Suggested short title:

PROTEIN-LOSING GASTROENTEROPATHY.

A STUDY OF PROTEIN-LOSING GASTROENTEROPATHY IN PATIENTS WITH GASTROINTESTINAL TRACT CANCERS AND ALBUMIN METABOLISM

by

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PREFACE

This manyscript is the product of a year of research done in the experimental surgical laboratories at McGill University. The experimental work embodied in this thesis represents an attempt to contribute to the problem of hypoproteinemia in exudative enteropathy and also the albumin metabolism in man. The clinical importance of the condition lies in the fact that progressive protein loss in the gut leads to weight loss, cachexia, and eventually shortening the life of the individual. The surgical correction of the diseased portion of the gut, expecially in the case of malignancies, appears to be the major goal of the research carried out inthis problem, but the basic studies on the pathogenesis of the condition must be the primary requirements for such an achievement.

This work was carried out in association with and continued guidance of Dr. M. M. Hoffman, of the Department of Medicine, Royal Victoria Hospital, Montreal, P.Q., Canada, to whom goes the full credit for initiating this investigation and in sparing so much of his valuable time in going over this manuscript.

For making these studies possible, I would like to express my gratitude to Dr. D. R. Webster, Director of Experimental Surgery.

I also wish to thank Dr. L. G. Stephen-Newsham for his continuous help and direction during the course of the research, especially in the problems involving Radioactive Isotope, Physics and Mathematical Analysis and wish to thank Dr. G. W. Lehman and Dr. A. N. Freedman for

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I am very much indebted to Drs. R.D. McKenna and Ivan T. Beck of Gastroenterology Department, Dr. H.F. Moseley, Director of Accident Service, Dr. M. Silverberg of Montreal Children's Hospital, and Dr. Wait, Dr. P. Capello, Dr. W. Depow for their help in allowing me to carry out studies on their patients.

I should like to thank Mr. John Fraser, Photography Department, Royal Victoria Hospital, for his valuable assistance in preparing the photographic materials which appear in this thesis. I also wish to thank Mrs. M. Paasuke for the typing of the manuscript.

Finally, I wish to thank Dr. W. D. Miller who has given me so much courage to do this year of research. I also wish to express my appreciation for the privilege of working in the Department with Drs. V. Piccone, E. Charrette, H. Shibata and J. Gentile, which made this year a very fruitful and pleasant one.

Peter Sum.

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TABLE OF CONTENTS

I. INTRODUCTION

The complete cycle of albumin metabolism is now known in its broadest outline. The site of albumin synthesis had long been implicated to be in the liver by clinical observations and more recent studies on isolated perfused rat liver with radioactive labelled amino acid have confirmed thse impressions[1,2], but the mechanism of its breakdown remained to be elucidated until 1959 Birke et al.[3] and 1960 Wetterfors et al.[4] demonstrated that a large percentage of breakdown occurred in the stomach and small intestine. In 1961, Katz et al.[5] demonstrated the rate of catabolism of albumin in rats to be about 20% in the gastro-intestinal tract, 25% in the liver and 50% in the muscle and skin.

Hypoproteinemia is a common finding in a variety of diseases, including gastrointestinal tract disorders. It may be due to (1) excessive loss, (2) protein breakdown, or (3) defect in the synthesis of the body protein. The excessive loss is seen in nephrotic syndrome[12], ulcerative colitis, regional ileitis, burns, haemorrhage and plasma-pheresis[6]. The excessive breakdown is seen in cases of hypermetabolism, such as hyperthyroidism, fever, neoplasia and adrenal cortex over-activity[69]. The defect in the synthesis of body protein may be due to inadequate dietary intake, as in syndromes of maldigestion and in mal-absorption syndrome, starvation, kwashiorkers, Hirschsprung's disease[3]. It also may be due to hepatic dysfunction[70], as in cirrhosis, portal hypertension and also in cardiac diseases such as congestive heart failure[41] and constrictive pericarditis[7]. Very often more than one of these will be the etiological factors for such condition, as in case of

empyema with amyloidosis where the patient will have poor appetite, exudation and fever.

From the turn of this certury, more than fifty cases of hypoproteinemia have been collected with clinical evidence of oedema when no dietary deficiency existed and there was no evidence of cardiac, hepatic or renal disease; it has been recognized as a clinical entity under the name of idiopathic hypoproteinemia, and was first described by Cope and Goaphy in 1935, who suggested the condition might be due to increased protein loss(9). The mechanism of idiopathic hypoproteinemia in humans was intensively studied by Albright et al. in the middle 1940's by infusing a large amount of human albumin intravenously into the individual with the disease and by meticulous nitrogen balance studies when it was found that the protein was catabolized at an increased rate(10). In 1949, Albright et al., using the newly developed radioactive labelled albumin (RISA), demonstrated that the disorder of hypoproteinemia was not due to the decreased rate of synthesis but rather the increased destruction, as evidenced by the greatly increased rate of disappearance of intravenously injected RISA. In 1950, Kinsell et al. failed when attempting to show alteration in protein synthesis by using labelled amino acid (S^{35} methionine)(8). In 1957, Schwartz and Thomsen, using albumin I-131, performed turnover studies in three patients with idiopathic hypoproteinemia and concluded that an increased rate of degradation was the physiological derangement. The latter authors suggested the name Idiopathic Hypercatabolic Hypoproteinemia(11). In 1957, Citrin et al. described a case of hypoproteinemia and oedema associated with hypertrophic gastritis

(Menetrier's Disease)[22]. They recovered from RISA on gastric suction of this patient as compared with the controls and postulated the basic cause of hypoproteinemia lay in the gastric mucosa. Their report created interest in the studies of gastrointestinal tract disorders as a cause of hypoproteinemia and oedema. Coincidentally, Steinfeld et al. also reported increased radioactivity in stool in a case of ulcerative colitis after intravenously RISA injection[14]. Gordon, in 1959, introduced the use of polyvinyl pyrrolidone labelled with I-131 (PVP -I-131) which is not hydrolysed by intestinal proteolytic enzymes and this material was studied on nine patients with idiopathic hypercatabolic hypoproteinemia. He reported more radioactivity in the stool of these patients than in those of several controls. This finding was confirmed by four additional cases of Schwartz and Jarnum[15]. Gordon re-affirmed that idiopathic hypercatabolic hypoproteinemia resulted from an abnormal leakage of plasma protein into the gastrointestinal tract - "An exudative gastroenteropathy". Recently, in 1961, Marshak et al. classified this syndrome into the following clinical varieties:[16].

1. Primary

    a. Mucosal hypertrophy of stomach with a giant fold

    b. Exudative enteropathy of Gordon with no hyperplasia but lymphangiectasia.

2. Secondary

    a. Regional enteritis

    b. Ulceration

    c. Primary sprue

    d. Mesenteric vascular occlusion (Zuidema, 1961).

    e. Cancer of gastrointestinal tract.

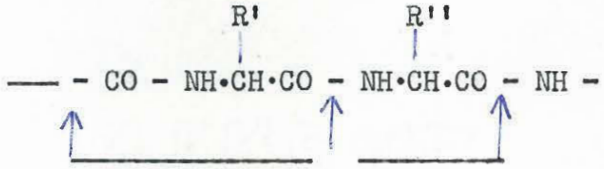
Gastrointestinal malignancies may play an important role as one of the etiological factors for hypoproteinemia. In 1943, Abel et al.[13] described the metabolic abnormalities in the gastrointestinal tract of cancer patients. One of the abnormalities was low serum albumin which was found in 59 out of 100 gastrointestinal cancer patients with no evidence of dietary impairment. Therefore they postulated the condition was probably due to hepatic dysfunction in the synthesis of albumin. In 1956, Steinfeld studied a few patients with gastrointestinal tract tumours with RISA[17]. He suggested two possible mechanisms in these cancer patients which would cause hypoproteinemia and oedema. The mechanisms are: (1) an increase of plasma volume, (2) a failure of albumin production to keep up with degradation. In order to achieve a sound understanding of the syndrome of exudative enteropathy, it is important to consider normal protein metabolism in more detail.

II. PROTEIN METABOLISM

A. Definition and General Properties of Proteins

Proteins may be defined as compounds of high molecular weight, consisting largely or entirely of chains of alpha-amino acids united in peptide linkage. The constituent amino acids can be obtained by hydrolysis of the proteins.

The amino acids have the general formula $R \cdot CH(NH_2) \cdot COOH$ where R is any one of a variety organic groupings as shown below. The peptide bonds of a polypeptide chain are CO-NH-(Amide) linkage of the following type



peptide bonds

The molecular weights of the protein vary from about 13,000 to many millions. Most proteins, because of their molecular size, are not diffusible through the membranes such as collophane and, like the polysaccharides, are actually of the colloidal dimensions and exhibit the properties associated with the colloidal state of matter. Some are soluble in pure water; some require the presence of salt or small amount of acid or base to dissolve. One group is soluble in certain concentration of alcohol, although (with the exception of the recently discovered proteolipids) proteins are generally insoluble in organic solvents. The structure protein known as scleroproteins are dissolved only by reagents which cause considerable alterations in their structure.

The average progein is an unstable compound. In response to exposure to heat, extremes of pH, surface action, or various reagents,

the native protein undergoes a series of changes known as denaturation, resulting in alteration in a number of its properties.

B. Biological Functions of Plasma Proteins.

1. Nutritive: The nutritive functions of the plasma proteins are probably attributable largely to the albumin fraction due to its quantitative dominance. Intravenously administered albumin has been shown in fact to be efficiently, although slowly, utilized by humans.

2. Osmotic effects of plasma proteins: The osmotic effects of plasma proteins cause water to flow from the protein-free interstitial fluid into the blood vessels. On the other hand, the capillary blood pressure is a filtering force tending to drive protein-free ultrafiltrate into the interstitial spaces in the opposite direction to the osmotic effect of the colloid.

The osmotic effect of the plasma proteins depends mainly on the serum albumin and to a smaller extent on serum globulin. Since albumin has a smaller molecular weight (69,000) than globulin (150,000 - 1,300,000), a given weight of albumin contains more osmotically effective particles than the same weight of globulin; one gram per 100 ml. of albumin has an osmotic effect equivalent to 6 mm Hg., but globulin only 1.5 mm. Albumin comprises about 60% of total proteins thus contributing about 80% of osmotic effect (i.e. 24-30 mm Hg osmotic pressure).(71)

By the virtue of their osmotic effect, plasma proteins tend to retain fluid in the blood capillaries and thus maintain the plasma volume. The opposing effect of osmosis and capillary pressure

regulate the interchange of water between the plasma and tissue spaces (see Figure 1)[71].

3. Protein in acid base balance: From a quantitative standpoint, the buffering capacity of the plasma protein is not very great. In the whole blood, however, the combined buffering action of the haemoglobulin and the plasma protein is as important as that due to the bicarbonate and the other inorganic buffer system of the blood.

4. Transport function of plasma proteins: The proteins are essential for the transport of many compounds: -

Lipids (lipoproteins)

Steroid hormones

Fat soluble vitamins A, D & E.

Bilirubin (mainly associated with albumin, but also with alpha-globulin)

Metals: Iron (a beta-globulin - "transferrin")

Copper (an alpha-globulin - "ceruloplasmin")

Calcium(half bound on albumin)

Thyroxin (alpha-globulin)

In addition to specific carriers, mainly globulins, plasma albumin has been found to bind with many compounds (e.g. drugs and dyes).

5. Coagulation: In addition to fibrinogen and prothrombin, plasma contains a number of other components which particulate in process of blood coagulation, namely: AC - globulin, serum prothrombin conversion accelerators, antihemophilic globulin, antithrombin, cofactor, antithromboplastic lipoproteins, plasminogen, and the plasmin inhibitors.

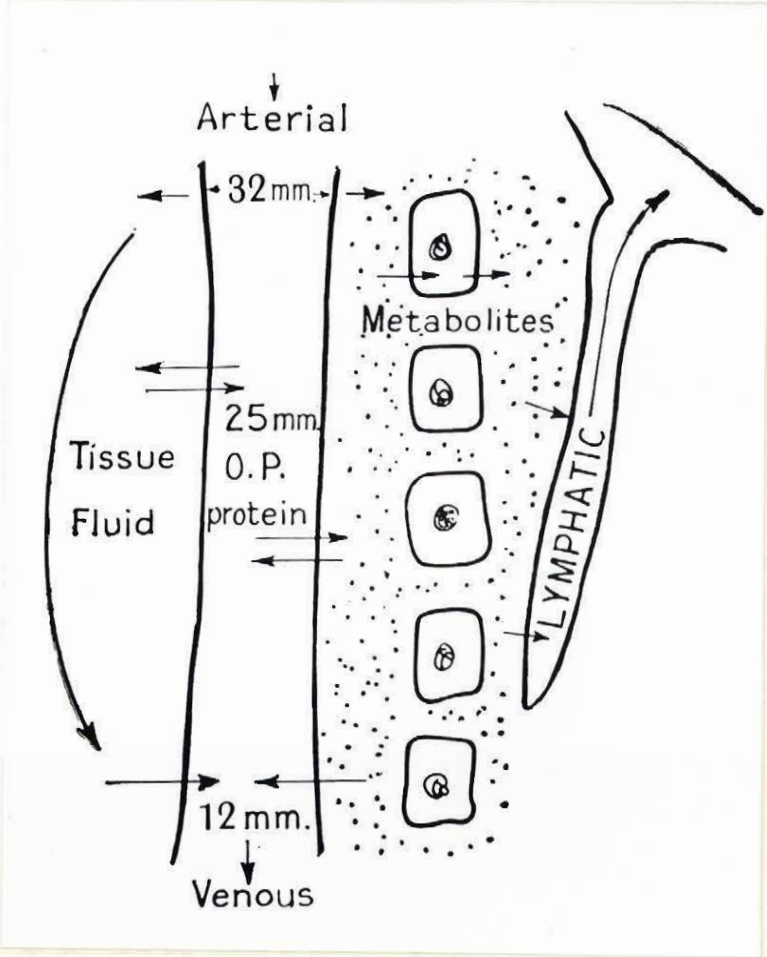


Figure 1

Fluid interchanges between plasma, tissue spaces and lymphatics.

(Samson Wright (1936): Proc. Roy. Soc. Med.)

6. Immunity: Reference has been made to the immunological function of the plasma proteins. The gamma globulin contains a large number of antibodies among which may be mentioned those against the influenza, mumps, poliomyelitis, measles, infectious hepatitis, typhoid, whooping cough and diphtheria. Two of the complements, a cofactor necessary in certain types of immunological reactions, are proteins of the globulin type.

7. Enzymes: The protein constituents of the plasma include a number of enzymes some of which are of clinical diagnostic importance, namely amylase, lipase, phosphatase, transaminase and glycolytic enzymes.

C. Digestion and Absorption of Proteins

Ingested proteins undergo digestion in the stomach and small intestine. This process consists essentially of hydrolysis into their constituent amino acids with polypeptides as intermediate products.

Gastric digestion

The factors in the gastric juice important in this connection are -

(1) Hydrochloric acid

(2) Pepsin, a proteolytic enzyme. The functions performed by hydrochloric acid are: -

(a) Conversion of protein to acid metaprotein

(b) Activation of the pepsinogen to pepsin

(c) Provision of an optimum rH for peptic activity (about 1.5 to 2.2, varying somewhat from different proteins). Under optimum condition, in vitro, pepsin is capable of splitting proteins

to the state of amino acids but under normal condition of gastric emptying these have very little digestive action beyond the state of peptones, 45-70% of the ingested protein being in the form of polypeptide at the time it leaves the stomach.

Digestion of proteins and protein products in the intestine is continued by proteolytic enzymes of the pancreatic and intestinal secretions. Pancreatic juice contains trypsinogen, chymotrypsinogen, and carboxypolypeptidase, the first two being activated by enterokinase, and enzyme secreted by the intestine. Carboxypolypeptidase breaks down polypeptides to simpler peptides and amino acids, whereas the other two enzymes act on the native protein to form proteoses, peptones, polypeptides, simple peptides and amino acids depending upon the length of the time the reaction is allowed to proceed. In addition to enterokinase, the intestinal juice contains dipeptidase and amino polypeptidase (formerly jointly termed erepsin) which split polypeptides to amino acids.

Nucleoproteins are split by proteolytic enzymes into proteins and nucleic acids. The protein thus undergoes digestion in the stomach and intestine as outlined above. The nucleic acids are converted, by the action of nuclease in the lumen and the wall of the intestine, to nucleotides of purine and pyrimidine bases, which are hydrolyzed by phosphatase in the intestine into phosphoric acid and the nucleosides which are then hydrolyzed by nucleosidases to purine and pyrimidine bases.

The process of the protein digestion consists essentially of the production of progressively smaller peptides by cleavage of internal peptide linkage (endopeptidases) and liberation of amino acids by cleavage of the terminal peptide linkage (exopeptidases). It is possible, too, that small peptide molecules escape complete hydrolysis and are absorbed without harmful effects. There is immunological evidence, however, that intact native protein molecules may occur occasionally and may be absorbed from intestine in the unaltered state, constituting the basic bases for allergic reaction in certain cases.

Food proteins are generally readily digested (90-97%) under normal conditions, very little escaping in the faeces. The only important exceptions are the insoluble fibrous proteins, e.g. keratin, which is not hydrolyzed by the enzymes of the human digestive tract. Most proteins are profoundly altered by many procedures commonly used in the preparation of food. Proper cooking alters the physical state of the protein, usually making it more easily digestible.

With a few exceptions indicated above (that is, small peptides and occasionally native protein), food proteins enter the organism in the form of their constituent amino acids. Certain other aspects of protein digestion may have an important bearing on their nutritional value, namely variation in the rate of liberation of amino acids. The amino acids are readily soluble in water and promptly absorbed from the small intestine, mainly into the portal circulation to the liver and, to a much smaller extent, via the lacteals, into the thoracic duct and thence directly into the systemic circulation. Only small amounts of free amino acid are found in the intestinal contents during the process of

digestion, indicating the rapidity of their absorption. This is reflected also in the rather prompt postprandial increase in blood amino acid concentration.

D. Dynamic Equilibrium and Degradation (turnover) of Proteins.

It was realized even for some time prior to the use of isotopes, but particularly clearly since the introduction of labelling techniques, that the constituents of the body are in a constant state of flux[59,60]. All body proteins, including plasma protein, haemoglobin, and the intracellular proteins, continually undergo degradation and synthesis, more than half of the protein of the liver and intestinal mucosa being broken down and resynthesized in 10 days; the turnover is slower in muscles and erythrocytes[61,62]. Active resynthesis occurs even during the period of starvation, and active breakdown during the period of nitrogen equilibrium. Degradation of protein in one tissue may be accompanied by synthesis in the others. Antibody gammaglobulins, induced by active immunization, also undergo continuous breakdown and synthesis, the half-life of these and other plasma proteins being about 2 weeks[63].

Protein in one compartment of the organism may be drawn upon to supply the deficiency in another compartment. For example, either plasma protein or haemoglobin (in the dogs), given intravenously, may supply the protein requirement during the prolonged fasting periods. The apparent stability of the adult organism is the result of a balance between the rate of synthesis and degradation of its constituents. In a growing organism the rate of synthesis of many of its constituents must exceed the rate of breakdown in order that the new

tissue may be constructed. Wasting disease, starvation and related states are characterized by rates of catabolism which are greater than the rate of the anabolism.

Several methods of expression are currently used to express the rate of synthesis or breakdown of a body constituent. Most of these have been developed in connection with isotopic labelling technique. Sometimes the rate of synthesis is expressed directly in terms of mass of compounds transformed per unit time per unit weight of tissue or animal, namely moles of protein synthesized per day per kilo body weight. On other occasions the rate of turnover of a compound is stated as the percentage of the amount present which is metabolized per unit time (see Figure 2).

E. Metabolic Pool and General Pathway of Protein Metabolism.

Endogenous amino acids are in a state of flux, they and their metabolites constantly mixing with those derived from the diet (exogenous). This common metabolic pool is utilized for anabolic and catabolic reactions, and via transamination alphaamino acid may donate its alphaamino group to some carbon skeleton to form another amino acid.

Through certain intermediate compounds such as pyruvate, acetate, oxalacetate, alpha ketoglutarete, etc. the metabolism of protein is integrated with that of carbohydrate and fat. Alanine, for example, is reversibly converted by deamination to pyruvic acid which may be used for gluconeogenesis.

The concepts of dynamic state and metabolic pool have been invaluable in the interpretation of data resulting from the experiments with isotopic labelling. Contrary to classical theories, according to

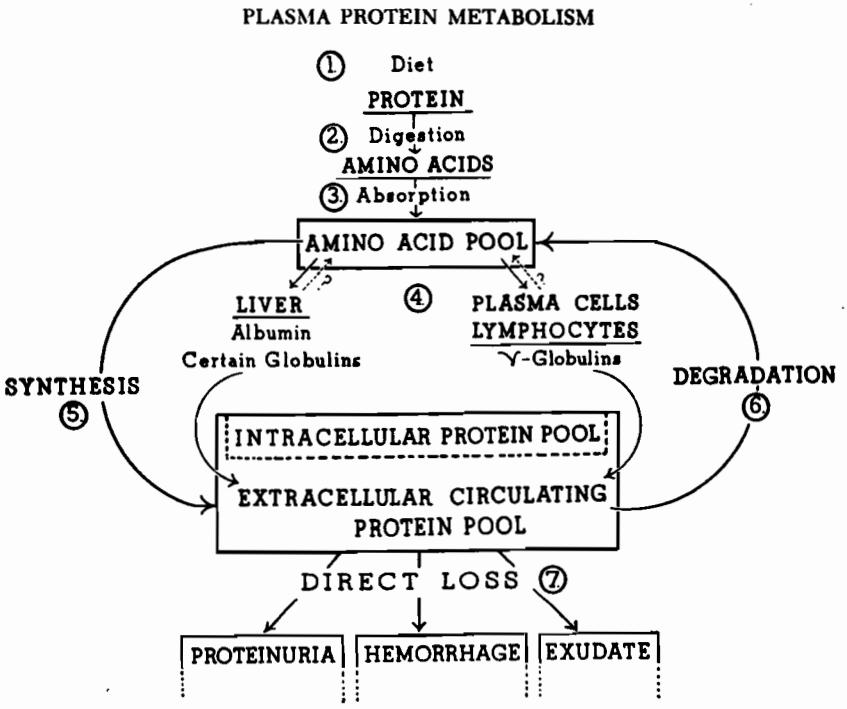


Figure 2

Plasma protein metabolism.

(The American Journal of the Medical Sciences, Vol. 231, No. 6, 1956, page 674).

which the exogenous glycine is metabolized by a different pathway from that of endogenous and should be degraded and excreted within approx. 24 hours, only a small fraction of the administered N^{15} was excreted as urea in the first 24 hours and several days were required to collect an appreciably fraction(64).

This is due to the glycine-N^{15} entering the common metabolic pool of that compound and the subsequent degradation of a mixture of glycine-N^{15} and glycine-N^{14}, and also to the contribution of some of the $-N^{15}H_2$ to other compounds.

The most important of the general metabolic pathways of amino acids are in the figure (see Figure 3), some followed special metabolic routes; among these are reactions leading to final excretion of sulfate (from methionine and cystine and creatinine, from glyanine and orginine). General features of the intermediary metabolism of amino acids of the most important from clinical stand point will be outlined here.

(a) Circulating amino acids: Amino acids absorbed from the intestine and escaping primary changes in the liver and those produced in proteolysis in the tissues and not re-utilized in situ for synthetic purposes, pass into the blood plasma and are distributed throughout the body.

(b) Urinary excretion: Comparatively little free amino acid is excreted in the urine under normal conditions. These substances pass freely into the glomerular filtrates but are very efficiently re-absorbed by the renal tubular epithelium. Even when the plasma level is raised by intravenous injection of amino acid mixtures, usually not more than 5% of the quantity administered escape in the urine.

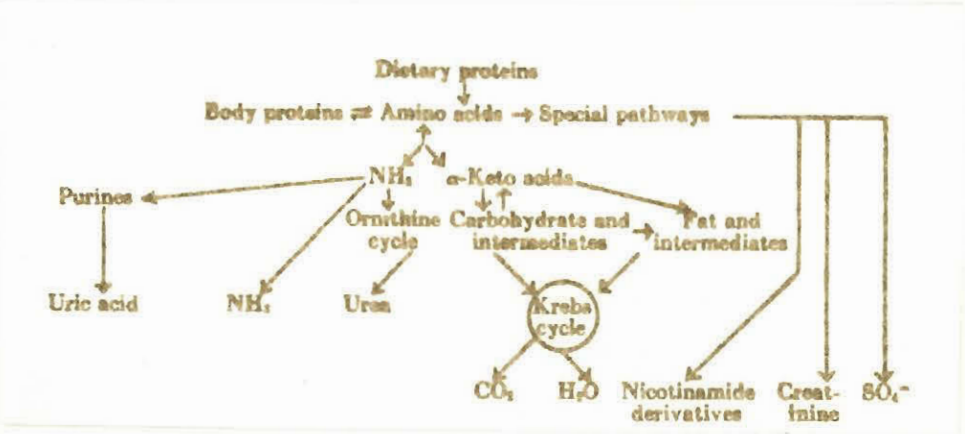


Figure 3

General pathways of protein and amino acid metabolism.

(From: A. Cantarow & M. Trumper: Clinical Biochemistry, 6th Edition, W.B. Saunders Co., 1962, page 131).

(c) Synthesis of nitrogenous substances: The amino acid pool is drawn upon for formation (i.e. replacement) of a large number of essential substances, e.g. enzymes, other cellular proteins, plasma proteins, haemoglobin, purines and pyrimidine, certain hormones (i.e. anterior pituitary hormones, insulin, parathyroid hormone, thyroxine).

(d) Transamination and deamination: With few exceptions, catabolism of amino acids begins with separation of amino (NH_2) group from the carbon skeleton, which then become a keto acid. These reactions occur mainly in the liver. For example; -

alanine ——> pyruvic acid + ammonia;

glutamine acid ——> glutavic acid + ammonia;

asportic acid ——> oxaloectic acid + ammonia.

These reactions are reversible and consequently amino groups of two amino acids may be exchanged, or an ammonia group may be transferred from an amino acid to an alpha-keto acid derived, for example, from the metabolism of carbohydrates, e.g. pyruvic, oxalaretic or alpha-keto glutaric acids with formation of a new amino acid. Pyridoxal phosphate, a pyridoxine derivative (vitamine B_6) is the coenzyme for transamination reaction. These interactions constitute an important mechanism for the intergration of protein carbohydrate and fat metabolism.

(e) Disposal of the nitrogen.

(i) Synthesis: Ammonia liberated from amino acid may be utilized, as indicated above, for amination of alpha-keto acid to form new amino acids. It also participates in the synthesis of

purines and pyrimidine, i.e. nucleotides and nucleic acid and also porphins.

Ammonia is a toxic substance and large concentrations do not accumulate in cells or extracellular fluids. One of the apparently important mechanisms of its detoxication consists in the synthesis of glutamine, an amido of glutamic acid.

This compound can thus serve as a carrier of ammonia which can subsequently be liberated from it by the enzyme glutaminase.

(ii) Urinary ammonia: In the cells of the distal portion of the uriniferous tubules, ammonia is liberated from glutamine (60% of the total urine ammonia) and the other amino acids (40%) and passed into the lumen of the tubules. This phenomenon, the extent of which is determined under normal conditions by the plasma pH, plays an important role in the Na conservation by the kidney and, therefore, in the regulation of acid base balance.

(iii) Urea formation: When amino acids are provided to the organism in excess of the requirements for synthesis of new protein molecules and other nitrogenous bustances, the excess nitrogen enters into the formation of urea which is the chief end product of alpha-amino nitrogen metabolism. This undergoes the so-called ornithine intrulline orginine cycle (see Figure 4). The urea enters the systemic circulation and is excreted from the body mainly in the urine. In normal animals, an increase in dietary protein is followed by an increase in the concentration of amino acids in the blood (which are taken up largely by the liver) and by an increase in urinary urea. When liver function is severely impaired, e.g. in acute hepatic

The over-all mechanisms for the formation of urea in the liver may be summarized in the following diagram:

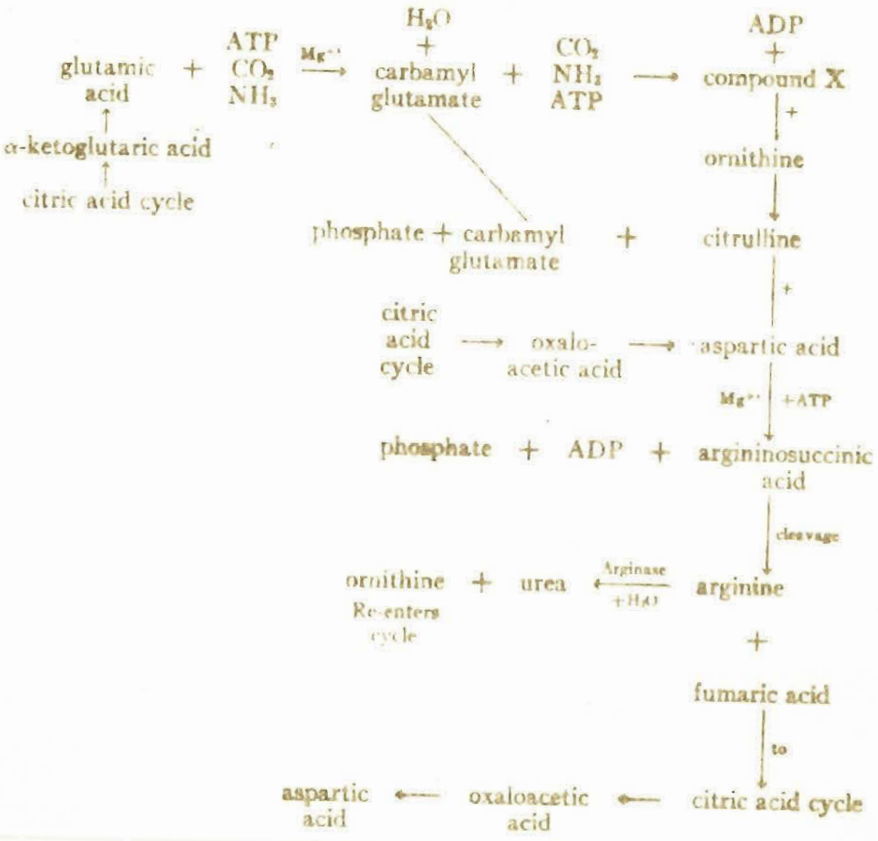


Figure 4

The over-all mechanisms for the formation of urea in the liver.

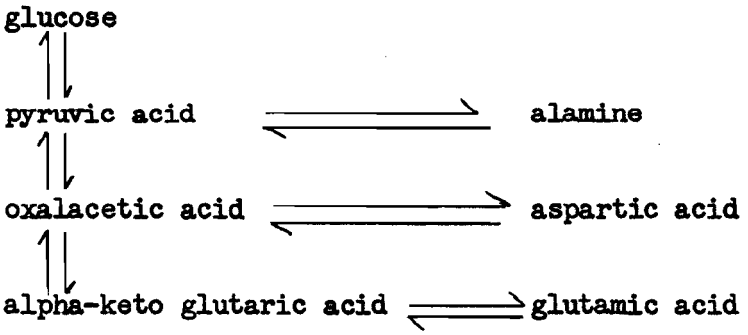
(From: E.S. West & W.R. Todd: Textbook of Biochemistry, 2nd Ed. The Macmillan Company, New York, 1956, page 1067).

necrosis, there is a rise in the blood amino acids and a fall in urea concentrations of blood and urine. Similarly, removal of the liver in an experimental animal is followed by a rise in the concentration of amino acid and ammonia in the blood and a fall in blood and urinary urea.

(f) Disposal of non-nitrogen residue

The alpha keto acids resulting from deamination may be re-aminated as indicated above, reforming the original amino acid. Certain of the carbon skeletons are used for special synthetic re-action. The remainder, not required for these replacement purposes, take the pathways of glucogenesis or ketogenesis.

(i) Glucogenesis: Most of the amino acids are convertible to carbohydrates (gluconeogenesis from protein). The routes vary with the compounds concerned, but all converge ultimately at pyruvic acid. The pathways of 3 glucogenic amino acids to pyruvic acid are particularly direct:



keto-glutamic acid, oxalacetic acid and pyruvic acid are inter-convertible by means of the tricarbocylic acid cycle. In the central nervous system, glutamic acid is converted to succinic acid via V-amino butyric acid. Pyruvic acid and glucose are connected by glytolytic series of reaction.

(ii) Ketogenic pathway: The keto acids derived from a few amino acids are more closely allied to fats than the carbohydrates; catabolism of these "ketogenic" amino acids produces ketone bodies. In comparison to glucogenic group, the ketogenic amino acids are in a minority, comprising only phenyl alamine, tyrosine, lencone and isollucine. Furthermore, certain of these amino adids are metabolized along pathways which are glucogenic as well as ketogenic.

III. DISEASES COMPLICATED BY EXUDATIVE GASTROENTEROPAHY

In 1961, Marshak et al.[16] classified the diseases complicated by excessive gastrointestinal plasma protein loss as follows: -

1. Primary.

a. Giant fold of stomach mucosal hypertrophy.

Plasma protein may be identified in gastric secretion[18,19,20] when peptic activity is completely inhibited. The anacid gastric juice from patients with atrophic gastritis may have a high content of plasma albumin[19], but the total protein leakage is not excessive since the volume of secretion is mall. Excessive plasma protein leakage may occur from the acutely inflamed or ulcerated gastric mucosa, and has been demonstrated in patients with adenocarcinoma[21], diffuse mucosal ulceration and giant hypertrophic gastritis (Menetrier's Disease)[22,23,24]. Hypoalbuminemia with oedema may be the presenting feature in these patients.

The diagnosis of diffuse gastric lesion causing excessive plasma protein loss may be uncertain even with radiologic, gastroscopic, histologic and cytologic studies of the gastric mucosa. An exploratory laparotomy may be necessary to differentiate among diffuse hypertrophic gastritis, lymphoma and adenocarcinoma.

Therapy of these gastric lesions may be dictated by factors other than the protein abnormality, i.e. evidence of neoplasm or bleeding. Resection of lesions may be necessary to control protein leakage[15], but the post-operative nutritional complications of an extensive resection for benign disease may be more serious than the pre-operative manifestations of that disease.

b. Exudative enteropathy of Gordon (no hyperplasia but lymphangiectasia). Intestinal lymphangiectasia.

Schwartz and Jarnum[15], Holman, Nickel and Sleisenger[25] and Waldmann et al.[26] have described patients with hypoproteinemia and increased enteric plasma protein loss associated with dilated intestinal lymphatic vessels. Although most of these patients presented hypoproteinemia and oedema without evidence of gastrointestinal disease, most of them later manifested diarrhoea and steatorrhoea. Many of these patients had effusion (ascitic or pleural) that were frequently chylous[72]. Hypoalbuminemia was often accompanied by hypogammaglobulinemia. In the study of Waldmann et al. a consistent pathological abnormality was the presence of dilated lacteals in the villi of small intestine which contained foamy lipophages and thickening of walls of mesenteric lymphatic vessels, with narrowing of their lumens[26]. These authors believe that these lymphatic abnormalities may result from an acquired defect of unknown cause in some patients, whereas in those with a family history, onset of disease in infancy and chylous effusions, there may be a congenital lymphatic malformation.

Some patients who fall into this category may show many features that suggest a diagnosis of non-tropical sprue (adult celiac disease). Onset of symptoms during childhood, with growth retardation in the presence of severe steatorrhoea, with typical bulky, offensive stools, and laboratory evidence of malabsorption may all suggest a diagnosis of non-tropical sprue. This diagnosis, however, may be considered more certain in patients who show atrophy of the villi of the small intestine mucosa, increased urinary excretion of 5 hydroxyindolacetic acid (5OHIAA) and subnormal xylose absorption and who respond

to a gluten-free diet[27,28]. Indeed, a non-tropical sprue may sometimes be diagnosed as exudative enteropathy if the diagnosis is being made without satisfying theee criteria. Although the patient may have steatorrhoea and subtotal atrophy of the villi of the jejunal mucosa, both consistent with a diagnosis of non-tropical sprue, a normal xylose absorption and normal urinary excretion of 5OHIAA, together with a lymphatic abnormality demonstrated in the mucosa of the small intestine, does not support that diagnosis. This evidence, together with a failure to respond to a gluten-free diet, led to the diagnosis of idiopathic protein-losing enteropathy in association with abnormal intestinal lymphatics. Albumin studies were consistent with this diagnosis.

The treatment of idiopathic protein-losing enteropathy (intestinal lymphangiectasis) has been disappointing. These patients have not responded to steroids, antibiotics or a gluten-free diet. Supportive therapy with albumin infusion, salt restrictions and diuretics, however, may control fluid retention.

2. Secondary

a. Regional enteritis and ulcerative colitis. (Inflammatory disease of the large and small intestine).

Gastrointestinal protein loss has been well documented in patients with chronic inflammatory disease of the small and large intestine[6,27,29,30]. Steinfeld et al. and Schwartz and Jarnum[23] reported hypoalbuminemia,increased albumin degradation and excessive enteric loss of I-131 labelled albumin or I-131 PVP in patients with regional enteritis and ulcerative colitis.

Few investigators, however, have studied protein loss in patients with acute gastroenteritis. King and Joske[31] described 2 patients with acute gastroenteritis that was associated with malabsorption. In both, there was a temporary depression of serum albumin, but plasma protein loss was not measured. Waldmann et al.[26] described a single patient with acute gastroenteritis in whom hypoproteinemia was associated with excessive enteric loss of plasma protein measured by excretion of I-131 PVP.

Sometimes there was excessive intestinal leakage of protein in patient, the slight diminution in the serum albumin level indicated a compensatory increase in albumin synthesis.

In case the patient presented with diffuse lesions of the small intestine, with partial atrophy of the villi (i.e. plasma protein loss and malabsorption), this pathologic process of undefined etiology did not respond to treatment with a gluten-free diet, steroids or broad spectrum antibiotics and the latter may cause death due to staphylococcal infection as a complication. Steroid may be beneficial to the patient in cases of acute or subacute diffuse granulomatous enteritis. Plasma protein loss and malabsorption, present during the acute phase, may subside with steroid therapy.

b. <u>Mesenteric vascular occlusion</u> (Zuidema, 1961[32].

Intestinal ischaemia[33,34,35] has been shown to result in absorption defects by several authors. Shaw and Maynard described 2 cases of acute superior mesenteric artery occlusion in which absorption studies were performed[34]. One of their cases was being followed for malabsorption syndrome.

In 1961, Zuidema et al.[32] demonstrated that an acute massive intestinal ischaemia can result from either embolization or thrombosis of the superior mesenteric artery, and a successful superior mesenteric embolectomy was performed and I-131 PVP enteric excretion was studied also. Two aspects of the studies are noteworthy. First, the major metabolic abnormality detectable was the persistently depressed serum proteins despite supplementary intravenous albumin. Second, I-131 PVP was excreted in the stool in abnormally high amounts (3.1% in 4 days versus an upper limit of normal of 1.5% in 4 days)[32]. Most of the other tests performed, including a jejunal biopsy, were normal. This clinical experience stimulated the following laboratory investigation.

c. Tumours of gastrointestinal tract. (Granulomatous and neoplastic disease involving the small intestine and mesentery).

Holman et al.[25] and Schwartz and Jarnum[23] described several patients who exhibited manifestations of hypoproteinemia and were found to have non-specific granulomatous lesions involving adjacent loops of jejunum. Macroscopic evidence of local lymphatic obstruction was sometimes present. The etiology of the granulomatous disease in these patients was not defined. Diagnosis of sarcoidosis, tuberculosis and regional enteritis were considered but no established.

Abnormal gastrointestinal loss of protein may be an important secondary manifestation of neoplastic involvement of the mesentery of the small intestine, and mesenteric and retroperitoneal lymph

node, particularly by lymphomatous disease. Such a loss was documented by Schwartz and Jarnum[23] in a patient with Hodgkin's disease, and is suggested by the hypoproteinemia occurring in patients with intestinal lymphoma[36].

d. Non-tropical and tropical sprue.

It has been clearly established that patients with non-tropical and tropical sprue[37,38,39,50] may also have an excessive enteric leakage of plasma proteins. Impaired absorption of amino acids may also contribute to the diminution in the concentration of serum proteins.

The severity of malabsorption or histologic change in the jejunal mucosa correlates poorly with the quantity of enteric protein loss as measured by I-131 PVP excretion[27].

The effect of the gluten-free diet of plasma protein loss has not been extensively studied in these patients. London et al.[38] described a patient with malabsorption, increased faecal excretion of intravenously administered I-131 and subtotal villous atrophy in whom the PVP excretion returned to normal after administration of a gluten-free diet.

IV. MECHANISM OF LEAKAGE IN EXUDATIVE GASTROENTEROPATHY

Several mechanisms are probably involved in passage of plasma proteins across the gastrointestinal mucosa both in normal and in pathologic states.

a. Passive diffusion between mucosal cells.

Plasma proteins may pass through the intercellular space of the mucosal epithelium by passive diffusion. Alternatively, extrusion of effete cells from the intestinal mucosa may also permit losses of plasma protein by diffusion between these spaces. The quantity of plasma protein crossing the mucosa would be proportional to the hydrostatic pressure and the concentration of plasma protein in the extravascular space of the lamina propria. This mechanism may be operative in patients with evidence of obstruction or stasis of intestinal lymphatics. This may occur as a result of granulomatous or neoplastic involvement of lymphatics. In intestinal lymphangiectasis[26] the dilatation of mucosal lymphatic vessels may reflect chronic lymphatic obstruction although the only demonstrable obstructing lesion is a thickening of the wall of larger lymphatic vessels. Waldmann et al.[26] suggest that dilated lymph vessels in the mucosa may rupture through the surface epithelium.

Increased lymphatic pressure has been suggested as the operative mechanism in patients with constrictive pericarditis[7,41]. Blalock et al.[42] observed that obstruction of the superior vena cava in dogs caused dilatation of intestinal lymphatic vessels. Although venous congestion resulting either from heart failure or from portal

hypertension may increase the transudation of lymph from intestinal capillaries, mucosal oedema with increased transepithelial loss of plasma protein may occur only when the capacity of the large lymphatic vessels in exceeded. Studies in patients with portal hypertension have not indicated excessive loss of plasma protein[40], but no studies have been reported of patients with portal hypertension complicated by tense ascites.

b. Active secretion by mucosal cells.

This mechanism seems an ulikely explanation for the passage of most plasma protein components across the gastrointestinal mucosa. Soergel and Ingelfinger[43], however, identified alpha -1 and alpha -2 glycoproteins in some specimens of rectal mucus that appeared to contain albumin. They suggest that these serum proteins may be integral components of rectal mucus as secreted by goblet cells.

c. Exudative through inflamed or ulcerated mucosa.

In certain diseases plasma proteins passing into the gastrointestinal tract may be constituents of inflammatory exudate from mucosa. Such losses would be expected in acute gastroenteritis, regional enteritis and ulcerative colitis.

d. Loss secondary to disordered mucosal-cell metabolism.

The plasma protein loss occurring in patients with non-tropical sprue may result indirectly from disturbed epithelial cell metabolism. In these patients the severity of mucosal inflammatory

change[37] or with the degree of steatorrhoea[37]. There is, however, not only atrophy of the mucosal villi but also degenerative cells, changes of disturbed orientation of the epithelial cells[27], changes that may facilitate the diffusion of plasma protein between the cells.

The mechanisms of plasma protein loss may not be finally elucidated until electron microscope techniques identify albumin within the mucosal epithelium in either the intracellular or the intercellular space.

V. METHODS OF INVESTIGATION

A. Plasma Albumin Turnover Studies

(Distribution and metabolism of plasma albumin).

There are several methods of investigating the distribution and metabolism of albumin. In 1937, Welch et al. (44) studied the condition by nitrogen balance technique and in the middle of 1940's Albright et al.(10) used a nitrogen balance method and the effect of infusion human albumin. Starling in 1951(45) introduced RISA which by immunochemical technique was shown to be an excellent physiological tracer. Berson et al.(46) measured albumin turnover by a method at extrapolating the daily plasma radioactivity over a period of 2-3 weeks to zero time. McFarlane(47) studied the albumin turnover by 'Metabolic Clearance" method(63). This technique requires less time and is valuable in pathological conditions where the plasma levels will not plot linearly. This technique was selected for the distribution and metabolism of albumin.

B. Studies of Plasma Albumin Excretion Into Gut.

1. Metabolic-balance studies: The rate of albumin catabolism and the fate of the component amino acids have been studied by the metabolic-balance technique after intravenous infusion of albumin(10,48). Balance data from patients with protein-losing enteropathy show that the amino acids of albumin are partly catabolized and partly re-utilized in protein synthesis(48). The metabolic-balance studies neither indicate the site of albumin degradation nor differentiate endogenous albumin catabolism from intestinal digestion of this protein. Faecal nitrogen

excretion may be normal in patients with excessive enteric leakage of plasma protein[10].

2. I-131 labelled polyvinylpyrrolidone (I-131 PVP)[49]: I-131 PVP has had a major role in the investigation of patients with protein-losing enteropathy. The introduction of this labelled polymer by Gordon in 1959[49] stimulated considerable interest in the problem of gastrointestinal plasma protein loss. The properties of this macromolecule that suggested its application to this problem were stability in the presence of proteolytic enzymes and insignificant absorption from the gastrointestinal tract[10,45,46,47,48,49]. Gordon showed that faecal excretion of I-131 PVP was increased after its intravenous injection in patients with suspected protein-losing enteropathy; this finding has been confirmed in many subsequent studies[23,37,26,41,25]. Limiting factors in the use of I-131 are heterogeneity of the polymer and the fact that the distribution and catabolism of I-131 PVP and albumin (molecular weight of albumin 68,000 and that of PVP 40,000). Thus, faecal excretion of I-131 PVP does not quantitatively measure the gastrointestinal leakage of albumin[29,50], nor does the plasma disappearance of injected I-131 PVP reflect albumin degradation. In spite of these disadvantages, the I-131 PVP test is of proved value in screening patients for excessive gastrointestinal plasma protein leakage.

3. Chromium-51 labelled albumin[51]: In studies on the measurement of gastrointestinal blood loss utilizing Cr-51 labelled red cells , Ebaugh et al.[67] showed that Cr-51 Cl was poorly absorbed from the

gastrointestinal tract and was not excreted into the gut. Waldmann[51] has evaluated Cr-51 labelled albumin as a technique for measuring gastrointestinal loss of plasma protein. Because there is no gastrointestinal secretion or absorption of the nonprotein-bound Cr-51 Cl_3, the disadvantages of the iodide label are avoided. However, Cr-51 labelled albumin is degraded more rapidly than I-131 labelled or unlabelled albumin, so that its palsma disappearance does not reflect albumin catabolism. Although the technique using I-131 labelled albumin with amberlite is presently recommended for investigation of patients suspected of having protein-losing enteropathy, the method with Cr-51 labelled albumin may more accurately measure plasma albumin loss in the normal subject. Both techniques could be applied to the detection of the loss of other plasma proteins into the gastrointestinal tract.

4. <u>I-131 labelled albumin:</u> Information derived from studies using I-131 labelled albumin accurately reflects the metabolism of plasma albumin[29,45,52]. By isotope dilution the plasma volume and the intravascular and total albumin pools can be measured, and the rate of albumin degradation and, indirectly, the rate of albumin synthesis can be calculated from the plasma I-131 decay curve[45] (see Figure 5).

In patient with protein-losing enteropathy, the plasma albumin concentration and the total albumin pool may be either normal or reduced according to the capacity of the liver to synthesize that protein. The increased enteric loss will be reflected by an increased disappearance rate of plasma radioactivity.

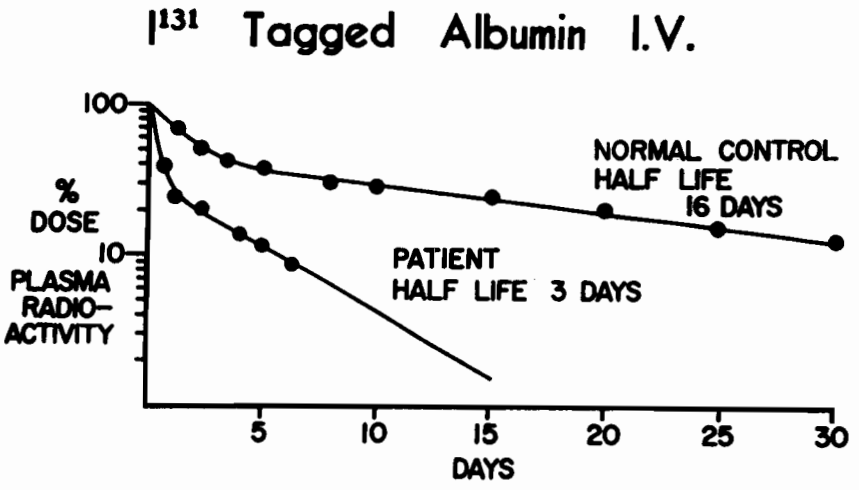


Figure 5

The plasma radioactivity in daily sample plotted on a semilogarithmic graph in a normal person and in a patient with a protein-losing gastroenteropathy

(a) Precipitation with trichloracetic acid (TCA): (This method was employed by Citrin et al. in 1957[22]).

The study of gastrointestinal plasma protein leakage with the use of I-131 labelled albumin is complicated by the secretion of inorganic iodide in saliva and gastric juice[53,54,68] and the re-absorption of iodide in the small intestine. Thus, after the intravenous injection of I-131 labelled albumin, the radioactivity present in the stomach results both from excretion of free iodide and from leakage of albumin-I-131. When proteolytic enzymes have been inhibited, albumin-bound I-131 can be separated from free iodide by precipitation of protein with trichloracetic acid. Using this technique, Wetterfors et al.[4] were able to measure the content of I-131 labelled albumin in secretions from the stomach and intestinal segments.

(b) Absorbed by resin, amberlite IRA 400: (Method employed by Jeejeebhoy et al. in 1961[29]).

Almost total iodide re-absorption in the intestine results in minimal faecal excretion. Thus, the quantity of gastrointestinal plasma protein leakage cannot be measured from the faecal I-131 content after intravenous injection of I-131 labelled albumin. Patients with protein-losing gastroenteropathy, however, may excrete significantly more I-131 in their stools than normal subjects[6,23,26]. In studies with intravenous injection of I-131 labelled albumin, Jeejeebhoy and Coghill overcame this proglem of iodide re-absorption by oral administration of an ion-exchange resin (amberlite). Iodide,passing into the intestinal lumen, is absorbed by the resin and is excreted in the stool. Thus, the faecal radioactivity with resin measures both the leakage of I-131 labelled

albumin into the whole gut and enteric excretion of nonprotein-iodide. The salivary and gastric secretion of free iodide may be reduced by administration of Lugol's iodide solution to decrease the specific activity of plasma iodide.

VI. PRESENT INVESTIGATION

A. Patients and Methods

This technique was chosen for the investigation because after considering its advantages over others (e.g. metabolic-balance studies, PVP I-131, and chromium-51, etc.) as mentioned and discussed separately under the methods of investigation.

The metabolism of plasma albumin, including its loss into the gastrointestinal tract, was studied in 16 patients using human labelled with I-131 RISA and amberlite, IRA 400 chloride.

The patients received a normal diet and had limited physical activity. They were separated into three groups (see Table I).

The control group (group I) consisted of patients in hospital for diseases other than those of the gastrointestinal tract; four had uncomplicated fractures and two were in the convalescent phase of infectious mononucleosis. None of them showed any clinical evidence of protein deficiency or gastrointestinal disorder.

The second group (group II) consisted of three patients with non-gastrointestinal cancer. One had pulmonary carcinoma with brain metastasis; one had carcinoma of the prostate without evident metastases; one had carcinoma of the prostate with evident metastases and the third had carcinoma of the lip without metastases.

In the third group (group III) were patients with gastrointestinal tract malignancies who showed no signs of gastrointestinal bleeding at the time of study. Case 10 had carcinoma of the hepatic flexure with pulmonary metastases. Two patients with carcinoma of the stomach were included: Case 11 had a recurrence following subtotal gastrectomy nine months before

Group	Patient	Diagnosis	Sex	Age	Serum albumin* g.%	Average daily fecal excretion of radioactivity % dose per day	Albumin degradation rate % per day
I— 1	M	Convalescent infectious hepatitis	M	23	3.7	2.0	6.8
2	L.	Convalescent infectious mononucleosis	M	21	4.6	0.9	8.4
3	B.	Fracture of femur	M	20	4.86	1.7	19.0
4	L.	Fracture of femur (open reduction)	M	60	3.51	0.3	29.0
5	M.	Fracture of tibia and fibula	F	55	5.75	2.0	21.0
6†	G.	Fracture of left hip	M	17	3.27	1.5	19.0
II— 7	C.	Carcinoma of lung	M	47	4.59	1.1	20.0
8	D.	Carcinoma of prostate	M	69	4.22	1.6	14.0
9	K.	Carcinoma of lip	M	67	4.53	1.8	20.0
III—10	J.	Carcinoma of colon	M	47	3.02	3.1	22.0
11	J.	Carcinoma of stomach	M	67	5.0	2.3	25.0
12	S.	Carcinoma of stomach	M	51	3.79	15.0	34.0
13	D.	Carcinoma of esophagus	M	51	3.3	11.0	22.0
14	B.	Carcinoma of stomach	M	63	2.66	11.0	26.0
15	L.	Carcinoma of colon, preoperative	M	73	4.95	10.0	25.0
		Carcinoma of colon, postoperative	M	73	4.62	2.8	17.0
16	B.	Carcinoma of rectum	M	84	3.96	1.9	18.0

*Determined by conventional serum protein electrophoresis.
†Obese patient on low caloric diet.

Table 1

Groups of patients studied.

study, while case 12 had extensive systemic metastases. Case 13 had carcinoma of the oesophagus and case 14 had carcinoma of the stomach. Case 15, with carcinoma of the ascending colon, was studied before and after operation. There was no evidence of metastases at the time of operation. Case 16 had a defunctioning colostomy for inoperable carcinoma of the rectum.

The rate of catabolism of plasma albumin was measured by the RISA metabolic clearance method[45,46,47,52,63] This technique involves the measurement daily of the amount of radioactivity in both plasma and urine over a period of five days. From these data the plasma albumin pool and the rate of plasma albumin turnover were calculated. All other values of albumin metabolism were derived from these parameters. The rate of albumin turnover had been expressed as albumin degradation rate and is recorded as per cent per day of the albumin pool. The mathematical and graphical methods used were those described by Veall and Vetter[65].

RISA was labelled with approximately one iodine atome per molecule of albumin[63,66]. Before use it was dialyzed and the free iodine content was seldom greater than 1%.

Amberlite IRA 400 is an ion-exchange resin, strongly basic quartenary ammonium (polystyrene) type, anion exchange resin $RN(CH_3)^+Cl$.

During the study the thyroidal uptake of I-131 was blocked by the administration of Lugol's solution, 10 minims twice daily. The amount of RISA administered intravenously varied between 30 and 50 microcuries. The dose to be given was drawn into a 2 ml. disposable plastic syringe and the content of radioactivity determined; a suitable standard was prepared simultaneously.

The plasma volume was determined by the isotopic dilution technique[65]. Daily blood samples were taken over a period of five days and measured for radioactivity. The urine was collected every 24 hours for five days. The radioactivity in plasma and urine was measured in a well-type scintillation counter (see Figure 6), Model 810, connected to a linear amplifier (Baird-Atomic) model 218 and a (B-A) 510 pulse-height analyser, single-channel with a Model 131-A scaler.

The excretion of plasma albumin into the gastrointestinal tract was determined by the technique introduced by Jeejeebhoy and Coghill[29]. This method employes an ion-exchange resin which absorbs iodide. The amberlite IRA 400 chloride was given by mouth, 5 gms. every four hours for a period of 96 hours, beginning one day after the administration of RISA. Stool was collected in a large paper container. Its radioactivity was measured by a 4 Geiger-tube chamber[57] (see Figure 7) connected to amplifier (B-A), Model 216 E and scaler (B-A) Model 131-A. The radioactivity in the faeces was expressed as the average daily excretion in per cent of the administered dose.

B. Results

In the six controls, the average daily faecal radioactivity ranged from 0.3% to 2% of the dose (see Figure 8). Jeejeebhoy and Coghill reported the faecal radioactivity of the three controls to be 1.7% to 1.9% of the dose. The albumin degradation rate was 6.8% and 8.4% per day for the two medical patients and 19% and 29% per day

Figure 6

The Well Scintillation Counter

(Picture taken from Isotope Laboratory, Royal Victoria Hospital, Montreal, P.Q.)

Figure 7

Geiger-Muller Chamber Counter

(Picture taken from Isotope Laboratory, Royal Victoria Hospital, Montreal, P.Q.)

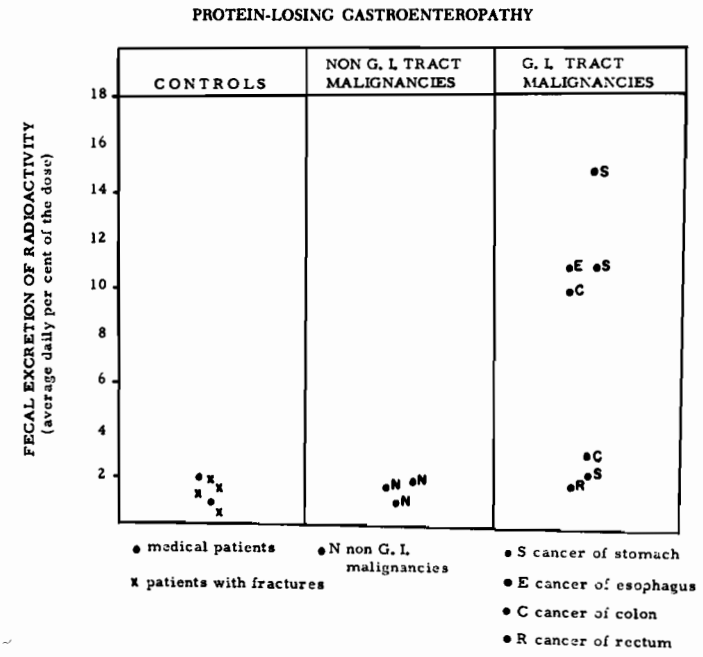


Figure 8

Protein loss into the gastrointestinal tract

for the four patients with fractures. Jeejeebhoy and Coghill found the albumin degradation rate in normal subjects to be from 3.2% to 4.1% per day.

In the patients with cancer that did not involve the gastrointestinal tract, the average faecal excretion of radioactivity was 1% to 1.8% of the dose per day. These values fall within the range of the control group. All patients in this group had increased albumin turnover as shown by the daily degradation rate of 14-20%.

Of the seven patients with gastrointestinal cancer, four showed a remarkable increase in the loss of radioactivity in the faeces. The values ranged from 10% to 15% of the dose per day. Two had only slightly increased radioactivity in the faeces (2.3% and 3.1% of the dose). In a larger series these latter values might be statistically different from the control group; they were considered not to represent increased excretion in the present study. In Case 15, resection of the cancer of the ascending colon reduced the excretion of faecal radioactivity from 10% to 2.9% of the dose per day; concurrently, the albumin degradation rate dropped from 25% per day to 17%. The patient (Case 16) who had a defunctioning colostomy for non-resectable cancer of the rectum showed an increased degradation rate but no increase in faecal radioactivity.

The albumin degradation rate for group III was 17% per day.

VII. DISCUSSION

Protein-losing gastroenteropathy has now been demonstrated in many different diseases. Among those of surgical interest are ulcerative colitis[6,30], regional enteritis[6,36], gastric cancer[19,21], Menetrier's disease[15,21,55], portal hypertension[56] and constrictive pericarditis[7]. The present study had demonstrated that a similar phenomenon also occurs in cancer of the oesophagus and colon.

In the present investigation, four of seven patients with gastrointestinal cancer showed a remarkable increase of radioactivity in the faeces following the intravenous administration of RISA. These four patients included one with cancer of the oesophagus, two with gastric carcinoma, and one with cancer of the colon. Two other patients (Cases 10 and 11) had slightly increased excretion of faecal radioactivity which was not considered significant. In one patient (Case 16) the excretion rate was normal. Protein loss into the gastrointestinal tract had been demonstrated to accompany gastric carcinoma by several investigators. The present study confirms this and also demonstrated that the same phenomenon occurs in cancer of oesophagus and colon. It may be concluded, therefore, that protein loss into the intestine may be associated with malignant lesions regardless of their location within the intestine. This study does not provide information concerning the possibility that protein-losing gastroenteropathy may also occur with benign neoplasia. Because of the small number of cases studied in this and other investigations, the frequency with which cancer of the bowel is associated with protein-losing gastroenteropathy is unknown.

The results obtained in the patient (Case 15), who had a carcinoma of the ascending colon, suggest that the lesion itself or adjacent mucosa is the major source of the excessive protein loss into the intestine. Before hemicolectomy, the average daily faecal excretion rate of this patient was 10% of the administered dose. After the resection of the tumour the excretion rate dropped to 2.8%. As was to be expected, there was a corresponding decrease in the daily rate of albumin degradation from 25% to 17%. The failure to demonstrate increased faecal loss of radioactivity in the patient (Case 16) who had a defunctioning colostomy, is probably due to the exclusion of the tumour from that portion of the intestine from which the faeces were collected.

The three patients (group II) with cancer at sites other than the gastrointestinal tract did not have an increased protein loss into the bowel.

Although the method used for measuring the turnover of albumin is only approximate[58], the results do reveal that patients who did not have abnormal loss of protein into the intestine had as high a rate of albumin degradation as those with abnormal loss of protein. Nevertheless, the highest rate of albumin turnover, 34% per day, was observed in the patient (Case 12) who also had the greatest loss of protein in the faces (15% of the dose per day). Whether the protein-losing gastroenteropathy will be associated with hypoalbuminemia will depend on the extent of the loss and the ability of the body to compensate for it by increasing the rate of albumin synthesis proportionally. Of the four patients with excessive protein loss, two had serum albumin levels below 3.5 gms. per

100 ml. These patients represent uncompensated protein-losing gastroenteropathy. The serum albumin concentration of the other two patients exceeded 3.5 gms. per 100 ml. and they may be considered to represent compensated protein-losing gastroenteropathy.

VIII. SUMMARY and CONCLUSIONS

Protein loss into the gastrointestinal tract and the daily rate of albumin degradation were studied in 16 patients after the intravenous administration of I-131 labelled albumin.

In three patients with carcinoma at sites other than the gastrointestinal tract, the protein loss into the intestine was the same as that observed in six control subjects.

Excessive loss of protein into the intestine was demonstrated in two patients with cancer of the stomach, in one patient with cancer of the oesophagus, and in one patient with cancer of the colon.

In one patient, resection of the cancer of the colon was followed by a marked reduction in the abnormal loss of protein. It is suggested that the major source of protein loss in such patients is the tumour itself or adjacent mucosa.

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