁₂ is the usual cause, and Addisonian pernicious anaemia the classical example. Malabsorption of vitamin B₁₂ has now been adequately documented as the cause of myelopathy, as follows: in patients with jejunal diverticulosis, fish tapeworm infection, ileal resection for regional enteritis, and intestinal strictures or blind loops.

There are, however, other patients with concomitant intestinal and nervous system disease in whom B₁₂ deficiency does not appear to be the causal link: for instance, the recently described patients with primary amyloidosis, diarrhoea, and neurological signs,¹³ patients suffering from Whipple’s disease complicated by infiltrative cerebral complications or multi-focal leucoencephalopathy,¹⁴ and a small group of patients with jejunal diverticulosis whose myelopathy seems to get worse despite treatment with vitamin B₁₂.¹⁵

It was long doubted whether myelopathy ever complicated tropical sprue, coeliac disease, or idiopathic steatorrhoea.¹⁶ Distal paraesthesia in these conditions were usually correctly attributed to anaemia or hypocalcaemia—or at most to a peripheral neuropathy.

The whole position has recently been revolutionized by a paper summarizing the experience of the Birmingham workers.¹⁷ The authors discuss the severe neurological complications affecting 16 patients with adult coeliac disease. The clinical features suggested peripheral neuropathy in most cases, but three patients also showed cerebellar signs, and one developed signs of “progressive muscular atrophy.” The nine necropsies showed widespread lesions scattered throughout the central nervous system (cortex, hypothalamus, cerebellum, brainstem, and spinal cord) as well as lesions of the sensory ganglia and peripheral nerves. The changes were pleomorphic and resembled in some respects those seen in the carcinomatous neuropathies. On the whole they did not resemble those seen in naturally occurring human deficiency states. The authors could not incriminate B₁₂ deficiency in any of these cases—or, for that matter, any other specific cause. The relation of these severe neuropathies to steatorrhoea remains obscure.

In the case under discussion the neuropathological changes were very scanty both in relation to the florid clinical findings and to the extensive denervation atrophy shown histologically in the muscles. Moreover, the neuropathological abnormalities seem to have been confined to the peripheral nervous system, which is unlike what the Birmingham authors describe. The only central changes—those in the anterior horns—seem to have been secondary to more distal involvement of the peripheral nerves.

The presence of an arteritis in this patient further complicates an already complex situation. I doubt that this arteritis was the cause of his neuropathy, as no arteritis lesions were found in the nerves despite an extensive search. Topographically speaking the arteritis itself seems to have been of a most unusual kind, confined as it was to skin and muscle. Polyarteritis nodosa confined to these tissues (and sparing the viscera) is not a concept I am familiar with. On the evidence available I don’t think one can diagnose the cause of this man’s severe neuropathy.

Professor Booth: Thank you very much, Dr. Pallis. Professor Harrison, do you have any views on this arteritis?

Professor C. V. Harrison (13): I’ve never seen this picture except in polyarteritis.

Dr. Evans: Could I just come back to the paper of Cooke and Smith?¹⁸ Their conclusion was that “little is known of the cause of this disorder. We suspect from the nature and inconsistency of the pathological findings that multiple factors are concerned, and that the relation between steatorrhoea and neuropathy is not to be explained simply as cause and effect.” In other words, they are saying they had described a heterogeneous collection of lesions, didn’t know what caused them, or whether in fact any one thing was responsible. The other point that I would like to stress is that in none of their cases is there the severe degree of neurogenic atrophy of muscle that is present in this case.

Professor Booth: We are left with a puzzle. Dr. Swallow, this was your problem in Chelmford with Dr. Hatfield. Have you anything to add at this stage?

Dr. J. H. Swallow (14): No, I don’t think so. There is, however, one question I should like to ask. Can one relate the prognosis of gluten enteropathy to the degree of histological improvement following the taking of a gluten-free diet for a number of years? Do patients in whom the histological appearances of the small intestinal mucosa return to normal do better than those who do not show such a degree of improvement?

Dr. CREAMER: In my experience there is no relationship at all. Only about half go back to normality; some have a complete remission and stay well in spite of an abnormal biopsy, though the surface cells improve and become more columnar.

Professor Booth: Any final comments there, Dr. Neale?

Dr. Neale: No, except that I remain baffled. I was wondering about the skin lesions. I suppose that clinically they would have done for polyarteritis, though we did not think of this as a possible diagnosis. At the time when the patient had active skin lesions he didn’t have a neuropathy, and the skin healed as the neuropathy developed, which makes things even more difficult.

Professor Booth: We have seen some effects of malnutrition in this patient which I have never seen before; we’ve seen a
gut lesion which none of us can tell you the cause of, and I
think we still remain baffled as to the basic cause of coeliac
disease.

We are grateful to Professor J. P. Shillingford and Dr. E. D.
Williams for assistance in preparing this report, and to Mr. W.
Brackenbury for the photomicrographs.

The appointments held by the speakers at the conference are
listed below:

(1) Lecturer in Gastroenterology, Royal Postgraduate Medical
School.
(2) Reader in Anatomy, University of London.
(3) Professor of Medicine, Royal Postgraduate Medical School.
(4) Consultant Physician, St. Thomas’s Hospital.
(5) Lecturer in Morbid Anatomy, Royal Postgraduate Medical
School.
(6) Lecturer in Chemical Pathology, Royal Postgraduate Medical
School.
(7) General Practitioner, Essex.
(8) Hon. Medical Registrar, Hammersmith Hospital.
(9) Assistant Lecturer in Medicine, Royal Free Hospital.
(10) Late Senior Medical Registrar, Hammersmith Hospital.
(11) Reader in Morbid Anatomy, Royal Postgraduate Medical
School.
(12) Senior Lecturer in Medicine (neurology), Royal Postgraduate
Medical School.
(13) Professor of Morbid Anatomy, Royal Postgraduate Medical
School.
(14) Consultant Physician, Chelmsford & Essex Hospital.

REFERENCES FOR CLINICAL HISTORY

1. Arthur, A. B., Clayton, B. E., Cottens, J. W. T., and
2. Harris, O. D., Cooke, W. F., Thompson, H., and Waterhouse,

REFERENCES

8. Holt, L. E., Snyderman, S. E., Norton, P. M., Rolman, E., and
9. Saunders, S. L., Truswell, A. S., Barbezat, G. O., Wittman, W., and
11. Smith, W. T., French, J. M., Gottsman, M., Smith, A. J., and Wakes-
13. Cooke, W. T., Cox, E. V., Fone, D. J., Meynell, M. J., and Gaddie,

NEW APPLIANCES

The Higgins Extractor

Mr. G. E. Dunkerley, consultant orthopaedic surgeon, Royal Portsmouth Hospital, Portsmouth, writes: The instrument described and illustrated below was designed to facil-
itate the extraction of London Splint Company type Kuntscher nails from the femur.

The idea resulted from advice given by Dr. Anthony Higgins, who saw the method in use while working in the orthopaedic department at the Massachusetts General Hospital, Boston, U.S.A.

A set of three Dormer screw extractors (set C, sizes 4, 5, and 6), obtainable from any engineers’ tool suppliers, price 11s. 6d., forms the basis of the tool, one of which should be made up for each size of extractor. The holder consists of a bright mild-steel sleeve 1 in. (2 cm.) in diameter and 1½ in. (3.8 cm.) long, into one end of which the Dormer screw extractor is brazed and pinned (Figs. 1 and 2). Into the other end of the sleeve is screwed and pinned a bright mild-steel rod ½ in. (1.3 cm.) in diameter, 11 in. (28 cm.) long, which is bent into the shape shown. The whole is then chromium-plated.

In order to remove the Kuntscher nail its tip is exposed at operation and the bolt extractor is screwed into it in an anticlockwise direction. The hold on the nail is then suffi-

Mr. R. F. Manning, engineer, Royal Ports-
smouth Hospital, who also supplied the details of the extractor and the diagram.

FIG. 1

FIG. 2