

## Protein metabolism in inflammatory bowel disease

J POWELL-TUCK

*Gastrointestinal Unit, Charing Cross Hospital, London*

**SUMMARY** Major loss of body protein mass in inflammatory bowel disease is much less common than weight loss, which is often attributable to losses of other body, particularly water and fat. It does occur, however, in a few patients, especially in those with compromised food intake. It is due principally to the combined effects of diminished intake and excessive intestinal losses of amino nitrogen.

Nitrogen metabolism is influenced not only by protein nutritional state and net nitrogen intake but also by disease activity. There is some evidence for abnormally low secretion of growth hormone in adolescents with inflammatory bowel disease and growth failure.

Low serum albumin concentrations are not necessarily related to protein undernutrition and are the combined result of relatively reduced albumin synthesis, increased intestinal losses, and maldistribution between intravascular and extravascular spaces. Concentrations in the plasma of IgG and acute phase reactants may be raised despite increased losses into the bowel lumen.

The prevention of total body protein depletion is achieved principally by maintaining adequate and often not supranormal intakes of a balanced source of amino nitrogen in a balanced diet given orally, enterally, or parenterally, combined with a medical or surgical approach to reduce disease activity: supranormal energy intakes are not beneficial.

Individual patients with inflammatory bowel disease are sometimes seen to have considerable weight loss, diminution of muscle mass, and hypoalbuminaemia. The assessment of nutrition has been comprehensively covered but, nevertheless, it seems relevant to present some hitherto unpublished data collected at St Mark's Hospital during 1977-8.

Thirty three patients who were admitted to hospital for treatment of ulcerative colitis of varying extent and severity were questioned as to what they regarded as their "normal" weight, and previous outpatient records were examined to corroborate this estimate. The patients were then weighed and weight loss estimated. All but four of the patients had weight loss, ranging from 0.25 to 17 kg.

Twenty four of these patients underwent measurements of the mid upper arm circumference and of skin thickness using a steel tape and a Holtain caliper at combinations of the standard biceps, triceps, infrascapular and suprailiac sites. The arm muscle circumference was calculated, as described by Gurney and Jelliffe.<sup>1</sup> The body fat content was estimated from the skin fold measurements using

the method of Durnin and Womersley.<sup>2</sup> The measurements obtained were compared with those taken from normal lean controls matched for age and sex. The triceps skin folds were reduced compared with those of the controls ( $p < 0.01$ ; Student's *t* test). Mean calculated fat free mass was 50.7 kg in the patients and 52.0 kg in the controls. Mean fat content of the controls (18.1 kg) was significantly greater than that of the patients (13.8 kg) ( $p < 0.05$ ; Student's *t* test unpaired). Arm circumference did not differ significantly between the patients and controls ( $p > 0.05$ ). A demonstrable loss of fat stores had occurred in the patients, but no demonstrable loss of total body protein was observable by the method used in the group as a whole.

### Nitrogen balance

In the healthy person a hypothetical intake of 10 g of nitrogen (62.5 g protein) is balanced by an output of nitrogen in the urine of about 8.5 g (7 g as urea) and in the faeces of about 0.75 g, with the remaining 0.75 g in other secretions. If input of nitrogen is gradually reduced urine excretion of nitrogen

Correspondence to: Dr J Powell-Tuck, Gastrointestinal Unit, West Middlesex Hospital, Isleworth, Middlesex TW7 6AF.

diminishes correspondingly, so that negative nitrogen balance does not occur until intake drops below about 4–5 g nitrogen. At this point urine losses of nitrogen do not drop further and remain at the “obligatory” level of 4–5 g nitrogen.<sup>3</sup> Thus a normal diet of about 60 g nitrogen can be regarded as having a reserve of about 5 g nitrogen.

#### FAECAL LOSSES OF NITROGEN IN INFLAMMATORY BOWEL DISEASE

Buckell *et al*<sup>4</sup> measured the saline extractable, trichloroacetic acid precipitable, protein fraction of 50 colitic and eight control stool specimens by a dye binding (Ponceau S) technique. The observed protein loss per 24 hours from the colitic cases ranged from 0.1–26 g compared with losses of not more than 1 g from the controls. Estimation of nitrogen loss using the Kjeldahl technique in some patients showed a nitrogen loss greater than that accounted for only by protein, because amino acids and peptides were also present in the stool. Their nitrogen content amounted to about half that estimated from the stool protein content. Thus it can, for clinical purposes, be estimated that the total nitrogen lost in the stools of such patients varies from normal to low in mild disease to about 6.5 g/24 hours in severe colitis.

If dietary nitrogen input were maintained at normal levels and ureagenesis compensated for the difference between intake and faecal losses it might be predicted that negative nitrogen balance would not occur until stool nitrogen losses exceeded about 5 g. In other words a normal dietary nitrogen intake might be considered to be sufficient for all but the most severely ill patients with colitis, but patients with colitis would have a greatly reduced dietary reserve and would tend to go into negative nitrogen balance if there were any fall in their intake. This concept is supported by the data gathered from three patients studied in the era before steroids,<sup>5</sup> in which two patients maintained positive, or zero balance, on intakes of nitrogen of 12.6 g and 11.5 g despite respective faecal losses of 8.2 g and 3.0 g. In the first case balance was achieved by daily urine losses of nitrogen diminishing to 4.5 g. A third patient, however, was in negative nitrogen balance with an intake of 4.4 g, a faecal output of 6.8 g, and an obligatory urine nitrogen loss of 4.3 g/24 hours.

#### INTAKE OF NITROGEN IN INFLAMMATORY BOWEL DISEASE

Though nitrogen intake may be slightly diminished in “outpatient” inflammatory bowel disease, in the potentially surgical inpatient with acute colitis, subacute obstruction, sepsis or fistulae dietary intake may be severely compromised or lost

entirely. It is this small subgroup of actively ill patients who are most likely to be in negative nitrogen balance, with diminished intake and increased faecal losses.

The interaction of drug treatment and nitrogen balance was illustrated in a study of three patients by Clark and Lauder.<sup>6</sup> In one patient with Crohn’s disease positive nitrogen balance was achieved when steroids were started, not as a result of diminution of faecal nitrogen losses, but by stimulation of appetite and therefore an increase in nitrogen intake.

Though nitrogen absorption is highly efficient,<sup>7</sup> in some cases of short bowel syndrome stool nitrogen losses may approximate to oral intake, suggesting malabsorption.<sup>6</sup> Under these circumstances positive or zero nitrogen balance may only occur at high levels of intake.

#### Whole body and tissue protein metabolism

A third patient in Clark and Lauder’s study<sup>6</sup> showed that nitrogen intake and faecal losses are not the sole determinants of nitrogen metabolism in inflammatory bowel disease. This patient, with an intra-abdominal abscess, due to Crohn’s disease, was in negative nitrogen balance despite faecal losses of only 3.5 g nitrogen and an intake of 17 g. It was only after drainage of the abscess that positive balance was achieved on the same intake.

The effect of inflammatory bowel disease on whole body protein flux, synthesis, and breakdown has been estimated by the method of Waterlow *et al*<sup>8</sup> using a tracer dose of <sup>15</sup>N glycine given to 19 undernourished patients with ulcerative colitis or Crohn’s disease in the parenterally or enterally fed state.<sup>9</sup> Rates for synthesis and breakdown were 2.1 and 1.7 g protein/kg/24 hours at an erythrocyte sedimentation rate (ESR) 10 mm in the first hour, increasing to 4.0 and 3.3 for an ESR of 100. Flux synthesis and breakdown correlated significantly with disease severity, judged either by ESR or ranking by an observer who knew the patients but who did not know the rates of protein turnover.

Studies subsequent to the publication of that paper have further examined the possibility that such a correlation could be spurious if confounded by other variables, such as indices of nutritional state, or intake of nutrients/kg. The following variables were submitted to correlation matrices, stepwise regression, and factor analysis: flux; rank; erythrocyte sedimentation rate; body weight (absolute and as per cent ideal); weight (kg) divided by height (m) squared; arm circumference; creatinine excretion; age; sex; serum albumin concentration; intake per kg per 24 hours of nitrogen and energy; and 3-methylhistidine excretion. The only significant

correlations with flux were rank, erythrocyte sedimentation rate, and protein and energy intake per kilogram. Protein and energy intake expressed per kg confounded the correlation of disease severity and flux by about 15%, but when subtracted, still left highly significant correlations between rank or erythrocyte sedimentation rate and flux ( $p < 0.001$  in both cases).

The rates of protein synthesis in the small and large intestine in man are not known. In young rats McNurlan *et al*<sup>10</sup> used "flooding" doses of <sup>14</sup>C leucine to show that the small intestine contributes about 15% to the total body synthetic rate by virtue of its high fractional synthetic rate. The colon contributes about 2.6%. If these values were roughly true in man it is clear that for local tissue changes to account for a doubling in the measured total body protein synthetic rate, the protein synthesis occurring in the whole small bowel would need to increase about eight-fold, or in the whole colon by about 40-fold. Investigation of the pattern of proliferation of epithelial cells in ulcerative colitis<sup>11</sup> does not support such a change, particularly as rates of proliferation do not seem to change in response to changes in disease activity. It seems more likely that the observed changes in whole body protein turnover are the result of a more generalised effect, probably on several tissues within the body.

#### **Growth failure in adolescents and hormonal milieu in inflammatory bowel disease**

Several studies<sup>12-13</sup> have suggested that the growth failure associated with inflammatory bowel disease in adolescents can be largely corrected by increasing nutrient intake. Motil *et al*<sup>14</sup> studied the effect of increasing an intake of 2.3 g protein and 67 kcal/kg/24 hour to 3.2 g protein and 97 kcal/24 hour, using <sup>15</sup>N glycine as tracer. Rates of flux, synthesis, and breakdown increased with the higher intake, resulting in a 30% increase in nitrogen retention.

Protein metabolism is probably governed by hormonal milieu. No comprehensive study of the endocrine state of patients with inflammatory bowel disease has been made, but five studies<sup>12-17</sup> have been made of growth hormone secretion. In three<sup>15-17</sup> growth hormone secretion was diminished in response to night or some other stimulus such as insulin hypoglycaemia. This cannot be explained by undernutrition, as in undernourished adults (Glynn MJ, Powell-Tuck J, unpublished observations), children,<sup>18</sup> and patients with anorexia nervosa<sup>19-20</sup> growth hormone values are usually raised. Thus some metabolic defect independent of reduced intake and undernutrition probably exists in inflammatory bowel disease. One study, however, showed

that growth hormone treatment is not effective in promoting growth in inflammatory bowel disease.<sup>21</sup> Two studies<sup>15-17</sup> suggested that insulin resistance might be a factor in inflammatory bowel disease, but insulin infusion with parenteral feeding has little effect on protein turnover in non-diabetic adult patients with inflammatory bowel disease.<sup>22-23</sup>

#### **Albumin and the acute phase reactants**

Jarnum *et al*<sup>24</sup> showed increases in fractional loss of intravascular albumin concentration in patients with both ulcerative colitis and Crohn's disease. Such increases in loss correlate with the severity of the disease and the clearance of <sup>59</sup>Fe dextran in the faeces, an indication of intestinal protein loss. Thus much of this loss of albumin may be the result not of true catabolism but of leakage into the intestine. That this itself cannot explain the hypoalbuminaemia so often associated with inflammatory bowel disease is illustrated by the similarly increased losses of IgG from the intravascular space—yet IgG concentrations may be normal or raised in inflammatory bowel disease. Rates of albumin synthesis may be relatively depressed in inflammatory bowel disease as normal rates are observed despite hypoalbuminaemia.<sup>24</sup>

In nutritional conditions of protein deprivation, but not short term starvation,<sup>10</sup> albumin synthesis would be expected to be diminished. Distribution of albumin between intravascular and extravascular spaces may be changed in inflammation, sepsis, and surgical trauma and will substantially affect serum albumin concentration.<sup>25</sup> Thus serum albumin is likely to be determined by all these factors combined with the excess losses into the intestine. Therefore its relation to protein nutritional state may be weak.

Serum concentrations of certain proteins like orosomucoid, C-reactive protein, and acid glycoprotein, the acute phase reactants, rise in active inflammatory bowel disease and fall with treatment.<sup>26-27</sup> C-reactive protein and serum amyloid A protein concentrations tend to be higher in Crohn's disease than in ulcerative colitis, and the increase of the latter may be related to amyloid deposition,<sup>28</sup> which occurs in Crohn's disease but has not been described in ulcerative colitis.

#### **Conclusion**

The protein metabolism of the various tissues of the body will respond to the various differing stimuli that may occur in inflammatory bowel disease. The net nitrogen intake (intake minus faecal losses) will be one of the most important influences. Protein

deprivation may produce different effects to starvation.<sup>10</sup> Specific nutrient deficiencies like zinc<sup>29</sup> and potassium and calcium depletion<sup>30</sup> will influence protein metabolism. There will be the effect of the patient's nutritional state and the temperature of the environment in which he or she is situated. Intestinal bacterial overgrowth will have its effect.<sup>31</sup> Drugs, particularly corticosteroids,<sup>32</sup> will act directly as well as indirectly to reduce the body's response to sepsis or inflammation. Surgical trauma<sup>33</sup> will have an effect of its own as well as, by resection, remove stimuli to protein turnover resulting from inflamed bowel. Thus in practical terms it is important when studying protein metabolism in inflammatory bowel disease to define as far as possible the various conditions that are operating. The study of protein metabolism in these diseases is in many ways the study of protein metabolism in disease states and undernutrition in general.

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