Clinicopathological Conference

Non-responsive Coeliac Disease

DEMONSTRATED AT THE ROYAL POSTGRADUATE MEDICAL SCHOOL

ARRANGED BY DR. R. H. DOWLING AND DR. KRISTIN HENRY

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Dr. R. H. Dowling (1): Although this morning’s clinicopathological conference is called “non-responsive coeliac disease,” it is not strictly true to say that the disease was non-responsive, but rather that it was resistant to conventional therapy. This also raises the question how one should define coeliac disease.

Case History

The patient was aged 38 when she died in March 1970, after a long and complex illness. The history began in 1961 when the patient was pregnant and anaemic, with a haemoglobin of 58%. At that time she was treated with iron, folic acid, and blood transfusion. In 1963 she again became anaemic during pregnancy and on this occasion she required folic acid treatment alone.

Diarrhoea first began in 1967, when the patient was passing about six pale watery stools per day. A barium follow-through showed only rapid transit of contrast material. Because her diarrhoea settled spontaneously, nothing further was done until, in the next year, the diarrhoea recurred, but now with the characteristics of steatorrhoea: pale, bulky, offensive stools.

In June 1969, when four months pregnant, the patient developed more persistent diarrhoea with vomiting and weight loss. Because of pregnancy further barium studies were not possible and there was no jejunal biopsy. In July she was treated rather empirically with 30 mg of prednisone per day. This made little difference to her diarrhoea but unfortunately treatment was complicated by dyspepsia and two weeks later she developed a severe melaena requiring 16 pints (9 l.) of blood transfusion.

In September 1969 a 7-month-old fetus was delivered by caesarean section. Three days later she again developed a melaena and required transfusion with a total of 30 units of blood. The obvious question was whether the prednisone had induced an ulcer. A further barium meal and follow-through showed oesophageal reflux and dilatation of the small intestine with clumping of barium but no peptic ulcer. Dr. Livingstone from Dorking General Hospital, whom we are pleased to have in the audience this morning, found that the serum albumin was greatly reduced to between 1·0 and 2·1 g/100 ml. The serum alkaline phosphatase was raised (14 King Armstrong units) and there was xylose malabsorption, shown both by blood levels and by urinary excretion. The lactose tolerance test was “flat,” and a Figlu test was positive suggesting folic acid deficiency.

She was therefore diagnosed as having malabsorption of uncertain cause. However, she again improved spontaneously and, since with the help of codeine phosphate or Lomotil tablets her diarrhoea was limited to one or two stools per day, she was discharged from hospital.

In 1969 her symptoms recurred, and over a four month period she had lost about 25 kg in weight, transforming a woman in her mid-thirties into a pale, grey-haired emaciated patient, who looked like a woman of 65. She had had glossitis and recurrent aphthous ulceration. Even with large doses of codeine phosphate she had three bulky semi-formed stools and she had developed gross ankle oedema. At that time she was referred to Hammersmith Hospital. On admission she was obviously very ill. She was pigmented but there was no clubbing of the fingers—a feature particularly described in “resistant” forms of coeliac disease. She had obvious ankle oedema, and although there were neither masses nor enlargement of liver or spleen, she had signs suggesting ascites.

Intestinal Function

The diagnosis at that time was malabsorption due to either coeliac disease or Crohn’s disease, with protein-losing enteropathy to explain the hypoproteinaemic oedema.

Tests of proximal small bowel function showed that she was unable to absorb glucose normally, the peak blood sugar rise is a 50-g glucose tolerance test being only 12 mg/100 ml.
She had a low serum folate at 2 mg/ml (normal 6-0-21-0) despite her daily 5 mg folic acid tablets. Clearly she could not absorb this monogluminate form of folic acid. Again, she had a very low urinary xylose excretion after 25 g of xylose by mouth. She had pronounced diarrhoea, the average stool wet weight being 1,000 g/day (normal<150 g/day) with steatorrhoea, the faecal fat values ranging between 15 and 40 g/24 hours when the dietary fat intake varied between an estimated 20 g/day (restricted fat intake coupled with anorexia and vomiting) and 70 g/day. She was also losing excess nitrogen in her stools (4-8 g/day on 70-g dietary protein intake).

The urinary indican of 148 mg/24 hour was only mildly raised (normal less than 100 mg/24 hours) and was quite compatible with the degree of malabsorption. It presumably indicated spill-over of unabsorbed hydrolysed protein into the colon, where the colonic bacteria break down tryptophan.

The extent to which coeliac disease also involves the distal small bowel varies from case to case. The Schilling test showed that this patient also had ileal disease: she completely failed to absorb vitamin B₁₂, either when given alone (0-08% of dose excreted in urine/24 hr) or with intrinsic factor (0-16%), suggesting that the coeliac disease involved the entire small intestine. Dr. Doe confirmed the presence of gross protein-losing enteropathy, about 10% of a dose of intravenous chromium-51 chloride being excreted over a 5-day period (normal <1%).

**Complications and Associated Diseases**

**LIVER DISEASE**

In addition to hypoalbuminaemia, the prothrombin time was 26-35 sec (control, 11-13 sec) which responded initially to treatment with vitamin K. There was also severe deficiency of factors VII, IX, and X. She had a very low serum cholesterol level (55-56 mg/100 ml), which is hardly surprising in such severe malabsorption, particularly with ileal involvement. The serum alkaline phosphatase was still raised (22 KAU), and, since the serum 5-nucleotidase level of 31 IU (normal, 2-17) was also raised, probably at least some of the alkaline phosphatase rise was due to liver disease rather than to bone disease. There was marked retention of bromosulphthalain (35% at 45 min). However, smooth muscle, antinuclear factor, and mitochondrial antibodies were negative, as was Australia antigen, and the liver scan was normal.

**Pancreatic Function**

Pancreatic function was checked (by Mr. Luis Gutierrez, of the Department of Surgery) in two different ways: firstly by giving a Lundh test meal by mouth and then by giving intravenous secretin. During the two-hour period after the test meal both the peak tryptic activity of 7-6 μEq/min/ml (normal, 15-5-395) and the mean tryptic activity of 4-6 μ Eq/min/ml (normal, 9-6-20), were well below the normal values, suggesting pancreatic insufficiency. However, when 1 unit of Boots secretin/Kg was given intravenously, the maximum concentration and peak output of bicarbonate at 103 Eq/l. and 27-3 Eq/hr were normal and the volume of duodenal juice was abnormally high, showing that with the appropriate signal, the pancreas responded normally. We think that the diseased proximal intestine here was incapable of releasing the "trigger" enzymes secretin, pancreozymin, and perhaps also enterokinase in response to the test meal but that with the appropriate signal, intravenous secretin, the pancreas responded normally. This secondary form of pancreatic hypofunction is now well recognized in coeliac disease.

**Metabolic Bone Disease**

The patient had "tetany"—no frank tetanic spasm, but simply tingling around the mouth—positive Chvostek and Trouseau's signs, and serum calcium levels as low as 3-5 mN. She was obviously conserving calcium as avidly as possible, the urine calcium being only 0-3-0-6 Eq/24 hours. Serum phosphate levels were somewhat low (1-4-1-8 mN) and she also had hypomagnesaemia—a level of 0-9 mN being recorded on one occasion.

The radiologist's report suggested that there were no bone changes on x-ray examination, but Dr. Joplin thought that there was possibly a pseudo-fracture in the ilium. There were no changes of secondary hyperparathyroidism, but after a 1-mg intravenous dose of vitamin D the serum phosphate level rose by 20% over a five-day period and subsequently by 33% over the next few days—biochemical evidence that the patient did have osteomalacia, as well as tetany.

**Treatment and Progress**

The patient was treated with a gluten-free diet and her tetany was managed symptomatically with intravenous calcium gluconate and magnesium chloride infusions, and later with calcium by mouth in the form of Sandocal tablets—though this tended to aggravate her diarrhoea. Osteomalacia was treated with intravenous vitamin D, which also helped to alleviate the hypocalcaemia and signs of tetany. The response to the 1-mg dose of vitamin D should normally have lasted...
somewhere between three and six months, but her tetanic symptoms recurred after one month and she required a further dose of intravenous vitamin D. This relapse-remission pattern of “tetany” responding to vitamin D at monthly intervals happened on three different occasions.

We were also concerned about the severe hypoproteinaemia lest she was developing a secondary type of kwashiorkor, which may rarely occur in severe intestinal disease. She was given salt-poor albumin infusions and fortunately her serum albumin gradually responded. In spite of many setbacks and complications, she slowly improved over the next two months and her liver function tests returned to normal.

**Gluten Challenge**

In November 1969, she had a temporary relapse after accidentally being given gluten. A further jejunal biopsy showed marginal evidence of improvement on dissecting microscopy. This was particularly encouraging, since we know that in coeliac disease healing begins in the distal small bowel and proceeds proximally, and here, in spite of extensive disease, the jejunal biopsy seemed to show improvement. She was allowed home for Christmas. But while at home the patient ate a tin of ravioli—which, of course, is a rich source of wheat flour—and she again deteriorated with abdominal pain, vomiting, and tetany, which led to her readmission in early January 1970. Once again, she was given gluten accidentally; a ward orderly thought that her special lunch looked unappetizing and added gravy which had been thickened with flour, with the inevitable consequences. This illustrates the deleterious effects of trace amounts of gluten in some coeliac patients.

Dr. Joplin and his team measured calcium absorption and bone turnover using a double isotope technique—⁵⁷Ca by mouth, ⁴⁰Ca given intravenously. The test was designed to differentiate between endogenous calcium loss and malabsorption of exogenous dietary calcium.

The patient showed a tremendously increased avidity of bone for calcium but, surprisingly, calcium absorption was only marginally low. Of even greater interest, there was evidence of “calcium-losing enteropathy”: calcium pouring out of the gut in much the same way that she was losing protein.

In February and March there was a progressive downhill course. There were repeated episodes of subacute intestinal obstruction.

**Terminal Infections**

**DR. DOWLING:** Because of these repeated episodes of vomiting we had to treat the patient with intravenous nutrition, using vena caval catheters. She developed a urinary infection, which was treated with ampicillin. Later she developed a staphylococcal sepsicaemia, possibly related to the superior vena caval catheter in the neck, since swabs from this area grew staphylococci. This was a penicillin-resistant staphylococcus, which was treated with methicillin and gentamycin, and I think we did manage to get on top of the staphylococcal sepsicaemia before the patient died.

She developed severe pain in her mouth due to florid herpes of the lip, hard palate, nose and nasal septum. Since the distribution of this herpetic lesion was in the maxillary division of the 5th cranial nerve, we diagnosed herpes zoster, although this was not correct. However, an electronmicrograph of fluid taken from one of the vesicles in the patient’s mouth was absolutely characteristic of the herpes virus (Fig. 1). Unfortunately, it is impossible to distinguish between simplex and zoster on morphology alone, as both virus types appear identical.

**Clinical Diagnoses**

1. Extensive coeliac disease which was resistant to treatment both with a gluten-free diet and with corticosteroids.
2. Protein- and calcium-losing enteropathy.
3. Recurrent tetany associated with both hypocalcaemia and hypomagnesaemia.
4. Possible osteomalacia.
5. Raised serum IgA levels, possibly associated with lymphoma.
Portal inflammation and fibrosis of the liver with terminal hepatic coma, coagulation defects, and gastrointestinal haemorrhage.

Widespread infection with staphylococcal septicaemia, and herpes as terminal complications.

Pathological Aspects

Review of Biopsies

DR. K. Henry (3): The liver biopsy showed very extensive fatty change throughout the liver lobules, together with portal tract fibrosis, infiltration with inflammatory cells, and bile ductular proliferation. The cellular infiltrate was composed predominantly of polymorph neutrophils, with some mononuclear cells including an occasional plasma cell. The limiting plate was quite regular, and there was no evidence of an active chronic hepatitis.

The initial jejunal biopsy showed a very flat mucosa with no villi and with flattened enterocytes showing stratification of the nuclei. In addition there was an extensive mononuclear infiltrate of predominantly plasma cells with a few lymphocytes within the lamina propria. After a gluten-free diet the jejunal mucosa (Fig. 2) did show slight improvement, particularly in the height of the enterocytes. One could see a few stumpy villi, and this appearance corresponded well with those seen under the dissecting microscope.

Immediately after her death, samples of jejunum and ileum again showed extreme flattening of the mucosa with no villi and shortened enterocytes. A striking feature was the very prominent submucosal oedema. The muscularis propria was atrophic.

Necropsy Findings

The body was that of a grossly emaciated woman, weighing only 38 kg, although her height was 172 cm. Apart from a chronic herpetic ulceration of the right nostril and mouth, with extension on to the soft and hard palate, predominantly on the right side, the main findings were confined to the alimentary tract.

Small Intestine.—This longitudinal whole section mount of jejunum (Fig. 3) showed extensive submucosal oedema and a striking variability in the villous architecture—areas of complete flattening interspersed with areas of partial villous atrophy and yet other areas showing fairly reasonable-looking villi. There were some superficial ulcers. There was also prominent sub-epithelial hyalinization (Fig. 4), a feature initially described by Schein in patients with non-tropical sprue.2

In contrast to the jejunum, numerous punched out ulcers were found in the distal 65 cm of ileum (Fig. 5a), the largest measuring 4 cm in the long axis. One deep ulcer 40 cm from the ileocecal valve extended through to the serosa and was associated with fibrosis.

Large Intestine.—The large intestine was also involved in the ulcerative process. The ascending colon was irregularly dilated and thin-walled, and showed several transversely situated ulcers. The sigmoid colon was similarly involved (Fig. 5b) and like the rectum contained fresh blood.

Microscopical examination of the small and large bowel ulcers showed non-specific inflammation in a few. Most, however, presented a rather distinctive appearance, with a superficial zone of polymorph neutrophils overlying a mononuclear infiltrate of histiocytes and lymphocytes (Fig. 6) and endothelial swelling in adjacent capillaries. The ulceration was associated with some fragmentation of elastic fibres. Gram stains showed no organisms other than occasional Gram-positive cocci. Some ulcers had undergone healing.
Some sinuses were dilated and contained many large mononuclear cells showing an increased mitotic activity consistent with a virus infection. The spleen (210 g), though enlarged, appeared macroscopically normal, and histologically showed a few small foci of necrosis with an increase in polymorph neutrophils.

Skeletal System.—Decalcified sections of vertebra and iliac crest did not show evidence of osteomalacia or secondary hyperparathyroidism. No undecalcified bone was available.

Endocrine System.—Only one of the four "parathyroids" identified was genuine. This was not enlarged but did show loss of its normal fatty component.

Respiratory System.—There were pulmonary emboli with bilateral basal infarcts. There was also acute purulent bronchitis, broncholitis, and bronchopneumonia with secondary infection with Aspergillus fumigatus.

Cardiovascular System.—The heart was normal. Right femoral vein and bilateral subclavian vein thromboses were present.

Central Nervous System.—The brain (1,340 g) was macroscopically normal, but on microscopical examination showed Alzheimer Type II astrocytes consistent with the effects of hepatic coma.

Liver (1,545 g).—The cut surface was deep yellow colour and showed multiple 2-8 mm circumscribed depressed areas of necrosis (Fig. 7), appearances strongly suggestive of the necrotic lesions found in herpes simplex hepatitis; hence a sample of liver was sent to the department of virology for culture. Microscopy showed severe fatty change, portal fibrosis, and pericholangitis (similar to that seen in the liver biopsy) as well as numerous areas of coagulation necrosis (Fig. 8). In some of the immediately adjacent viable liver cell nuclei eosinophilic inclusions indicative of herpes infection were seen (Fig. 8 inset). The results of cell culture by the department of virology and the electron microscopic demonstration of intranuclear herpes virions in tissue-culture cells infected with one of the liver lesions (circled). (X 16,915.)

This contained numerous stones of pigment type. The wall was thickened and microscopy showed changes of chronic cholecystitis.

Reticulo-Endothelial System.—There was no macroscopic evidence of intra-abdominal lymphoma. Indeed the abdominal nodes were atrophic and fibrotic. The hilar and cervical nodes were a little soft but were not enlarged. Microscopy showed no destruction of nodal architecture, but the lymphoid follicles were poorly developed and lacked germinal centres.

Liver. This field in addition to the definite fatty change shows an area of necrosis, at the periphery of which eosinophilic intranuclear inclusions (inset) could be identified.

Liver. Whole-section mounts of intestine with ulcers in ileum (a) and sigmoid colon (b).
**Pathologist's Diagnosis**

1. Villus atrophy in resistant adult coeliac disease.
2. Ulceration of small and large intestine—probably due to intercurrent infection.
3. Herpes simplex hepatitis together with fatty change, pericholangitis and fibrosis.
4. Cholecystitis and cholecystolithiasis.
5. Acute bronchitis and bronchopneumonia and secondary aspergillosis infection.
6. Pulmonary emboli and infarction.
7. Right femoral vein thrombosis and bilateral subclavicular vein thromboses.
8. Terminal intestinal haemorrhage and hepatic coma.

I believe that this woman did suffer from adult coeliac disease and that the course of her illness was modified by the intestinal ulceration. There is no evidence of lymphoma, amyloid, vasculitis, or ischaemia as a cause of these ulcers. Steroids are an unlikely cause since she was only on these terminally and the ulcers were at various stages of evolution. They may well, like the necrotic hepatic lesions, be related to disseminated herpes simplex virus.

**Discussion**

**DR. DOWLING:** Considering the basic pathology here—the intestinal disease—perhaps we should consider: (1) whether we are dealing with coeliac disease, and why the patient did not respond adequately to a gluten-free diet; (2) the intestinal ulceration; and (3) the liver disease.

**SMALL BOWEL ULCERATION**

Many of the possible causes of ulceration of the small intestine (Table) are not relevant to the present patient. We can obviously exclude ectopic gastric acid production, a Meckel's diverticulum, or a Zollinger-Ellison syndrome. Crohn's disease and tuberculosis are clearly not likely. What about dysentery, particularly typhoid, although any type of baccillary dysentery may produce small bowel ulceration? The stools were cultured, looking both for dysenteric organisms and parasites, but none were found. Coeliac disease, which is what we believe the patient had, and tropical sprue can both produce ulceration in the small intestine. Small bowel ulceration in coeliac disease was first described in 1927 and since then about 20 cases have been described. Interestingly enough, the last two Conference of Clinicalopathological Conferences dealing with coeliac disease which were held here at the Royal Postgraduate Medical School described patients both of whom had disturbances of liver function and ulceration in the small intestine. We do not think there was any evidence of ischaemia, and while Dr. Henry mentioned that subjacent to some areas of ulceration there were changes in the capillary endothelium, I do not think there was evidence of ischaemia—either vascular occlusion or arteritis. Is that correct, Dr. Henry?

**DR. HENRY:** Yes.

**DR. DOWLING:** Dr. Henry mentioned that there were foci of lymphocytes and histiocytes adjacent to the ulceration, and Hourihan and Weir have also described lymphomatous foci in association with ulceration in coeliac disease. They suggested that many of the previously reported cases of ulceration of the small bowel in coeliac disease were associated with lymphoma, so this is obviously a controversial issue.

Many of you will wonder whether this patient was treated with diuretics and potassium supplements, and the answer is "Yes". Did she have enteric-coated potassium (the main drug responsible for producing intestinal ulceration)? The answer is "No". She did, in fact, have effervescent potassium tablets, but we do think this is likely to have produced her distal small bowel and colonic ulceration. Corticosteroids, of course, can produce intestinal ulceration but the distribution of ulcers seen in this patient has not been described after steroids.

**DR. HENRY:** With regard to the presence of lymphoma, in the cases so far reported of lymphoma associated coeliac disease either the abdominal lymph nodes were involved or, if not, there was a definite localized tumour within the small bowel. Neither of these findings were present in this patient. However, the appearance of the cellular infiltrate in the base of the ulcers does resemble that seen in a progressive (lymphoid) hyperplasia of the small intestine described by Whitehead in which condition some patients did subsequently develop a true lymphoma.

Returning now to the ulcerative process occurring in this patient, we must remember that there was ulceration not only of the small intestine but of the large bowel as well, and this latter finding has not been described previously as a complication of coeliac disease. In the only one of the 20 cases reviewed by Bayless et al. was the large bowel involved, and this was a patient reported by Himes et al., in whom there were a few superficial erosions of the colon. As to the question of the aetiology of these ulcers there appear to be three main possibilities. These are either that the ulceration is a direct complication of coeliac disease itself, or that the whole illness is an as yet undefined entity masquerading as coeliac disease, or lastly, and in my view the most likely, that the ulcerative process is due to an intercurrent infection such as herpes simplex.

**VASCULITIS**

**DR. DOWLING:** Dr. Doe, there was no evidence of vasculitis in this case, but you have studied some other coeliac patients with vasculitis who had cryoglobulinaemia.

**DR. W. F. DOE (4):** We studied four such patients. Two of these patients were, clinically at least, similar to the case being discussed today. Each had initially responded clinically and morphologically to gluten withdrawal and each subsequently relapsed and died with unresponsive coeliac disease following accidental gluten challenge. At necropsy one of these patients had jejunal ulceration and it was suggested that the deposition of immune complexes had initiated a vasculitis and may have contributed to the jejunal ulceration. However, in today's case there was no evidence of vasculitis and no search for cryoglobulins was made during life.
DR. D. J. EVANS (5): You have not really established by strict criteria that this patient has adult coeliac disease. All that you have established is that her hospital diet was not gluten-free, and that she had a flat mucosa.

DR. DOWLING: I would like to return to this important point at the end if our discussion, but first, could we move on to the question of liver disease.\(^2\) We have seen liver disease in patients with coeliac disease occasionally in the past, and I wonder if Dr. Neale would care to comment on this.

DR. G. NEALE (6): I do not think there is any literature on this. Quite clearly this patient was extremely malnourished and this would explain the fatty infiltration. The pericholangitis is found in many conditions, particularly inflammatory bowel disease. But the necrotic lesions are most unusual. Dr. Henry has shown these to be due to the herpes virus, and I would welcome the virologists’ comments on whether the patient may have had an overall deficiency in immune response which allowed the virus to behave in this aggressive manner.

PROFESSOR A. P. WATSONER (7): This is the picture of herpes hepatitis, which is seen usually only in infancy. Of the very few reported cases of a frank herpes hepatitis in adults, one was a woman who was 28 weeks pregnant at the time of clinical onset.\(^3\) It may be argued that there is a link with this case in that the steroid physiology is different in pregnancy and that today’s patient was under treatment with steroids. However, I think the link in this case is with malnourished children with kwashiorkor, in whom a similar condition may occur not only in infancy, but up to several years of age. Here we have a severely malnourished woman, with several adventitious conditions, under treatment with corticosteroids, and—as many people harbour herpes simplex virus asymptomatically—it is not surprising that a frank clinical manifestation of the infection occurred. Those who saw the patient during her life without knowing her age must have been astonished to find that she was only 38. I think that sums up the pathogenesis from the virological viewpoint.

VOICE FROM AUDIENCE: May I ask what is the immune mechanism that stops herpes virus breaking out in the population in general?

DR. JUNE ALMEIDA (8): The immunology of recurrent herpes simplex is not fully understood and what is known appears paradoxical. Those who suffer from recurrent herpes have good titre of neutralizing antibody to the virus while those who do not suffer from the condition have no antibody to it.\(^4\) One could suggest that those who have recurrent attacks, and also have antibody, live in a state of cold war with the virus and when something happens to upset the balance of virus and antibody then the virus is expressed. It is during times of stress, or infection with some other organism, that herpetic attacks occur.

DR. G. POSTE (9): Although the clinical presentation was certainly suspicious of herpes zoster, the characteristics of the isolated viruses were clearly those of herpes simplex. Typically intranuclear inclusions and multinucleate cells were found in the infected cell cultures. However, the principal characteristic which gave it away as herpes simplex is the speed at which these cytopathic effects appeared after infection of the cell cultures.

BONE DISEASE

DR. DOWLING: Turning now to the bone disease, recurrent tetany, the magnesium problems, and the calcium-losing enteropathy from which the patient suffered—Dr. Joplin, would you care to comment about this?

DR. G. F. JOPLIN (10): The normal range of endogenous faecal calcium is 4 to 10 milliequivalents a day. A group of nine consecutive untreated coeliacs\(^6\) showed a mean of 16 mEq/day for this endogenous loss from the gut, while today’s case was losing about 25 milliequivalents a day—which is about as much as some of us are taking in our total day’s ration by mouth. This same group of nine patients all had a high trapping metabolic turnover of the skeleton as shown by 47 Ca; today’s patient was found fairly typical of the coeliac population. The cause of this high trapping of calcium isotopes is very complicated, but it is an invariable association with vitamin-D-deficiency osteomalacia. So as we have no other explanation for this high turnover (such as Paget’s disease or thyrotoxicosis) it almost certainly represents a degree of osteomalacia.

The last point is her calcium absorption. In comparison with normal subjects, today’s case shows a very low absorption figure indeed. Nevertheless, some absorption was occurring, possibly correlating with Dr. Henry’s finding that at necropsy some villi were histologically fairly normal. Her major problem was with the gut loss. The magnesium problem is an allied one; she probably malabsorbed magnesium in the presence of a low vitamin-D—which she must almost certainly have had at one stage—and this was rectified by intravenous infusions.

DR. DOWLING: Could we return to Dr. Evans’s question—did this patient in fact have coeliac disease? We may define coeliac disease by two criteria: firstly, that the patient should have the characteristic morphological changes on jejunal biopsy (which were present here); secondly, that there should be an unequivocal response to gluten withdrawal from the diet. Perhaps one might add a third criterion—that the patient will relapse when challenged by reintroducing gluten to the diet. Although the evidence is marginal, this patient did show some initial improvement on a gluten-free diet; she started to grow stunted villi, and her enterocytes started to increase in size. Furthermore she relapsed on three occasions when inadvertently challenged with gluten. So I think we can call this coeliac disease.

RESPONSE OR NOT?

DR. NEALE: Can we really say that there was a morphological response when Dr. Henry has shown us so beautifully how variable mucosal appearances may be over a very short segment of jejunum.

DR. HENRY: This is a difficult question. The immediate post-mortem section of jejunum certainly showed a completely flat mucosa, but looking at a longitudinal section of jejunum taken at necropsy (the immediate post-mortem samples being transverse sections), you saw how there were runs of flat mucosa alternating elsewhere with a more lumpy appearance and even occasional small villi, and how small focal areas of superficial ulceration were also present. To me the important factor was that there seemed to be an improvement in height of the enterocytes after gluten withdrawal.

DR. NEALE: Could the ulceration have been due to infection?

DR. HENRY: That would be the most likely diagnosis.

DR. DOWLING: I am sure that we learn much more by examining cases such as this where the clinical picture does not conform to the expected pattern or where treatment has failed, than from patients with textbook stereotype of disease, which behave in a predictable way. Thank you very much.
**Hospital Topics**

**Late Embolectomy**

**W. T. MORRIS**


**Summary**

Embolectomy with a balloon catheter even up to two months after embolism may be successful. Late embolectomy, meaning operation more than 48 hours after embolism, should be undertaken in a hospital where all facilities for arterial reconstruction are available.

**Introduction**

The earlier arterial emboli are removed the better the prognosis for the ischaemic tissue. Martin, King, and Stephenson found that when embolectomy was performed within 48 hours of embolism the ischaemic symptoms were relieved in 92% of the patients, but in only 70% after 48 hours. There have been many records of successful late embolectomy. Spencer and Eiseman performed eight successful embolectomies by instrumentation and flushing eight hours to 21 days after embolism. Cranley, Krause, Strasser, Hoffner, and Fogarty claimed that 10 out of 11 embolectomies by balloon catheter done between four days and one month after embolism were successful. Hepp and Klaüs recorded that seven out of 17 patients who had had late embolectomies "were discharged with healed extremities." Tarnay gave an account of 21 embolectomies performed later than 24 hours after embolism. Of the 21 patients nine were improved and in five the peripheral pulses were restored. Similarly Mlliken recorded four successful embolectomies performed five days to three months after embolism.

It does not seem to be generally accepted, however, that late embolectomy with a balloon catheter can succeed. We think it should always be attempted when the limb is viable and the state of the patient allows it. Tsapogas, Kakkar, and Gleave stated that embolectomy is the treatment of choice up to 48 hours after embolism but that conservative measures should be used after this time. Some widely read textbooks still suggest that to be successful embolectomy must be performed early. Bailey and Love's *Short Practice of Surgery* advises embolectomy if a main artery is affected, if the patient is fit for operation, and, generally speaking, within 10 hours of the emergency, thus implying that it is not

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**References**