PROTEIN-LOSING GASTROENTEROPATHY

A. M. DAWSON, M.D., M.R.C.P.

Senior Lecturer in Medicine and Honorary Consultant Physician, Royal Free Hospital, London, W.C.1

HYPOALBUMINÆMIA may reflect a deficiency of albumin or dilution of a normal amount of albumin in an enlarged volume of extracellular fluid. A deficiency may be due to an impaired synthesis or increased catabolism of the protein. Apart from overt excessive loss of serum albumin from the body in the nephrotic syndrome or severe burns, excessive catabolism has not commonly been invoked to explain hypoproteinæmia in diseased states—especially those of the gastrointestinal tract, for starvation, due either to impaired intake, digestion or absorption of food stuffs seemed to offer a superficially satisfying explanation. But most patients with gastrointestinal disease and hypoproteinæmia do not have much evidence of impaired digestion or absorption of protein, for the faecal nitrogen is rarely raised except in severe malabsorption and if the food intake were normal this would usually adequately cover the extra loss. Although the exact amount of protein needed to maintain nitrogen equilibrium is unknown, as attested by a recent review by Platt, Miller and Payne (1961), there is little doubt that the one-time generous suggestion of 70 to 120 g. a day is quite unnecessarily large. Indeed, Chittenden (1905) did careful nitrogen balance studies both on himself, on Army personnel, and on Yale athletes and all reported improvement in subjective well-being and physical prowess after a year on some 35 to 45 g. of protein a day, besides the fact that they maintained nitrogen equilibrium. In an ill person the assumption that 35 to 45 g. of protein a day is adequate should be treated with caution for the effect of the stress of ill-health on optimal protein requirements is unknown. Still, being wise after the event, one may well wonder why we have accepted for so long the explanation of starvation as the cause of hypoproteinæmia in such a wide variety of gastrointestinal diseases. Furthermore, it has been repeatedly demonstrated that although simple starvation does cause hypoproteinæmia, it is a late manifestation of this state (Keys, Taylor, Mickelson and Henschel, 1946).

Recently it has been realized that a variety of gastrointestinal disorders are associated with an increased rate of destruction of serum proteins (Citrin, Sterling and Halstead, 1957; Gordon,

1959; Jarum and Schwartz, 1960; Steinfeld Davidson, Gordon and Greene, 1960) and that the site of this destruction is the bowel. It seems that the bowel leaks plasma into the lumen of the gut which is digested to form peptides and amino acids; these in turn are absorbed into the blood stream, and so the faecal nitrogen is not raised.

Hypoproteinæmia results because, surprisingly the liver has a very limited reserve in its ability to synthesize albumin and in these diseased states, loss soon outstrips the synthetic reserve of the liver. Similarly, if ^{131}I -labelled albumin is given intravenously, although it rapidly disappears from the body by leaking into the bowel, yet this substance is in turn digested in the intestinal tract and the water-soluble radioactive products are absorbed, thus the faecal radioactivity is often not raised. In the following paragraphs some of the techniques will be described which have partly overcome these difficulties. They have been used to demonstrate qualitatively the leak of large molecules into the gut and also to try and assess this phenomenon quantitatively.

Techniques to Demonstrate Loss of Protein into the Gut

The ^{131}I -PVP Test

Gordon (1959) has introduced an ingenious technique whereby he has tried to circumvent the problem of the digestion and absorption of any radioactive albumin which has leaked into the bowel. He labelled another macromolecule, polyvinylpyrrolidone (PVP), with ^{131}I . When given intravenously it was suggested that this would leak through sites which were permeable to serum albumin and if it entered the gut there would be negligible reabsorption of the radioactive label as ^{131}I -PVP is not acted upon by digestive enzymes and so the label would be recovered and counted in the faeces. To produce a stable radioactive polymer he prepared a special form of PVP whereby a benzene ring had been introduced so that this could be labelled by diazotization (Gordon, 1958). His initial studies showed that some 90% of the substance when fed orally could be recovered in the faeces; later batches have been more disappointing and recoveries have been between 50 and 70% (French,

Ragins, Pollard and Dickason, 1961). A slightly less stable form of the polymer has been used which gave a faecal recovery after oral feeding of approximately 40% (Dawson, Williams and Williams, 1961). The advantage of this preparation is that the commercially available form of PVP may be used as the starting material and the radioactive polymer can be prepared in any hospital isotope unit. If the radioactive PVP is obtained from an outside source, this must be either dialyzed or passed through an ion-exchange column before use for even the best preparations decompose on storage and if given without this precaution an unknown proportion of the radioactivity will be free iodine.

The patient's thyroid is blocked with 10 gr. of potassium iodide three times a day for one day prior to and throughout the test. Ten μ c of sterilized ^{131}I -labelled PVP are given intravenously. Twenty-four-hour collections of urine and faeces are obtained separately for four days. As a large amount of the radioactivity is secreted in the urine in the first 24 hours great care must be taken to prevent any contamination of faeces by the urine as this would give a completely erroneous result. This raises very difficult technical problems when trying to use this method in patients who are incontinent. The stools are usually counted in a ring geiger counter and the radioactivity excreted in the four-day collection of faeces is expressed as a percentage of the intravenous dose given. It is usual to test each batch of PVP on normal persons as well as the patients to be investigated.

Both Gordon (1959) and Dawson and others (1961) using slightly different polymers found that normal persons excreted in their faeces up to 1.5% of an intravenous dose. A raised faecal excretion of PVP, which suggests that a portion of the gastrointestinal tract is excessively permeable to PVP and so, presumably, to albumin, is found in a large variety of patients with hypoalbuminaemia and a hypercatabolic state. Neither diarrhoea, steatorrhoea nor hypoproteinaemia from such causes as the nephrotic syndrome or cirrhosis gives a false positive result. It should be clearly realized that this is an empirical test and one cannot expect to express the results obtained in terms of grammes albumin leaking into the gut each day. This can be explained on many counts. PVP is not albumin, its molecular weight is approximately 40,000 while that of albumin is 69,000. Its shape is different, and it is not charged, so that it only roughly mimics the distribution of albumin in the body. These differences might explain why intravenous PVP is rapidly taken up by the reticulo-endothelial system (Ravin, Seligman and Fine, 1952) and de-iodinated, in contrast to

^{131}I -labelled albumin. This leads to a far more rapid fall in serum radioactivity after an intravenous injection of ^{131}I -PVP than after ^{131}I -labelled albumin, and so a small amount of faecal ^{131}I -PVP may represent an appreciable amount of albumin. In addition, in observations on the oral recovery of PVP it was found that when patients were constipated they excreted less of the label, presumably due to the action of colonic bacteria breaking the radioactive bond, followed by absorption of the radioactive iodine by the colon. If these limitations are recognized and the results are interpreted with circumspection the test can be a useful, simple and rapid way to assess the presence of protein-losing gastroenteropathy. This was underlined by the good correlation between the serum albumin and the recovery of PVP in the stools when serial observations were made on patients during different phases of their disease (Dawson and others, 1961).

^{131}I -Albumin Turnover

The use of iodinated human serum albumin in studying metabolic disorders in man has now been in vogue for over ten years (Sterling, 1951), and providing precautions are taken in the technique of iodination, to prevent denaturation of the protein, this is now accepted as a valid tracer of albumin metabolism (McFarlane, 1957). By this technique one may calculate the total albumin in the extravascular and intravascular compartments of the body and also its rate of catabolism. If one accepts the fact that the patient is in a steady state one may also calculate the amount of albumin being synthesized by the liver each day. This technique has been applied to patients with various gastrointestinal disorders and hypoproteinaemia (Citrin and others, 1957; Jarnum and Schwartz, 1960; Steinfeld and others, 1960) and also those with so called idiopathic hypoproteinaemia (Schwartz and Thomson, 1957; Cattell and Norris, 1957; Gordon, Bartter and Waldman, 1959). Such patients have a reduced albumin pool in conjunction with an increased rate of catabolism. The rate of albumin synthesis is normal or slightly increased and certainly not decreased as would occur if malnutrition of any variety were the cause of the hypoproteinaemia. But this technique does not demonstrate the site or cause of the increased catabolism, which can only be done by direct intubation of the stomach or small intestine with aspiration of the radioactive protein. This is, of course, an extremely tedious procedure for a routine test, but has been of great value as a research tool in defining that an exudation of serum protein into the bowel does in fact occur (Citrin and others, 1957; Holman, Bickel and Slesinger, 1959).

Jeejeebhoy and Coghill (1961) have apparently overcome this difficulty of defining the site of increased albumin catabolism. They considered that any albumin broken down in the intestine to iodinated amino-acids and free iodine might be trapped by an ion-exchange resin taken orally. The resin-radioactive complex would then be too large to be absorbed and so pass unscathed through the bowel to be recovered in the faeces where the radioactivity could be measured. In fact by frequent feeding of an ion-exchange resin over 80% of oral ^{131}I -labelled albumin was recovered in the faeces. This is in contrast to the normal value of less than 2% faecal recovery of radioactivity if resin is not fed. Combining this oral resin technique with the standard methods of albumin turnover they have been able to estimate the proportion of the total albumin degraded each day due to entry into the bowel.

^{51}Cr -labelled albumin

An alternative way of labelling albumin is with ^{51}Cr (Gray and Sterling, 1950). ^{51}Cr is poorly absorbed (Ebaugh, Clemens, Rodman and Peterson, 1958) and Waldman (1961) postulated that if ^{51}Cr -labelled albumin leaked into the gut the label would pass quantitatively into the faeces and faecal radioactivity would reflect the albumin lost. His preliminary report suggests that the results are promising in the demonstration of a qualitative leak of protein into the gut but more work is needed to determine that ^{51}Cr -labelled albumin behaves in a metabolically normal manner before one may interpret the results on a quantitative basis.

Normal Albumin Metabolism

The site of normal albumin catabolism has been reinvestigated with the recognition of the entity of protein-losing enteropathy. McFarlane (1957) deduced that the site of catabolism must be intimately connected with the intravascular pool and suggested the gastrointestinal tract. The recent demonstration of appreciable transfer of serum albumin into the gut of the cat (Ullberg, Birke, Ewaldson, Hansson, Liljedahl, Plantin and Wetterfors, 1960) and to the sheep (Campbell, Cuthbertson, Mackie, McFarlane, Phillipson and Sudsaneh, 1961) shows that the gut is an important normal site of catabolism in some animals. In man, by perfusion techniques, it has been calculated that over half of the albumin normally destroyed each day probably first leaks from the mucosa of the stomach and upper jejunum into the gut lumen (Wetterfors, Ullberg, Liljedahl, Plantin, Birke and Olhagen, 1960). The observations of Jeejeebhoy and Coghill (1961) using an oral ion exchange resin combined with ^{131}I -labelled albumin

confirm this. These results also demonstrate that there is probably another site of albumin degradation besides the gut. This is supported by the observations on the effects of adrenal steroids which, although they shorten the albumin half-life (Sterling 1960), do not increase the leakage of albumin into the gut (Jeejeebhoy and Coghill, 1961) or increase the permeability of the gut to ^{131}I -PVP (Wilkinson, 1961).

Protein-Losing Gastroenteropathy

Ulcerative Lesions of the Gastrointestinal Tract

Excessive loss of protein into the gut associated with hypoproteinaemia has now been demonstrated in patients with carcinoma of the stomach (Jarnum and Schwartz, 1960), regional ileitis (Holman and others, 1959; Steinfeld and others, 1960; Dawson and others, 1961) and ulcerative colitis (Steinfeld and others, 1960; Dawson and others, 1961). A simple consideration of the gross pathology gives a reasonable explanation as to why this should occur.

Giant Rugal Hypertrophy of the Stomach

This is a rare condition characterized by gross hypertrophy of the gastric mucosa and often hypoproteinaemia and oedema. This condition was the first in which loss of protein into the gut was definitely demonstrated as being the cause of the shortened half life of serum albumin and the probable cause of hypoproteinaemia (Citrin and others, 1957). Indeed, this case report gave impetus to all subsequent studies. Since then other patients have been described with this condition as has the curative effect of sub-total gastrectomy in the disordered metabolic state (Schwartz and Jarnum, 1959; Dawson and others, 1961). Whether the leakage of protein is merely an expression of a normal rate of protein exudation over an increased surface area of gastric mucosa or whether there is also increased permeability of the gastric mucosa is unknown.

Idiopathic Steatorrhoea

This is often associated with hypoproteinaemia. Results of the use of the ^{131}I -PVP test have been reported by various workers. Schwartz and Jarnum (1959) found a high excretion of ^{131}I -PVP in a patient with this disease. Dawson and others (1961) studied four patients with this condition. The only one with a low plasma protein had a high PVP excretion and both the plasma protein and PVP excretion returned to normal when remission was induced by a gluten-free diet. On the other hand Parkins (1960), investigating ten such patients, found an abnormal loss of PVP in the stools in some patients but could not correlate this either with hypoproteinaemia or the ability to absorb

protein. Recently London, Bamforth and Creamer (1961) reported two patients with idiopathic steatorrhœa who presented with gross œdema due to an intestinal protein-losing state. The structural lesion in the jejunum is loss of villi so that one must postulate an increased permeability of the intestinal mucosa to protein which in some patients results from the action of gluten on the mucosal cell.

Idiopathic Hypoproteinæmia

By now a large number of patients have been described whose main disability is œdema associated with hypoproteinæmia for no apparent reason. One such patient was shown by Albright, Bartter and Forbes (1949) to catabolize serum protein more rapidly than normal, for albumin infused intravenously was rapidly excreted in the urine as non-protein nitrogen. This hypercatabolic state was confirmed in other patients using ^{131}I -labelled albumin (Schwartz and Thomson, 1957, Cattell and Norris, 1957) and such patients were shown to have a gastrointestinal mucosa which was apparently permeable to the macromolecule PVP (Gordon, 1959; Schwartz and Jarnum, 1959). It has therefore been concluded that the gut is the site of the excessive albumin catabolism. This has been confirmed with ^{51}Cr -labelled albumin (Waldman, 1961). A lesion may be found in the gut at laparotomy and even sometimes on intestinal biopsy which is characterized by dilated intestinal lymphatics (Gordon and others, 1959; Jarnum and Peterson, 1961). The condition is often associated with chylous ascites and Jarnum and Peterson (1961) using ^{131}I -labelled albumin demonstrated, in one patient, that the ascitic fluid protein rapidly equilibrated with the plasma protein. This would suggest that there was rapid equilibration between plasma and splanchnic lymph which then either leaked into the abdominal cavity to form ascites or leaked into the intestine to be digested and lost from the body's albumin pool. Although patients with hypoproteinæmia and unexplained gastrointestinal protein loss may well have this lymphatic condition, it should be remembered that unless careful examination of the gastrointestinal tract is undertaken frank and less esoteric gastrointestinal diseases may declare themselves later

(Holman and others, 1959). One might expect that in severely affected persons the fasting serum and urinary amino-acids would be raised, for such patients are in a permanent post-absorption state with respect to proteins. This has not been commented on but one such patient initially reported by Bound and Hackett (1953) with hypoproteinæmia and an increased urinary and serum amino nitrogen has been more recently shown to be suffering from protein-losing gastroenteropathy (Dawson and others, 1961).

Congestive Heart Failure

A low serum albumin occasionally complicates congestive heart failure. This is usually ascribed to either hæmodilution or cardiac cachexia with impaired liver function, but Davidson, Waldman, Goodman and Gordon (1961) described four patients with chronic congestive heart failure and gross hypoproteinæmia which was associated with a rapid turnover of plasma albumin due to gastrointestinal protein loss. Three of the patients had constrictive pericarditis and the other had an atrial septal defect. This metabolic state was reversible and was cured when the heart failure was corrected by appropriate cardiac surgery. Davidson and others (1961) suggest that a high intra-venacaval pressure may cause lymphatic stasis and leakage into the bowel.

Conclusion

Protein-losing gastroenteropathy has been seen to be a ubiquitous cause of hypoproteinæmia in a variety of disorders. In any patient with unexplained œdema and hypoproteinæmia this should be excluded by using the PVP test or, if the facilities are available, by using one of the modifications of the albumin turnover technique. Once a protein-losing state has been demonstrated the gastrointestinal tract must be thoroughly investigated to exclude any localized curable lesion. This will often mean a laparotomy. With this approach in mind it is quite probable that many patients with 'idiopathic hypoproteinæmia' will be shown to have a protein-losing state but, on the other hand, it is probable that some patients will be shown to have an as yet poorly delineated cause for their œdematous state.

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