

Turnover of plasma proteins¹

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Studies of plasma protein turnover have been used extensively over the last 20 years both under experimental conditions and in clinical medicine. They have shown that disturbed plasma protein metabolism is a very common phenomenon in disease, probably as common as an elevated erythrocyte sedimentation rate.

Abnormal Serum Total Protein Concentration

Only turnover studies can reveal the mechanism behind an abnormal serum concentration of a given protein. Albumin, the major fraction of serum protein, is usually low when total serum protein is low and hence basic causes of hypoproteinaemia are much the same as those of hypoalbuminaemia: (1) increased catabolism which occurs in a variety of acute conditions such as acute infections, trauma including major surgery and myocardial infarction; (2) abnormal protein loss, which may be due to burns, severe proteinuria or gastrointestinal protein leakage; (3) decreased synthesis which is most often caused by liver disease or malnutrition and/or malabsorption; (4) haemodilution, which occurs in pregnancy, in some cases of cirrhosis of the liver and in surgical patients who have been overhydrated, especially when renal insufficiency is also present.

The causes of hyperproteinaemia are fewer, because it is never due to decreased catabolism or abnormal retention. They include increased synthesis of immunoglobulins, either by normal clones (in chronic inflammatory conditions such as cirrhosis of the liver) or by abnormal clones (myelomatosis), which may produce a significant increase in total serum protein concentration; and haemoconcentration which is seen in severely dehydrated patients (cholera, pyloric stenosis) and increases haemoglobin as well as serum protein concentration.

A normal total serum protein concentration does not necessarily imply normal concentration of individual fractions. It may, for instance, mask hypoalbuminaemia with hypergammaglobulinaemia,

as seen typically in cirrhosis of the liver. Similarly, normal concentration of a particular protein fraction does not necessarily imply normal turnover; in chronic inflammatory bowel disease serum immunoglobulin concentrations are usually normal but their metabolism is not (*vide infra*).

The only way to determine the effect of a given disease on the metabolism of specific plasma proteins or to establish the mechanism of an altered serum concentration is by means of turnover studies.

Methods of Studying Turnover

RADIOIODINE-LABELLED PROTEINS

Turnover studies with labelled protein in man were begun by Sterling in 1951 using ¹³¹I which, in many respects, turned out to be an ideal label. However, from a theoretical point of view radioiodine-labelled proteins have a major disadvantage in that they only measure protein degradation or breakdown.

Before labelling the protein in question must be isolated in pure, undenatured form, usually by means of gel filtration. The labelling must be performed gently and according to certain rules which ensure that the final labelled product remains undenatured and metabolically homogeneous. One widely adopted method is to use monoiodine-chloride (ICl) as oxidizing agent (McFarlane, 1958). The radioactive iodide is oxidized to iodine which labels the protein by binding to tyrosine. After intravenous injection the labelled protein should behave like the body's unlabelled protein as regards both distribution and breakdown.

Since all methods of calculation are based on the disappearance rate of the protein label from the body, thyroid uptake of radioiodide must be prevented by administration of stable iodide throughout the study; this also minimizes the radiation dose to the thyroid gland. The renal excretion of the label must be rapid in comparison with the rate of breakdown of the labelled protein molecule, eg, the normal metabolic clearance of labelled albumin is about 200 ml plasma per 24 hours whereas renal clearance of iodide is 200 ml plasma in eight minutes.

The practical procedure is common to all

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clinical turnover studies. A known amount of labelled protein is given intravenously. Blood is withdrawn after 10 minutes (for determination of plasma volume and intravascular protein mass) and thereafter at daily intervals for the duration of the study, which may be a few days or several weeks depending on the purpose of the study. The excretion of label is followed either by analysis of urine, and, in patients with gastrointestinal disease, stools collected as 24-hour specimens or by using a total body counter. Total body counting is simpler, and also more accurate as even the most meticulous collection of excreta fails to account for 5 to 10% of the total loss, probably due to some iodide excretion in sweat.

CALCULATION

Turnover data are usually obtained either by measuring the loss of label and calculating the clearance or by analysis of the plasma radioactivity curve. These methods do not give true turnover data since only degradation is measured. However, provided a steady state is maintained with constant distribution and intravascular mass of the protein during the study, then the amount of protein degraded daily must equal the amount of protein synthesized daily.

Metabolic clearance (fig 1)

This is calculated from the daily excretion of radioiodide in urine and the daily average plasma concentration of the labelled protein, a calculation which is analogous to that of many renal function tests. In patients with presumed gastrointestinal protein leakage the iodine lost in the stools must also be taken into account. The metabolic clearance is determined daily for eight to 10 days, and the average value is taken as the value closest to the true metabolic clearance.

Analysis of the plasma concentration curve

The plasma disappearance curve of labelled protein can be treated mathematically in a number of ways, the simplest being the two-compartment model. The labelled protein disappears from plasma partly by metabolic degradation and partly by transfer to an extravascular pool. When equilibrium is attained, the slope of the curve reflects metabolic breakdown. This model was the first to be applied to plasma protein turnover studies (Sterling, 1951). However, the two-compartment model represents an oversimplification because it assumes an even degradation in both intra- and extravascular compartments which is incorrect. The degradation takes place within or very close to the intravascular compartment. For this reason the two-compartment model leads to falsely high degrada-

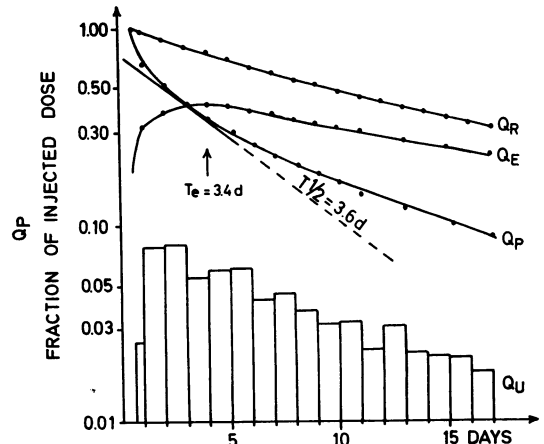


Fig 1 Calculation of metabolic clearance in a study with radioiodine-labelled protein. All quantities (Q) are expressed as percentages of injected dose.

Q_U : Daily urinary excretion of radioiodide 'liberated' through protein breakdown. Q_P : Plasma concentration of labelled protein.

Q_U/Q_P : Daily plasma clearance of labelled protein, where Q_P denotes mean concentration within the 24-hour period.

The metabolic clearance is taken as the average of Q_U/Q_P in seven to 10 consecutive days.

Q_R : The amount of labelled protein remaining in the body = $(I - \sum Q_U)$.

Q_E : Extravascular labelled protein = $(Q_R - Q_I)$.

Q_I = total intravascular labelled protein.

Intravascular fraction of total protein mass can be estimated from Q_P/Q_R at T_e , the time of 'equilibrium', where Q_E attains maximal activity and is horizontal (Campbell et al, 1956; Pearson et al, 1958).

tion values, especially when the degradation is abnormally high.

Matthews (1957) introduced the more correct multicompartiment model in plasma protein turnover studies (fig 2). She split up the plasma curve into a number of exponential functions, usually two or three. From their intercepts and slope constants the fractional catabolic rate, ie, that fraction of the intravascular protein mass which is degraded per day, can easily be calculated by a simple formula which expresses catabolic rate as the reciprocal of the integrated time-concentration area from time zero to infinity (Nosslin, 1966).

Slope constants and intercepts also make possible the calculation of a distribution ratio, ie, that fraction of the protein which is located intravascularly.

When using plasma curve analysis for calculation of protein degradation, it is essential to prolong the study until the final slope of decreasing plasma activity can be established with reasonable accuracy. It may take two or three weeks. If daily whole body

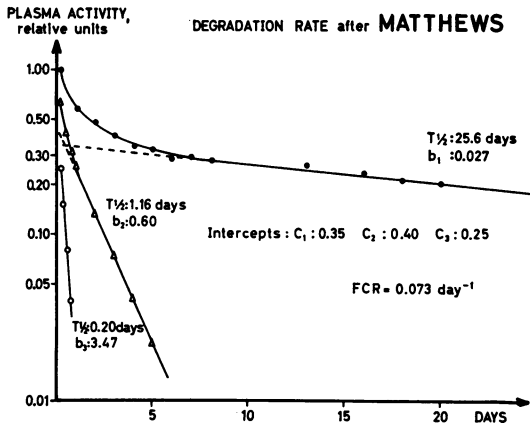


Fig 2 Calculation of fractional catabolic rate (FCR) in a multicompartiment model (Matthews, 1957). The plasma activity curve is solved as a number of exponential functions each defined by its intercept with the y axis at t_0 (c) and its slope constant (b). FCR is equal to $(c_1/b_1 + c_2/b_2 + \dots + c_n/b_n)^{-1} \times \text{day}^{-1}$.

counting can be performed, a final slope of total body radioactivity can be obtained within three weeks (fig 3). This slope always equals the final slope of plasma radioactivity.

¹⁴C-CARBONATE

As mentioned above, with radioiodine-labelled proteins only the degradation rate of proteins can be determined. With the introduction in 1963 of the ¹⁴C-carbonate method (McFarlane, 1963; Reeve, Pearson, and Martz, 1963) it became possible to make a direct measurement of the rate of hepatic synthesis of plasma proteins. Following intravenous injection of ¹⁴C-carbonate some of the ¹⁴C is combined with ammonia and ornithine in the liver

cells to give 6-¹⁴C-arginine, which now enters both microsomal protein synthesis and urea production through the Krebs-Henseleit cycle. The specific activities of the guanidine carbon of protein arginine and of urea carbon are identical.

The synthesis rate of a given protein can be calculated when urea production and ¹⁴C activity accumulated in urea and in the arginine of the protein under study are measured:

$$\frac{\text{Total } ^{14}\text{C in urea carbon}}{\text{Mass of urea carbon synthesized in same time}} = \frac{\text{Total } ^{14}\text{C in guanidine carbon of protein arginine}}{\text{Mass of corresponding protein carbon synthesized in same time}}$$

The study of the patient can be concluded within four to six hours. However, the amount of analytical work involved is so extensive that it has prevented the application of the method on a large scale. The great advantages of the method are that it provides a direct determination of synthesis rate, that the synthesis rate of a number of proteins produced in the liver can be measured in one study, and that it determines the rate of synthesis over a relatively brief period so that rapid changes of protein synthesis can be studied. Samuel, Jarnum, and Jeejeebhoy (1969) found by this method that a four-fold increase in the rate of albumin synthesis occurred in four malnourished Indian patients with tropical sprue when they were treated with intravenous amino acid infusions (Aminofusin, Pfrimmer). When patients are in a steady state, very good agreement has been found between the rate of synthesis of albumin determined directly by ¹⁴C-carbonate and indirectly by means of ¹³¹I-labelled albumin. It may be concluded that for most clinical studies radioiodine-labelled proteins are acceptable for plasma protein turnover studies.

Normal Values

The table shows turnover values in normal subjects for a number of proteins which are present in plasma in relatively large concentration. The two proteins which are normally present in highest concentration in plasma, albumin and IgG have fractional catabolic rates of about 9% of the intravascular mass per day. All other proteins studied have higher catabolic rates. The table also shows that the distribution ratio depends on the molecular size of the protein; proteins with large molecules like IgM and fibrinogen are predominantly located in the intravascular compartment.

The serum concentration and the synthetic rate of immunoglobulins are much more variable than those of albumin and transferrin. The most probable ex-

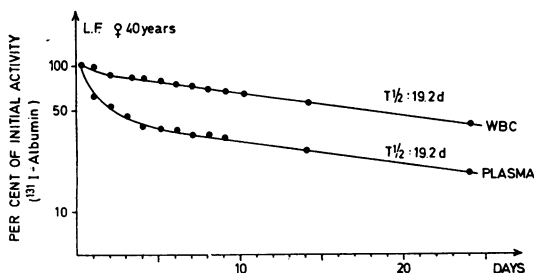


Fig 3 Whole body activity curve (WBC) compared with plasma activity curve over more than three weeks. The final slopes are identical. Only whole body counting yields the final slope within a week.

Plasma Protein	Serum Concentration (g/l)	Fractional Catabolic Rate as Percentage of Intravascular Mass (IVM) per Day	Synthetic Rate (g/175 cm/day)	Distribution Ratio IVM as Percentage of Total Mass
Albumin	42 (10%) ¹	9 (9%)	11 (16%)	45 (8%)
Transferrin	2.2 (8%)	17 (7%)	1.1 (21%)	49 (5%)
IgG	11 (17%)	7 (21%)	2.1 (28%)	58 (12%)
IgM	0.8 (35%)	11 (14%)	0.3 (41%)	74 (15%)
Fibrinogen	3.6	25	2.2	84

Table Normal turnover values of certain plasma proteins

¹Coefficient of variation.

planation is that albumin and transferrin have fairly constant functions. Albumin maintains the oncotic pressure of plasma, and transferrin acts as transport medium of iron from the intestinal tract and iron stores to the bone marrow. In contrast, the synthesis and degradation of immunoglobulins are to a large extent dependent on the strength of antigenic stimulation, which probably varies considerably from individual to individual and with social criteria. Thus the IgG in apparently healthy Indians in Bombay has been shown to be markedly higher than in control subjects from western Europe (Jarnum, Jeejeebhoy, and Singh, 1968a), probably due to a much higher incidence of infectious disease and therefore a much stronger antigenic stimulation in India. Living at high altitudes also seems to affect immunoglobulin turnover. We studied albumin and IgG turnover in healthy subjects before, during and after eight days exposure to an altitude of 3456 m in Switzerland (Westergaard, Jarnum, Preisig, Ramsøe, Tauber, and Tygstrup, 1970). Albumin degradation remained constant, whereas the catabolism of IgG was significantly increased ($P < 0.01$). The reason for this is unknown.

Another remarkable effect of the stay at high altitude was a shift of labelled protein from the vascular bed to extravascular compartments, probably due to the increased capillary permeability which is known to occur at high altitude. Figure 4 shows that on returning to sea level plasma ¹³¹I-activity from ¹³¹I albumin was lower and whole-body ¹³¹I activity higher than predicted from the levels found at high altitude; this can only be explained by an extravascular shift of the protein.

Clinical Applications

Clinical studies of plasma protein turnover have been popular over the last 20 years, probably because the use of radioiodine-labelled proteins is safe, and numerous reports have appeared on protein turnover in disease with known disturbances of protein metabolism. For the sake of clarity I shall

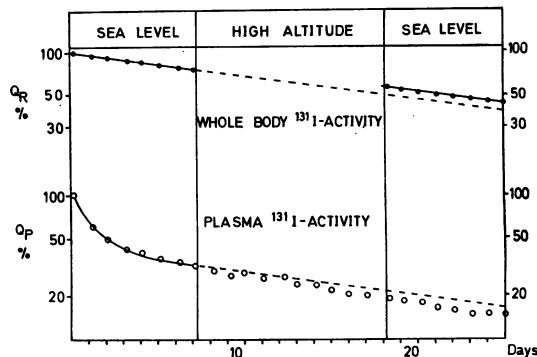


Fig 4 Whole body and plasma activity of ¹³¹I-albumin before and after an eight-day stay at high altitude. On return to sea level whole-body activity was higher and plasma activity lower than predicted. The most probable explanation is that part of the intravascular protein mass shifted to the extravascular compartments at high altitude (Westergaard et al, 1970).

Q_R = amount of labelled protein remaining in the body
 Q_P = plasma concentration of labelled protein

discuss them under two headings: hypoanabolic and hypercatabolic states.

HYPOANABOLIC STATES

Congenital deficiency of plasma protein synthesis is usually characterized by a very low plasma concentration or complete absence of a particular protein. Such disorders usually present clinically as might be expected, eg, recurrent infections in agammaglobulinaemia, severe iron deficiency anaemia in atransferrinaemia, or megaloblastic anaemia when transcobalamin is absent. However, in analbuminaemia severe oedema would be expected whereas in fact these patients may have only slight oedema and be otherwise unaffected.

Acquired deficiency of plasma protein synthesis is quite common. Thus, a low synthesis rate of albumin and transferrin is an almost constant finding in severe malnutrition whether due to mal-

absorption or dietary deficiency, and may occur also in cirrhosis of the liver.

Various types of a- or hypo-gammaglobulinaemia are now well recognized and may be either idiopathic or a complication of another disease, for instance, hypogammaglobulinaemia in lymphatic leukaemia.

HYPERCATABOLIC STATES

Hypercatabolic hypoproteinaemia may be due to a true endogenous hypercatabolism or to an abnormal protein loss.

Endogenous hypercatabolism

Endogenous hypercatabolism of albumin is known to occur in thyrotoxicosis and in Cushing's disease or in patients treated with glucocorticosteroids. It is seen very rarely in patients with severe hypogammaglobulinaemia. We have reported a 54-year-old man with hypogammaglobulinaemia who died from generalized *Pneumocystis carinii* infection, and whose serum albumin was only 2 g per litre due to a sevenfold increase in the rate of catabolism; he had neither proteinuria nor intestinal protein loss (Jarnum, Rasmussen, Ohlsen, and Sorensen, 1968b).

An analogous and also unexplained increase of catabolism of IgG is sometimes found in patients with myotonic dystrophy (Wochner, Drews, Strober, and Waldmann, 1966).

ABNORMAL PROTEIN LOSS FROM SKIN, KIDNEY OR GUT

Skin diseases

Extensive second and third degree burns have a profound effect on plasma protein turnover. The concentration of serum albumin and of immunoglobulin (IgG, IgA and IgM) falls initially, due to a combination of increased catabolism, exudation through the damaged skin and especially extravascular accumulation of plasma protein (Birke, Liljedahl, Plantin, and Reizenstein, 1968). Albumin synthesis is decreased despite the fact that the colloid osmotic pressure is low and the supply of calories and amino acids is high. The modern treatment in a warm (32°), dry atmosphere increases albumin synthesis significantly, but not to normal levels (Birke, 1970). However, the synthesis rate of immunoglobulins is markedly increased. The result is that from 10 to 21 days after burning the serum concentration of immunoglobulins is elevated, with the notable exception of patients who ultimately die from sepsis as these show no elevation of serum IgG (Birke, 1970).

Renal disease

The physiological role of the kidney in plasma pro-

tein turnover is limited. Proteins of molecular weight less than 50 000 which pass the glomerular membrane seem to be catabolized by tubular cells. In both animals and man radioiodine-labelled light chain dimer (molecular weight, 44 000) given intravenously was shown to be catabolized by the kidney (Strober, Mogielnicki, and Waldmann, 1973). Similarly the catabolism of lysozyme (muramidase), with a molecular weight slightly smaller than light chain, has been shown to occur mainly in the kidney, the catabolic rate in nephrectomized patients being only 15% of the normal fractional catabolic rate of 76% per hour (Hansen, Karle, Andersen, and Ølgaard, 1972).

In the nephrotic syndrome the plasma protein pattern and turnover are profoundly altered, but most of the changes can be explained by the fact that proteins which are not normally filtered can pass through the damaged glomerular membrane, especially those of relatively low molecular weight such as albumin and the smaller immunoglobulins. As a result, the catabolism of low molecular weight proteins such as light chain, which is normally filtered, is unchanged, while the catabolic rate of albumin (molecular weight 68 000) is increased. In a study of 30 adult nephrotic patients with a normal or almost normal glomerular filtration rate we found that the endogenous catabolic rate of albumin, ie, that part of total albumin turnover which is not due to albuminuria, was increased in 19 (Jensen, Rossing,

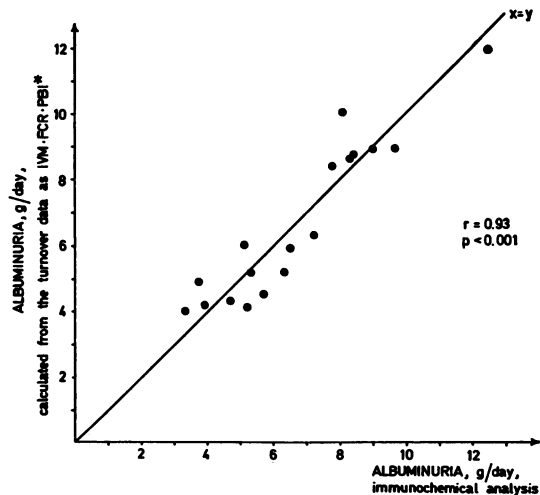


Fig 5 Relation between direct (immunochemical analysis of the urine) and indirect (^{125}I -albumin study) determination of albuminuria in 18 adult patients with nephrotic syndrome. $\text{IVM} \times \text{FCR} \times \text{PBI}^* = \text{intravascular albumin mass} \times \text{fractional catabolic rate} \times \text{protein-bound fraction of urinary } ^{125}\text{I}$.

Andersen, and Jarnum, 1967). Furthermore, the increase in endogenous catabolic rate was positively correlated with the degree of albuminuria. This finding agrees well with the suggestion (Sellers, Katz, and Rosenfeld, 1961) that in nephrosis filtered proteins are partly catabolized by tubular cells. The validity of the results of ^{131}I albumin studies in the nephrotic syndrome is indicated by the close correlation between the amount of albuminuria calculated from the plasma ^{131}I albumin disappearance and the protein-bound radio-activity of the urine, and that determined directly by immunochemical analysis of the urine (Jensen *et al*, 1967), as shown in figure 5.

Gastrointestinal disease

The gastrointestinal tract was not recognized as a site of abnormal protein loss until 1957. In that year Citrin and his associates showed that the cause of severe hypoalbuminaemia regularly present in Ménétrier's disease (or giant hypertrophic gastritis) was an abnormal protein leakage through the enormously enlarged rugae of the stomach (Citrin, Sterling, and Halsted, 1957). Two years later an abnormal gastrointestinal protein leakage, demonstrated by means of ^{131}I -labelled polyvinylpyrrolidone, was reported as the probable cause of the rare condition idiopathic hypoproteinaemia (Gordon, 1959; Schwartz and Jarnum, 1959).

Since then a great variety of gastrointestinal diseases have been shown to be associated with abnormal gastrointestinal protein loss. They may be grouped according to whether the epithelium is normal, abnormal or lost (Jarnum, 1963). When the epithelium is lost, as in ulcerative colitis, it is not surprising that large amounts of protein-rich exudate escape to the intestinal lumen.

In Ménétrier's disease there is a great increase in the surface area of the gastric epithelium, which may explain the protein loss since, even under normal conditions, some protein leaks through the gastrointestinal epithelium. Other protein-losing diseases with abnormal epithelium are carcinoma of the stomach or colon and non-tropical sprue. However, in sprue protein is not lost in all cases.

The largest gastrointestinal protein loss we have seen has occurred in patients with congenital malformations of intestinal lymphatics; stasis produces a club-shaped dilatation of the small-intestinal villi (fig 6) because the chyle is trapped in the central lacteals of the villi. The epithelium is normal even when studied by electron microscopy, but it is possible that multiple tiny ruptures occur so that the protein-rich chyle escapes into the gut lumen.

The same mechanism explains the protein loss seen in some cases of chronic constrictive pericarditis in which the marked elevation of the central venous



Fig 6 *Intestinal villi in a jejunal biopsy from a patient with intestinal lymphangiectasia. The villi are almost club-shaped due to dilated lymphatics. The epithelial membrane may burst (lower left corner) and protein-rich interstitial fluid and chyle leak into the intestinal lumen.*

pressure obstructs the outflow of lymph to the venous system, and causes 'lymphatic hypertension' which again produces stasis in the lacteals of the villi.

Detection and Quantitation of Gastrointestinal Protein Loss

Intestinal loss of protein results in loss of the same fraction of the intravascular mass of all plasma proteins (Waldmann and Schwab, 1965), and a number of radioisotope-labelled macromolecular compounds have been used to detect or measure increased gastrointestinal protein leakage. Ideally the test substance should be a plasma protein labelled with a radioisotope which does not change the metabolic behaviour of the protein and is not absorbed from the gut. Simultaneous determinations of the faecal excretion of the isotope and disappearance rate of the labelled protein from plasma would permit calculation of the turnover and distribution of the protein, and also of that part of its degradation which is due to leakage into the gut. So far ^{67}Cu -caeruloplasmin seems to be the only compound which fulfils these requirements (Waldmann, Morell, Wochner, Strober, and Sternlieb, 1967). Unfortunately, it is not practicable for clinical studies because of its high cost and the brief half-life of the isotope (62 hours).

When $^{51}\text{CrCl}_3$ is injected intravenously the ^{51}Cr labels plasma proteins, predominantly transferrin, in a matter of seconds. The subsequent faecal ^{51}Cr clearance offers a good estimation of gastrointestinal protein loss (van Tongeren and Reichert, 1966); this is apparent from the good correlation between faecal ^{51}Cr clearance and the fractional catabolic

rate of albumin (Jarnum, Westergaard, Yssing, and Jensen, 1968c) which is an indirect indicator of the size of the protein loss. However, endogenous turnover cannot be determined with ^{51}Cr -labelled proteins because binding of ^{51}Cr to protein is unstable.

^{59}Fe -labelled iron dextran may also be used to detect and measure gastrointestinal protein loss (fig 7, Jarnum *et al*, 1968c). The ^{59}Fe is not excreted in the urine, a great advantage when contamination of the stools with urine is difficult to prevent as, for example, in infants.

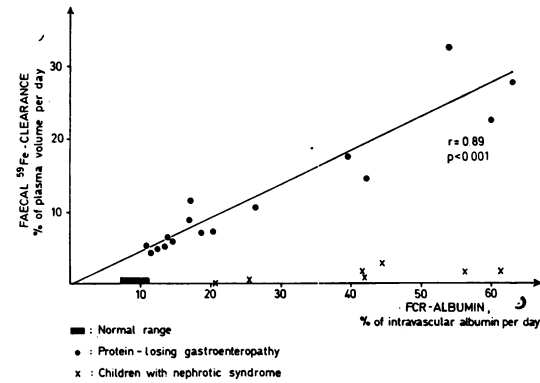


Fig 7 Faecal clearance of ^{59}Fe and fractional catabolic rate (FCR) of albumin after intravenous injection of ^{59}Fe -labelled iron dextran and ^{131}I -albumin in 16 patients with protein-losing gastroenteropathy and seven children with the nephrotic syndrome. A high correlation was present in patients with protein-losing gastroenteropathy (Jarnum *et al*, 1968).

Protein Turnover and Protein Loss in Chronic Inflammatory Bowel Disease

Chronic inflammatory bowel disease practically always produces a change of serum protein pattern and turnover. In a study of 78 patients, 42 with Crohn's disease and 36 with ulcerative colitis, who were compared with 78 matched healthy controls, we found that the same distinctive changes in serum protein concentrations were present in both diseases (Weeke and Jarnum, 1971). The concentrations of orosomucoid and haptoglobin were increased in most cases, and the concentrations of albumin, caeruloplasmin and transferrin were depressed.

The 'acute phase reactants', orosomucoid, α_1 -antitrypsin, α_1 -antichymotrypsin and haptoglobin, were clinically useful, since their serum concentrations reflected the grade of activity of the disease. Patients with active Crohn's disease who responded favourably to medical treatment had significantly higher immunoglobulin levels than patients who did

not respond (fig 8). The same relationship has been observed by de Dombal (1969) in patients with ulcerative colitis. We found the same trend in ulcerative colitis, but not on a statistically significant level.

We have performed turnover studies with radioiodine-labelled albumin and IgG simultaneously in about 100 patients with Crohn's disease or ulcerative colitis. In most of the patients we also estimated the intestinal protein loss either by means of ^{59}Fe -labelled iron-dextran, which could be done simultaneously owing to the high energy level of gamma rays from ^{59}Fe , or by means of $^{51}\text{CrCl}_3$, which had to be done one week in advance due to the similarity of gamma ray energy of ^{51}Cr and ^{131}I . We found that an abnormal but, in most cases, moderate

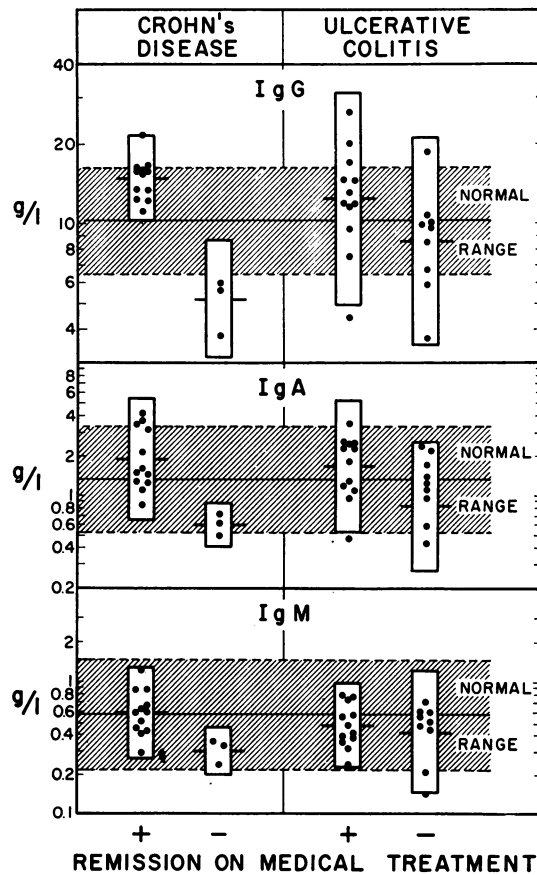


Fig 8 Immunoglobulin levels (mean \pm 2SD) in unoperated patients with moderate to severe Crohn's disease or ulcerative colitis. Mean \pm 2SD of the matched control material is also shown (hatched area). The y axis is logarithmic (Weeke and Jarnum, 1971).

intestinal protein loss is present in the great majority of patients and that albumin and IgG turnover are affected in a similar way in the two diseases. Data were analysed only from the 48 patients in whom the diagnosis was considered certain (Jarnum and Jensen, 1975), namely, 21 patients with ulcerative colitis and 27 with Crohn's disease. In all of the latter the diagnosis was confirmed by intestinal resection (performed one-half to five months later). The catabolic rates of albumin and IgG were elevated in practically all cases and there was a high degree of correlation between them, in ulcerative colitis ($r = 0.83$, $p < 0.001$) and in Crohn's disease ($r = 0.73$, $p < 0.001$). The data from patients with ulcerative colitis are given in figure 9.

In the majority of cases the proportional increase in the catabolic rate of IgG was greater than that of albumin. Since the excess catabolism is due mainly to intestinal protein loss, a preferential loss of IgG might be postulated. However, this is highly unlikely, since intestinal protein loss is 'bulk loss' which drains the same fraction of the intravascular mass of all plasma proteins regardless of their molecular size (Waldmann and Schwab, 1965). Therefore the hypercatabolism of IgG, which is well known to occur in other chronic inflammatory conditions such as cirrhosis of the liver and systemic lupus erythematosus (Andersen, 1964), is probably due not only to protein loss but also to 'endogenous' hypercatabolism of IgG. In non-inflammatory protein-losing enteropathies such as intestinal lymphangiectasis the catabolic rate of IgG is close to or lower than that of albumin (Bendixen, Jarnum, Søltoft, Westergaard, Weeke, and Yssing, 1968).

As mentioned earlier, the serum concentration of

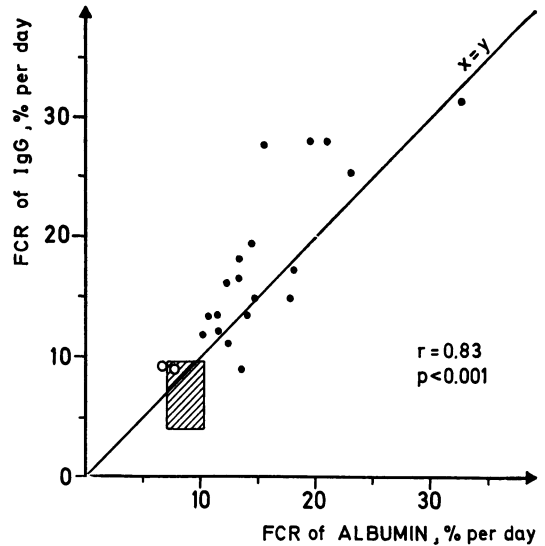


Fig 9 Albumin and IgG degradation in ulcerative colitis (n = 21).

IgG in ulcerative colitis and Crohn's disease is usually within the normal range, whereas serum albumin is depressed. We found an inverse relationship between serum albumin and catabolic rate due to the fact that the synthesis rate of albumin is largely unchanged in these conditions. In contrast, serum IgG concentration seems to be quite unaffected by the hypercatabolism which indicates that a significant increase of IgG synthesis has taken place. We used ⁵⁹Fe-iron-dextran to assess the size of

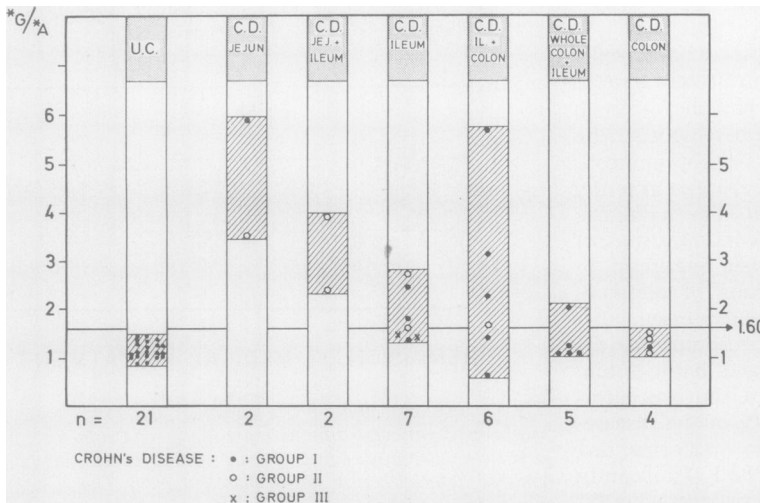


Fig 10 The ratio (*G/*A) between faecal ¹²⁵I excretion from ¹²⁵I-IgG and faecal ¹³¹I excretion from ¹³¹I-albumin in ulcerative colitis (UC, n = 21) and three groups of patients with Crohn's disease (CD, n = 26) localized to various sites of the intestinal tract.

intestinal protein loss. In an earlier study (Jarnum *et al*, 1968c) we found quite a good correlation between gastrointestinal ^{59}Fe clearance and the fractional catabolic rate of albumin in various types of protein-losing gastroenteropathy (fig 7). In this study of chronic inflammatory bowel disease a similar satisfactory correlation was found both in ulcerative colitis and in Crohn's disease. Furthermore the intestinal protein loss was unrelated to the anatomical extent of the lesion in Crohn's disease. Apparently, protein loss is more dependent on other factors such as the depth of the ulceration or the damage to lymphatics.

The faecal excretion of ^{131}I and ^{125}I from labelled albumin and IgG respectively turned out to be a useful guide to the topographic site of the lesion in Crohn's disease (fig 10) since the ratio of faecal ^{125}I from IgG to faecal ^{131}I from albumin increased as the location of the lesion became more proximal. This is probably due to a higher intraluminal proteolysis of albumin than of IgG. In an earlier study (Søltøft and Jarnum, 1969) we found that faeces from patients with chronic inflammatory bowel disease can break down albumin more rapidly than IgG, whereas faeces from patients with diarrhoea from other causes (postgastrectomy syndrome, gluten enteropathy, lactose malabsorption, small intestinal resection) showed quite the opposite. We have no explanation for this phenomenon.

This survey of plasma protein turnover has dealt mainly with clinical aspects. The intention has been to show that such studies, at least so far as the major plasma protein components are concerned, are relatively simple and can yield information on the pathogenesis of abnormal plasma protein concentration patterns which are helpful both in diagnosis and in the assessment of therapy.

References

- Andersen, S. B. (1964). *Metabolism of Human Gamma Globulin (γ_{2e} -globulin)*. Blackwell, Oxford.
- Bendixen, G., Jarnum, S., Søltøft, J., Westergaard, H., Weeke, B., and Yssing, M. (1968). IgG and albumin turnover in Crohn's disease. *Scand. J. Gastroent.*, 3, 481.
- Birke, G. (1970). Regulation of protein metabolism in burns. In *Plasma Protein Metabolism: Regulation of Synthesis, Distribution and Degradation*, edited by M. A. Rothschild and T. Waldmann, p. 415. Academic Press, New York and London.
- Birke, G., Liljedahl, S.-O., Plantin, L. O., and Reizenstein, P. (1968). Studies on burns IX. The distribution and losses through the wound of ^{131}I -albumin measured by whole-body counting. *Acta chir. scand.*, 134, 27.
- Citrin, Y., Sterling, K., and Halsted, J. A. (1957). The mechanism of hypoproteinemia associated with giant hypertrophy of the gastric mucosa. *New Engl. J. Med.*, 257, 906.
- de Dombal, F. T. (1969). Prognostic value of estimating serum proteins in cases of ulcerative colitis in remission. *Gut*, 10, 491.
- Gordon, R. S., Jr. (1959). Exudative enteropathy: abnormal permeability of the gastrointestinal tract demonstrable with labelled polyvinylpyrrolidone. *Lancet*, 1, 325.
- Hansen, N. E., Karle, H., Andersen, V., and Ølgaard, K. (1972). Lysozyme turnover in man. *J. clin. Invest.*, 51, 1146.
- Jarnum, S. (1963). *Protein-Losing Gastroenteropathy*, p. 198. Blackwell, Oxford.
- Jarnum, S., Jeejeebhoy, K. N., and Singh, B. (1968a). Dysgammaglobulinaemia in tropical sprue. *Brit. med. J.*, 4, 416.
- Jarnum, S., and Jensen, K. B. (1975). Faecal radiiodide excretion following intravenous injection of ^{131}I -albumin and ^{125}I -IgG in chronic inflammatory bowel disease. An aid to topographic diagnosis. *Gastroenterology*, in press.
- Jarnum, S., Rasmussen, E. F., Ohlsen, A. S., and Sørensen, A. W. S. (1968b). Generalized pneumocystis carinii infection with severe idiopathic hypoproteinemia. *Ann. intern. Med.*, 68, 138.
- Jarnum, S., Westergaard, H., Yssing, M., and Jensen, H. (1968c). Quantitation of gastrointestinal protein loss by means of Fe^{59} -labeled iron dextran. *Gastroenterology*, 55, 229.
- Jensen, H., Rossing, N., Andersen, S. B., and Jarnum, S. (1967). Albumin metabolism in the nephrotic syndrome in adults. *Clin. Sci.*, 33, 445.
- McFarlane, A. S. (1958). Efficient trace-labelling of protein with iodine. *Nature (Lond.)*, 182, 53.
- McFarlane, A. S. (1963). Measurement of synthesis rates of liver-produced plasma proteins. *Biochem. J.*, 89, 277.
- Matthews, C. M. E. (1957). The theory of tracer experiments with ^{131}I -labelled plasma proteins. *Phys. med. Biol.*, 2, 36.
- Nosslin, B. (1966). Applications of tracer theory to protein turnover studies. *J. nucl. biol. Med.*, 9, 18.
- Reeve, E. B., Pearson, J. R., and Martz, D. C. (1963). Plasma protein synthesis in the liver. Method for measurement of albumin formation in vivo. *Science*, 139, 914.
- Samuel, A. M., Jarnum, S., and Jeejeebhoy, K. N. (1969). Influence of parenteral l-isomeric amino acids on absolute albumin synthesis rates in tropical sprue. *Scand. J. Gastroent.*, 4, Suppl. 3, 51.
- Schwartz, M., and Jarnum, S. (1959). Gastrointestinal protein loss in idiopathic (hypercatabolic) hypoproteinaemia. *Lancet*, 1, 327.
- Sellers, A. L., Katz, J., and Rosenfeld, S. (1961). Plasma albumin catabolism in experimental nephrosis. *Nature (Lond.)*, 192, 562.
- Sterling, K. (1951). The turnover rate of serum albumin in man as measured by I^{131} -tagged albumin. *J. clin. Invest.*, 30, 1228.
- Strober, W., Mogielnicki, R. P., and Waldmann, T. A. (1973). The role of the kidney in the metabolism of serum proteins. In *Protein Turnover: Ciba Foundation Symposium 9* (new series) p. 25. Associated Scientific Publishers, Amsterdam, London, New York.
- Søltøft, J., and Jarnum, S. (1969). Faecal proteolysis of albumin and IgG in Crohn's disease and ulcerative colitis. *Digestion*, 2, 282-288.
- van Tongeren, J. H. M., and Reichert, W. J. (1966). Demonstration of protein-losing gastroenteropathy: the quantitative estimation of gastrointestinal protein loss using ^{51}Cr -labelled plasma proteins. *Clin. chim. Acta*, 14, 42.
- Waldmann, T. A., Morell, A. G., Wochner, R. D., Strober W., and Sternlieb, I. (1967). Measurement of gastrointestinal protein loss using ceruloplasmin labeled with ^{63}Cu . *J. clin. Invest.*, 46, 10.
- Waldmann, T. A., and Schwab, P. J. (1965). IgG (7 S gamma globulin) metabolism in hypogammaglobulinemia. Studies in patients with defective gamma globulin synthesis, gastrointestinal protein loss, or both. *J. clin. Invest.*, 44, 1523.
- Weeke, B., and Jarnum, S. (1971). Serum concentration of 19 serum proteins in Crohn's disease and ulcerative colitis. *Gut*, 12, 297.
- Westergaard, H., Jarnum, S., Preisig, R., Ramsøe, K., Tauber, J., and Tygstrup, N. (1970). Degradation of albumin and IgG at high altitude. *J. appl. Physiol.*, 28, 728.
- Wochner, R. D., Drews, G., Strober, W., and Waldmann, T. A. (1966). Accelerated breakdown of immunoglobulin G (IgG) in myotonic dystrophy: a hereditary error of immunoglobulin catabolism. *J. clin. Invest.*, 45, 321.