A case of unexplained gastrointestinal protein loss

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EDITORIAL SYNOPSIS This is a well-documented case report of a patient with the extremely rare condition, idiopathic protein-losing enteropathy without lymphangiectasia. A necropsy report is included.

Excessive leakage of plasma proteins into the gastrointestinal tract has been shown to be the cause of ‘hypercatabolic’ hypoproteinaemia when this is not explicable by proteinuria or exudative skin lesions (Citrin, Sterling, and Halsted, 1957; Steinfeld, Davidson, and Gordon, 1957; Gordon, 1959). Gastrointestinal protein loss is the principal functional abnormality in patients with giant hypertrophy of the gastric mucosa (Citrin et al., 1957) and intestinal lymphangiectasia (Schwartz and Jarnum, 1959). It also occurs to a variable, but usually lesser, extent in many neoplastic, malabsorptive, inflammatory, and granulomatous diseases of the stomach (Jarnum, 1961b) and intestine (Steinfeld et al., 1957; Holman, Nickel, and Sleisenger, 1959; Parkins, 1960; Jeejeebhoy and Coghill, 1961). Mild gastrointestinal protein loss has been demonstrated in some diseases, such as pancreatic and post-gastrectomy steatorrhoea, which do not grossly affect the gastrointestinal mucosa (Jarnum, 1961b). Davidson, Waldmann, Goodman and Gordon (1961) have described the syndrome in severe prolonged congestive heart failure, but no such loss is found in patients with hepatic cirrhosis (Jarnum, 1961b; Rubini, Sheehy, Meroney, and Louro, 1961).

This report describes a patient with severe intestinal plasma protein loss for which no cause could be found.

CASE REPORT

The patient was a tug-boat captain who was born in India of English parents in 1915. During his early life he had three notable illnesses: in the first he had recurrent bouts of vomiting and swelling of the legs when at school in Britain, then when aged 15 he had an attack of rheumatic fever from which there were no sequelae, and finally, while a merchant seaman in the Far East at the age of 21 he had a serious illness with violent indigestion and considerable oedema causing him to be returned to Britain, by which time he had recovered without treatment. The patient thereafter remained well until the onset of his final illness at the age of 44, in 1959. From that time he had persistent oedema of the legs except when treated with diuretics for two periods. Frequently, exacerbations of the oedema seemed to occur after a bout of vomiting and abdominal discomfort, and were followed by profuse diarrhoea, which was usually watery, although occasionally the faeces were pale, bulky, and offensive. During this period the serum albumin ranged from 1·8 to 2·3 g./100 ml. Two months before his final admission to hospital in November, 1963, he fractured the body of the fourth thoracic vertebra when he fell down a few steps. A month later the patient noticed paraesthesiae of the hands and feet and mild tetanic spasms of the hands.

On admission, the patient had oedema of the legs and lower trunk, moderate ascites, but no pleural effusion. There was generalized wasting of the muscles. The liver was palpable 3 cm. below the costal margin; it was smooth, rather firm and not tender, but the spleen was not palpable and the superficial lymph nodes were not enlarged. The jugular venous pressure was not raised, and clinical examination of the heart and peripheral vessels were normal except that the blood pressure was 100/60 mm. Hg and fell to 80/55 mm. Hg when standing upright. There were no skin lesions and the urine was free from protein. His height was 1·68 m. and his weight, when almost free from oedema, 49 kg. The dietitian (Dr. J. Woodhill) assessed that the patient's diet was normal and contained 90–100 g. protein, about 0·9 g. calcium, and 150 ml. alcoholic spirits daily.

LABORATORY INVESTIGATIONS Haemoglobin was 17·0 g.%, total leucocyte count 3,500/c.mm. (lymphocytes 455/c.mm.); blood urea 35 mg.%, serum K+ 3·5, Na+ 136, Cl− 92, and HCO−3 35 mEq./l.; serum bilirubin 0·2 mg.%, alkaline phosphatase 5 K.A.u.%, thymol turbidity 1 u., zinc sulphate turbidity 0·1 u., bromsulphalein retention 0·1 mg.% (= 1% of dose) at 30 minutes. The Mantoux test (1 : 100) was negative. The ascitic fluid was chylous in appearance and had a protein content of 630 mg.%. Culture for mycobacteria was...
negative. A chest radiograph showed a normal heart shadow, clear lung fields, and no visible lymph node enlargement. An E.C.G. showed no abnormality.

Protein metabolism Serum albumin level was 1·8 g.\% and globulin 1·7 g.\%; the electrophoretic pattern showed reduction of all globulin fractions. Albumin turnover was measured using the method of Jeejeebboy and Coghill (1961) modified in that Deacitide FF resin (Permutit) was given orally instead of Amberlite IRA-400. This study showed that the total body albumin content of the patient was reduced to less than half of normal, and that this change was due to an excessively high daily degradation rate for albumin of 0·63 g./kg. body weight compared with the normal 0·16 g./kg. (Table I). Faecal excretion of \(^{131}\)I albumin marker accounted for more than half of the total albumin degradation.

<table>
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<tr>
<th>TABLE I</th>
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<tr>
<td>ALBUMIN Turnover</td>
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<table>
<thead>
<tr>
<th>Patient</th>
<th>Control</th>
<th>Normal*</th>
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<tr>
<td>Serum albumin (g.%)</td>
<td>1·82</td>
<td>3·51</td>
</tr>
<tr>
<td>Total circulating albumin (g./kg. body weight)</td>
<td>0·69</td>
<td>1·54</td>
</tr>
<tr>
<td>Extravascular albumin (g./kg. body weight)</td>
<td>0·94</td>
<td>2·61</td>
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<tr>
<td>Total body albumin (g./kg. body weight)</td>
<td>1·63</td>
<td>4·15</td>
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<tr>
<td>Measured faecal albumin loss (g./kg. body weight/day)</td>
<td>0·35</td>
<td>0·18</td>
</tr>
<tr>
<td>Metabolic degradation rate of albumin (urinary (^{131})I) (%)</td>
<td>2·0</td>
<td>11·9</td>
</tr>
<tr>
<td>(g./kg. body weight/day)</td>
<td>0·28</td>
<td>0·16</td>
</tr>
<tr>
<td>Albumin half life (days)</td>
<td>1·8</td>
<td>1·59</td>
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1 Patient convalescent from uncomplicated myocardial infarction tested with the same batch of \(^{131}\)I albumin at the same time as the patient.


A barium meal and small intestinal barium study (Fig. 1) showed thickened mucosal folds at the lower end of the oesophagus, normal stomach, grossly thickened mucosa in the second part of the duodenum, and some flocculation in the small intestine.

A jejunal biopsy was normal.

A liver biopsy showed multiple small granulomata but no caseation or acid-fast bacilli were seen. There were considerable haemosiderin deposits in liver cells but no excess fibrosis.

Tests for malabsorption The blood glucose level (Hagedorn and Jensen) was fasting, 97 mg.\%, and after 50 g. orally, 183 mg.\% at 30 min. and 97 mg.\% at two hours. The plasma xylose level 30 min. after 25 g. orally was 32 mg.\% (normal). Bone marrow iron stores were normal.

Serum folate was 3·8 m\(\mu\)g./ml. (L. casei assay; normal > 3·5), H\(^3\) folate absorption 36\% of oral dose (normal > 25\%). The serum B\(_{12}\) level was 376 m\(\mu\)g./ml. determined by Euglena gracilis assay (normal > 150) and in the Schilling test 3\% (0\% after intrinsic factor) of the oral dose of vitamin B\(_{12}\) was excreted in urine in 48 hours. Faecal fat when the intake was about 50 g./day was 7·3 g./day based on a three-day collection.

Serum vitamin A when fasting was 0, and four hours after 105 g. orally 76 m\(\mu\)g.\% (normal > 150).

Prothrombin time was 26 sec. estimated by the Quick one-stage method (normal 14 sec.).

The serum calcium level was 5·5 mg.\% and urinary calcium 3·76 mg./day.

A bone biopsy showed osteoporosis but no widened osteoid seams.

![Barium study of stomach and small intestine.](http://gut.bmj.com/content/6/2/146)

**FIG. 1.** Barium study of stomach and small intestine.

**Gastrointestinal structure** A barium meal and small intestinal barium study (Fig. 1) showed thickened mucosal folds at the lower end of the oesophagus, normal stomach, grossly thickened mucosa in the second part of the duodenum, and some flocculation in the small intestine.

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**Course** The patient became almost free of oedema when he had lost 15 kg. after treatment with mersalyl, oral diuretics, and spironolactone for three weeks. Human serum albumin (50 g./day) was given for two weeks, but as the patient's serum albumin remained at 1·7 g.\% 150 g. albumin in concentrated solution was infused in 600 ml. fluid over a period of 12 hours. Immediately the patient suffered profuse watery diarrhoea with fever and the blood pressure fell to unrecordable levels. Several blood cultures were negative. He was treated with intensive intravenous fluid therapy, including more albumin. Prednisone 40 mg./d. was given for 10 days, but the diarrhoea persisted and became very much worse two weeks after his collapse. He developed oligoamic shock with anuria, and died a week later, despite further intensive therapy.

**Necropsy** (Dr. A. G. Liddeelow) There was generalized oedema and free fluid in the pericardial (50 ml.), pleural (right 600 ml., left 500 ml.), and peritoneal (600 ml.) cavities. On macroscopic examination, the stomach and
intestines were oedematous, but otherwise normal. There was no dilatation of lymphatic channels in the intestinal wall or mesentery and no enlarged lymph nodes in the abdomen, thorax, or any superficial group. Dissection of the posterior mediastinum revealed no tumour, lymph node enlargement or fibrosis in the course of the thoracic duct. The liver was enlarged (2,180 g.) and smooth on both external and cut surfaces. The portal vein and its tributaries and the spleen (150 g.) were normal, as was the pancreas. The adrenals were rather enlarged (combined weight 39 g.), and showed considerable areas of necrosis and haemorrhage, but there was an appreciable amount of surviving cortical tissue. The heart (280 g.) and great vessels were normal. Microscopical examination of the small intestine (preserved by formalin introduced immediately after death) showed no abnormality other than oedema of all coats and a few rather engorged lymphatics in the submucosa (Fig. 2). In particular there was no lymphatic dilatation in the serosa or villi, which were of normal length and shape, there was no cellular infiltration of the mucosa and there were no pigment deposits in the muscular layer. The mucosa of the stomach and large intestine was normal. The kidneys showed the histological changes of 'renal tubular necrosis'.

**DISCUSSION**

The findings during life and at necropsy clearly rule out any known cause of protein-losing enteropathy in our patient. The granulomata in the liver were presumed to be sarcoid. Because no granulomata were found elsewhere, and because there was no evidence of either impairment of liver function or of portal hypertension we believe that the gastrointestinal protein loss could not have been due to this disease. Most patients with 'primary' protein-losing enteropathy have intestinal lymphangiectasia (Waldmann, Steinfeld, Dutcher, Davidson, and Gordon, 1961) in which there is dilatation and hypertrophy of lymphatics in the submucosa and serosal surfaces of the intestine and in the mesentery, and usually involving the lacteals in the intestinal villi. In addition, there is enlargement of the abdominal lymph nodes due to dilatation of the sinuses, increased fibrous tissue, and some reticulum cell hyperplasia. In most patients there are lipofuscin deposits in the external muscular coat of the intestine.

However, in some patients with an indistinguishable clinical syndrome, jejunal biopsy (Jeejeebhoy, 1962), laparotomy (Holman et al., 1959; Donaldson, and Holt, 1963), or necropsy (Ulstrom and Krivit, 1960) have failed to demonstrate either abnormality of the lymphatics or lymph nodes or pigment deposits in the muscular coat. Even though in none of these previously reported patients have the investigations been sufficiently comprehensive to confirm the coexistence of significant gastrointestinal protein loss with no demonstrable anatomical abnormality of the gastrointestinal mucosa, the reports do suggest that the present case is not unique and that there is a well-defined syndrome of 'primary' protein-losing enteropathy without lymphangiectasia.

As yet there is insufficient evidence to decide whether all these patients with 'primary' protein-losing enteropathy represent variants of a single aetiological and pathological entity or whether there are at least two distinct diseases with a similar clinical syndrome.

This dilemma will not be resolved until the pathogenesis of 'classical' lymphangiectasia is better understood. There seems to be a probable relationship between lymphangiectasia and the

**FIG. 2.** Post-mortem appearance of the duodenal mucosa. × 120.
syndrome of 'chylous reflux with lymphatic deficiency' described by Kinmonth and Taylor (1964), who studied by lymphangiography a group of patients with lymphoedema of two or more limbs and chylous effusions. In these patients it was not possible to demonstrate retroperitoneal lymphatics or the thoracic duct normally, but on surgical exploration enlarged mesenteric lymphatics could be seen. These patients also had unexplained hypoalbuminaemia but no $^{131}$I-albumin or $^{131}$I-P.V.P. studies were performed. Mild lymphangiectasia may also be present in patients with constrictive pericarditis in which fibrosis in the posterior mediastinum or raised venous pressure may impede lymph flow along the thoracic duct (Davidson et al., 1961; Petersen and Hastrup, 1963). Intestinal lymphangiectasia may thus be the consequence of any abnormality of abdominal lymph drainage, either associated with acquired disease involving the thoracic duct or abdominal lymphatics, or with congenital lymphatic hypoplasia as in the syndrome of chylous reflux of Kinmonth and Taylor (1964). However, if the lymphatic hypoplasia involved the lymphatics of the intestinal mucosa itself, there would be no lymphangiectasia but the functional abnormality of 'chylous reflux' into the intestinal lumen would be similar to that seen in more proximal lymphatic obstruction.

Albumin is normally degraded in the body at a rate of about 10% of total circulating albumin daily (Jarnum, 1963), approximately half of this being due to loss into the gut (Wetterfors, Gullberg, Liljedahl, Plantin, Birke, and Olhagen, 1960; Armstrong, Margen, and Tarver, 1960). The method used for estimating albumin turnover in the present study (Jeejeebhoy and Coghill, 1961) has the advantage of simultaneously measuring both the metabolic degradation rate and gastrointestinal loss. However, it contains two potential sources of error. The binding of $^{131}$I marker by the orally administered resin may be incomplete, so that some $^{131}$I released from albumin by digestion in the gastrointestinal lumen may be reabsorbed and excreted in the urine (Freeman and Gordon, 1964). In addition, $^{131}$I released from albumin at extra-alimentary degradation sites could be excreted as iodide in the gastrointestinal secretions and then bound to resin (Hoedt-Rassmussen and Kemp, 1964). However, neither of these suggested sources of error would affect the determination of the total rate of albumin degradation (metabolic plus gastrointestinal loss), and abnormally high albumin degradation rates have not yet been described in the absence of collateral evidence for loss of protein into the gastrointestinal or urinary tracts or from the skin. Thus, although these criticisms of the method do not invalidate the conclusions reached, it is recognized that there may be a considerable error in the precise measurement of the gastrointestinal albumin loss.

The faecal excretion of albumin marker ($^{131}$I) by our patient (Table I) represents a measured daily gastrointestinal loss of 51% of his total circulating albumin. This is certainly an underestimate, for of the high urinary radio-iodine excretion representing 41% of total plasma albumin daily, only about a quarter can be attributed to normal channels of albumin degradation. The rest was presumably radio-iodine released from albumin in the gastrointestinal lumen, but which failed to be bound by the deacidite resin. This is understandable, for the resin was only given five times daily, and there would have been considerable periods when the small intestine contained no resin. We may therefore assume that our patient lost 50-80% of his plasma albumin into the gut each day, a much greater loss than any hitherto described, and a proportion that is comparable to the fraction of plasma albumin normally carried by the thoracic duct (Courtice, Simmonds, and Steinbeck, 1951; Petersen and Hastrup, 1963). This suggests a further possibility that the abnormality in our patient was an excessive permeability of the capillaries in the wall of the intestine, as postulated by Jarnum (1961a).

This enormous rate of protein loss explains the severe exacerbations of diarrhoea following infusion of concentrated albumin, for the osmotic effect of increased protein in the small intestine would aggravate the rate of fluid loss. Although intravenous albumin or plasma has been used successfully in patients with exacerbations of protein-losing enteropathy (Jeejeebhoy, 1962) and is widely recommended treatment, the occurrence of an osmotic diarrhoea has not been recorded. Great care should therefore be taken when giving protein infusions to patients with severe gastrointestinal protein leakage.

There was evidence of malabsorption in this patient with slight steatorrhoea, tetany, and malabsorption of vitamins A and B₁₂. A similar pattern of malabsorption not infrequently occurs in patients with intestinal lymphangiectasia and has been attributed to the re-excretion of fat from blocked abdominal lymphatic channels or to oedema of the intestinal mucosa (Waldmann et al., 1961; Mistilis, Skyring, and Stephen, 1965). It is presumed that either mucosal oedema or intestinal hurry accounts for the malabsorption observed in this case.

It appears that our patient manifested the syndrome of truly idiopathic protein-losing enteropathy without lymphangiectasia. The pathogenesis of this syndrome will only be clarified by intensive study of similar patients by such techniques as lymphangiography, electron microscopy of the
jejunal mucosa, laparotomy, and a therapeutic trial of a protein-free diet (Simpkiss and Sheldon, 1962).

We wish to acknowledge the help and encouragement given to us by Professor R. B. Blacket, under whose care the patient was admitted. For the investigations, willing help was given by the Pathology Department of Prince Henry Hospital under Professor W. R. Pitney and Dr. R. J. Bartholomew, and the Radio-isotope Department of Sydney Hospital under Dr. C. K. Hambly. One of us (J.H.S.) is in receipt of a grant from the Laura Bushell Trust.

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