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Research Article

Abnormalities of Albumin Metabolism in Patients with Hypogammaglobulinemia *

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An abnormally low concentration of serum gamma globulin occurs in association with a wide variety of clinical conditions (1, 2). This reduction in serum gamma-globulin concentration may be the result of decreased synthesis or of increased catabolism or loss. Hypogammaglobulinemia due to decreased synthesis (hyposynthetic) has been classified into four groups (2): 1) *Physiological hypogammaglobulinemia,* a condition occurring during the first year of life when the gamma globulin derived from the mother is catabolized before synthesis by the infant becomes adequate to maintain normal serum concentrations; 2) *congenital hypogammaglobulinemia,* a hereditary, sex-linked trait resulting in an extreme defect in gamma-globulin synthesis; 3) *acquired hypogammaglobulinemia secondary to neoplastic disease,* a disorder that occurs with neoplasms that affect the plasma cells, such as thymoma, chronic lymphocytic leukemia, Hodgkin's disease, and multiple myeloma; and 4) *idiopathic acquired hypogammaglobulinemia.* Many of the patients in groups 2, 3, and 4 have recurrent infections and associated chronic sinusitis, bronchiectasis, arthritis, and unexplained gastrointestinal tract disorders resembling sprue or ileocolitis (3, 4).

Hypogammaglobulinemia due to increased catabolism or loss (hypercatabolic) occurs in association with nephrosis (5) and protein-losing gastroenteropathy (6, 7). Certain features aid in differentiating hyposynthetic from hypercatabolic hypogammaglobulinemia. Patients with impaired synthesis have a much greater incidence of bacterial and fungal infections; have markedly reduced ability to synthesize specific antibodies in response to antigenic challenge; have negligible isohemagglutinin titers; and have a decrease or absence of plasma cells in the bone marrow, lymph

nodes, and intestinal tract (1, 2, 8, 9). In contrast, patients who have hypercatabolic hypogammaglobulinemia as their primary disorder have normal or only slightly reduced isohemagglutinin titers; have normal ability to synthesize antibodies; and have normal numbers of plasma cells (8–10). By using I^{131}-labeled gamma globulin to determine directly the turnover (synthetic rate) of gamma globulin, one finds rates approximately 10% of normal in the patients with impaired synthesis, whereas those with hypercatabolism have rates equal to or twice normal (6).

Until recently little attention has been directed toward the metabolism of proteins other than gamma globulin in patients with hyposynthetic hypogammaglobulinemia. In the present study the serum albumin concentration was determined in 24 patients with impaired synthesis of gamma globulin. Twenty of these patients had significant hypoalbuminemia. Six were studied by using I^{131}-labeled albumin to measure the circulating and total body albumin pools as well as the rates of albumin degradation and synthesis. I^{131}-labeled polyvinylpyrrolidone (PVP) was used to determine whether excessive gastrointestinal protein loss was present. In addition, the effect of therapy on the abnormalities of albumin metabolism was studied. A brief summary of this study has been presented previously (11).

Methods

The 24 patients included in this study entered the Clinical Center of the National Institutes of Health with serum gamma-globulin concentrations of 400 mg per 100 ml or less. That their hypogammaglobulinemia was attributable to defective synthesis was shown by various techniques. They all had isohemagglutinin titers of 1:4, or less, whereas the lower limit of the normal range is 1:32 (8). Antibody production in response to administration of exogenous antigens was markedly depressed in each of the 12 patients studied. The rate of gamma-globulin synthesis, studied with I^{131} gamma globulin, was 0.001 to

TABLE I

Clinical data on hypogammaglobulinemia patients studied with I^{131}-labeled albumin

Determinations	E.R.	A.J.	A.H.	I.T. Before therapy	I.T. After therapy	P.M. Before therapy	P.M. After therapy	M.Q. Before therapy	M.Q. After therapy
Hematocrit	29	38	31	37	39	41	43	39	39
Serum protein electrophoresis, g per 100 ml									
Albumin	2.4	2.7	3.2	1.8	3.5	3.3	3.7	1.6	3.2
Alpha₁ globulin	0.2	0.4	0.3	0.5	0.4	0.4	0.5	0.5	0.4
Alpha₂ globulin	0.5	0.9	0.4	0.7	0.6	0.8	0.9	0.9	1.0
Beta globulin	0.7	0.8	0.8	0.7	0.8	0.8	0.9	0.8	0.9
Gamma globulin	0.16	0.4	0.3	0.2	0.25	0.11	0.12	0.2	0.17
Fecal fat, g/day	16	70	8	16	1.3	41	3	8	4
Serum carotenoids, µg/100 ml	14	7	110	Not done	142	Not done	95	33	67
Serum cholesterol, mg/100 ml	124	90	158	110	240	154	212	70	190
D-Xylose-tolerance test, g/5-hour urine	2.1	1.6	2.4	Not done	3.5	Not done	5.3	1.4*	1.9* 8.4
Bromsulfalein retention, %/45 minutes	4	<1	8	3	4	8	Not done	5	Not done
Serum bilirubin, total mg/100 ml	0.3	0.2	0.3	0.3	0.3	0.2	Not done	0.2	0.1
Serum alkaline phosphatase, King-Armstrong U	12	9	10	12	14	16	16	9	Not done
Prothrombin time, patient/control in seconds	15/13.5	13/12.5	14/13	13/12.5	12/12	13/12	12/12	11/12	11/12
Blood urea nitrogen, mg/100 ml	17	18	7	9	15	10	9	4	7
Urine protein	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
Occult blood in stool, guaiac test	Weakly Pos.	Neg.	Neg.	Pos.	Neg.	Weakly Pos.	Weakly Pos.	Pos.	Neg.
Stool parasites or bacterial pathogens	Not done	None	Giardia lamblia	Salmonella newport	Neg.	Neg.	Neg.	Neg.	Not done

* Oral load of 5 g of D-xylose instead of usual 25 g.

0.008 g per kg per day in the 15 patients studied, whereas the range in normal control subjects was 0.03 to 0.05 g per kg per day. Twenty-two patients had either an I^{131} gamma-globulin study or a study of response to exogenous antigens, or both.

The patients' ages ranged from 11 to 64 years. Eight had congenital hypogammaglobulinemia, 11 had idiopathic acquired hypogammaglobulinemia, and five had hypogammaglobulinemia secondary to neoplasia (one with Hodgkin's disease, three with chronic lymphocytic leukemia, and one with thymoma). Twenty-one of the 24 patients had a history of recurrent bacterial infections, and of the 21, 20 had recurrent pneumonia, 18 had bronchiectasis, and 16 had sinusitis. Five of the 24 had arthritis, and 12 had significant diarrhea or steatorrhea. Of these 12, five had chronic *Salmonella* or *Shigella* infections, two had giardiasis, and five had no detectable enteric pathogens.

Six of the 24 patients were selected for detailed studies of their albumin metabolism. Groups 2, 3, and 4 of the types of hyposynthetic hypogammaglobulinemia described in the introduction were represented. Significant clinical features of these patients are summarized in Table I and in the appendix to this paper.

Total serum protein concentration was determined by a biuret method (12), and the albumin and gamma-globulin concentrations were determined by paper electrophoresis with a pH 8.6 barbital buffer (13). Xylose-tolerance tests were carried out according to Benson and associates (14), using the Roe and Rice assay method

(15). Serum carotenoids were assayed according to Carr and Price (16). Stool fat determinations were made on 3-day pools by the method of van de Kamer (17). Intestinal biopsies were performed with the instrument described by Brandborg, Rubin, and Quinton (18).

Metabolism of I^{131}-labeled proteins

I^{131} albumin (Risa T⁴)[1] was used to determine albumin turnover. The techniques for the preparation and labeling of gamma globulin are described elsewhere (7). The gamma globulin was isolated from normal serum by curtain electrophoresis and was then labeled with I^{131}, using the iodine monochloride method of McFarlane (19).

Thyroidal uptake of I^{131} released by breakdown of the labeled albumin was inhibited by the administration of 0.5 ml of Lugol's solution every 8 hours throughout the period of study. Approximately 100 µc of I^{131} protein was administered intravenously from a calibrated syringe to each patient. Blood samples were obtained without stasis from the patients at 15- and 30- minute intervals after administration of the iodinated protein and then 3 times a week for the next 15 to 20 days, and placed in bottles with Versene anticoagulant. Complete urine and stool collections were obtained throughout the period of study. The samples were assayed for radioactivity in a well-type scintillation counter with a thallium-activated

[1] Abbott Laboratories, North Chicago, Ill.

sodium iodide crystal and were compared with appropriate standards.

The serum albumin concentration was determined 4 or 5 times during a study, and the mean of these values was used for the calculations. There was no significant change in the serum albumin concentration during the study in any of the patients.

The data were analyzed according to the methods of Berson, Yalow, Schreiber, and Post (20) and Pearson, Veall, and Vetter (21). The following equations summarize the calculations.

I. Albumin pool size and distribution

Plasma volume (P.V.) = administered radioactivity/ radioactivity per milliliter of plasma at zero time (extrapolated from 15- and 30-minute values); total circulating albumin = P.V. × serum albumin concentration; radioactivity retained in body = administered radioactivity minus cumulative radioactivity in urine and stools; fraction body albumin intravascular = P.V. × plasma radioactivity per milliliter/ radioactivity retained in body. (This fraction is determined after completion of the equilibration of I^{131} albumin among the body compartments, after days 6 to 8) ; and total body albumin pool = total circulating albumin/fraction body albumin intravascular.

II. Albumin degradation and turnover

These values were obtained by two methods: method A, which depends on the rate of decline of whole body radioactivity, and method B, which depends on the daily relationship between urinary radioactivity and circulating radioactivity.

Method A. A semilogarithmic plot of the radioactivity retained in the body with time was used to determine the survival half-time of I^{131} albumin, $t_{\frac{1}{2}}$. Then, fraction of body albumin degraded per day = $0.693/t_{\frac{1}{2}}$ in days, and albumin turnover = total body albumin pool × fraction of body albumin degraded per day.

Method B. Fraction of circulating albumin degraded per day = urinary radioactivity per 24-hour period/mean circulating radioactivity during the same period. This fraction was determined for each collection period, and the mean value for the different periods was used in the following calculation. Albumin turnover = total circulating albumin × fraction of circulating albumin degraded per day.

As shown in Table II, the values for albumin turnover calculated by methods A and B are virtually identical. Since the patients appeared to be in a steady state with no significant change in serum albumin concentration during any of the studies, the rate of albumin synthesis is considered equal to value for albumin turnover.

Gastrointestinal loss of I^{131}-labeled polyvinylpyrrolidone (PVP)

I^{131} albumin that leaks into the gastrointestinal tract is rapidly catabolized, and the breakdown products are then absorbed. In contrast, the macromolecule I^{131} PVP [2] is unaffected by intestinal enzymes, and, therefore, it was used to obtain an estimate of intestinal protein loss according to the method of Gordon (22). The patients received 10 to 25 μc of I^{131} PVP intravenously from a calibrated syringe. The stools passed during the subsequent 4 days were collected as a single lot in a 1-gallon stainless steel can, were homogenized with silica gravel by agitation on a shaker, and were counted and compared with an appropriate standard. The results are expressed as percentage of the dose of administered isotope excreted in the 4-day feces collection.

Results

Serum albumin concentration in hyposynthetic hypogammaglobulinemia. The serum albumin concentration was below 3.6 g per 100 ml, the lower limit of normal in our experience, in 20 of the 24 patients (Figure 1). Hypoalbuminemia was present in a majority of patients in each of the three classes of hyposynthetic hypogammaglobulinemia studied. The eight patients with a serum albumin concentration below 3 g per 100
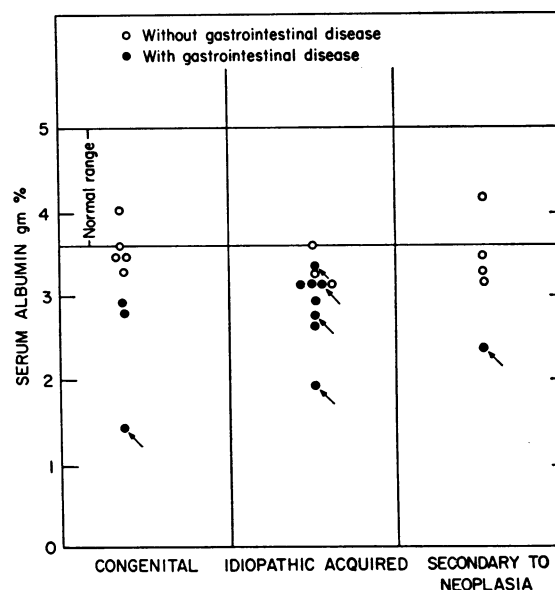

Fig. 1. Serum albumin concentration in 24 patients with hyposynthetic hypogammaglobulinemia. The patients with gastrointestinal disorders are indicated by the solid circles. The six subjects selected for I^{131}-labeled albumin turnover studies are indicated by the arrows.

[2] The I^{131} PVP used was prepared by the Radiopharmaceutical Service of the Pharmacy Department of the National Institutes of Health.

TABLE II

The metabolism of albumin and gamma globulin in patients with hyposynthetic hypogammaglobulinemia

Patients	Serum albumin	Total circulating albumin	Total body albumin pool	Albumin metabolism — Albumin catabolism							Gamma-globulin metabolism	
				Method A			Method B					
				I131 albumin survival t½	Fraction of body albumin degraded per day	Albumin turnover	Fraction of circulating albumin degraded per day	Albumin turnover	I131 in stool per day as % of body I131 albumin content	I131 PVP* 4-day fecal excretion	Serum γ-globulin	γ-Globulin turnover
	g/100 ml	g/kg	g/kg	days		g/kg/day		g/kg/day		% of dose	g/100 ml	g/kg/day
Controls [10]†	3.7–4.6	1.5–2.0	3.7–4.7	13–20	0.035–0.053	0.16–0.20	0.087–0.132	0.16–0.20	0–0.08	0–0.8	0.9–1.5	0.034–0.051
E.R.	2.1	1.1	3.0	20	0.035	0.10	0.092	0.10	0.05	0.6	0.16	
A.H.	3.1	1.2	3.1	18	0.039	0.12	0.086	0.10	0.10	0.7	0.31	0.0046
A.J.	2.7	1.2	3.1	21	0.033	0.10	0.091	0.11	0.09	0.8	0.40	0.01
I.T.												
Before therapy	2.5	1.0	2.3	7.4	0.094	0.22	0.219	0.22	1.5	1.7	0.15	
After therapy	3.6	1.4	3.5	14.0	0.050	0.17	0.119	0.17	0.2	0.3	0.20	0.0036
P.M.												
Before therapy	3.4	1.4	3.4	10.5	0.066	0.22	0.150	0.22	0.25	1.6	0.15	
After therapy	3.9	1.8	4.0	16.0	0.043	0.17	0.102	0.18	0.04	0.5	0.16	0.0009
M.Q.												
Before therapy	1.4	0.5	1.3	7.2	0.096	0.11	0.212	0.11	2.2	5.0	0.21	
After therapy	3.3	1.6	3.6	11.0	0.063	0.23	0.140	0.22	0.74	1.3	0.15	0.0004

* Polyvinylpyrrolidone.
† Controls for the turnover studies included normal volunteers and patients with idiopathic epilepsy.
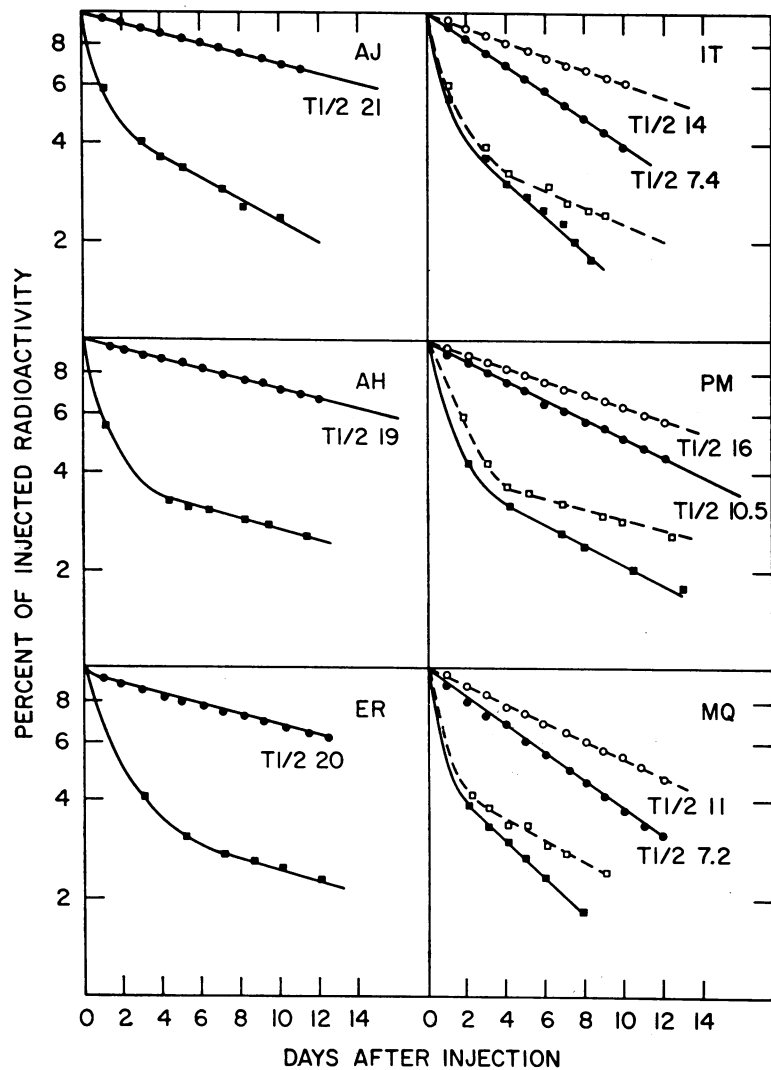
Fig. 2. Metabolism of I^{131}-labeled albumin in six subjects with hyposynthetic hypogammaglobulinemia. The upper curves, indicated by the circles, represent the decline in total body radioactivity with time. The lower curves, indicated by the squares, represent the decline in plasma radioactivity. Studies performed before therapy are indicated by the solid lines; those performed after therapy are indicated by the dashed lines.

ml all had significant gastrointestinal symptoms. The mean serum albumin concentration of the 12 patients with gastrointestinal tract disorders was 2.5 g per 100 ml compared to 3.5 g per 100 ml in the remaining 12 patients.

Protein turnover studies. Six patients were selected for studies of their albumin metabolism. All had diarrhea (Figure 1). The hypogamma-globulinemia was congenital in M.Q., secondary

to neoplasm in E.R., and idiopathic, acquired in the remaining four patients.

The results of the I^{131} albumin and the I^{131} PVP studies are presented in Figure 2 and Table II. The values for both the total circulating albumin and the total body albumin pool were reduced in each of the patients before treatment. This indicated that the reduced serum albumin concentrations were due to a deficiency of albumin and not

to an expanded plasma volume or to an abnormal distribution of the protein between the intravascular and extravascular spaces. The hypoalbuminemia of E.R., A.H., and A.J. appeared to be attributable to impaired synthesis unaccompanied by excessive catabolism or loss, since the rate of albumin synthesis for these patients was between 0.10 and 0.12 g per kg per day compared to the normal range, 0.16 to 0.20 g per kg per day. Excessive catabolism or loss of albumin was excluded in these patients because the half-time of survival of I^{131} albumin and the fraction of circulating albumin degraded per day were normal, and there was no excessive fecal excretion of isotope after the injection of I^{131} albumin or I^{131} PVP.

The results of the studies of I.T. and P.M. suggested that these patients were losing excessive quantities of albumin into the gastrointestinal tract, since before therapy the survival of iodinated albumin for each patient was significantly shorter than normal and an abnormally large fraction of the radioactivity administered intravenously as I^{131} albumin or as I^{131} PVP was excreted in the stool. The rates of albumin synthesis for these 2 patients were normal or slightly increased.

Both impaired synthesis of albumin and excessive loss into the gastrointestinal tract were responsible for the hypoalbuminemia of patient M.Q., since the albumin synthetic rate was 0.11 g per kg per day, the $t_{\frac{1}{2}}$ of albumin survival was 7.2 days, and excessive I^{131} PVP appeared in the stools.

Results of therapy. I.T., who had malabsorption and chronic intestinal infection with *Salmonella newport* in association with his hypogammaglobulinemia, was treated with a gluten-free diet and broad-spectrum antibiotics. After therapy, his stool cultures became negative and his malabsorption decreased markedly (Table I). His serum albumin concentration, the half-time of survival of iodinated albumin, and the fecal excretion of I^{131} PVP returned to normal, indicating a reversal of the previous excessive loss of albumin into the gastrointestinal tract (Figure 2 and Table II). His serum gamma-globulin concentration remained depressed, and the gamma-globulin synthetic rate following treatment was approximately 10% of normal (Table II), indicating that the primary defects in the plasma cells and in

gamma-globulin production had not been affected by therapy.

Treatment of patient P.M. with a gluten-free diet was followed by an increase in her serum albumin concentration and a return to normal of I^{131} albumin survival and of I^{131} PVP excretion. Her serum gamma-globulin concentration and the rate of gamma-globulin synthesis remained exceedingly low.

M.Q., with congenital hypogammaglobulinemia and associated ileocolitis, was treated with ACTH and then with prednisone. After therapy, the serum albumin concentration, albumin survival, albumin synthetic rate, and I^{131} PVP excretion returned toward normal. Again the gamma-globulin concentration and the gamma-globulin synthetic rate remained low after therapy.

Discussion

The present study has revealed a reduction in serum albumin concentration in a majority of 24 patients with all three pathological forms of defective gamma-globulin synthesis. The hypoalbuminemia was most marked in those patients with gastrointestinal symptoms. In the six cases where the metabolism of albumin was studied with I^{131} albumin and I^{131} PVP, three had diminished albumin synthesis as the major factor in their hypoalbuminemia, two had excessive enteric loss of protein, and one had both diminished albumin synthesis and excessive enteric loss.

Several observations concerning albumin synthesis in these patients deserve discussion. Although the calculated values for albumin synthesis for I.T. and P.M. were not below the lower limit of the normal range, nevertheless, these patients may be regarded as showing a relative defect in albumin synthesis because they were apparently unable to accelerate their synthetic rates in response to the stimulus of hypoalbuminemia. Patients with idiopathic pathological enteric albumin loss have increased their synthetic rates up to values as high as 0.4 g per kg per day in response to hypoalbuminemia comparable, in degree, to that of I.T. and P.M. (23). Thus, all six patients in the present study had defective albumin synthesis, either absolute or relative. According to current knowledge, a defect in albumin synthesis is not a logical consequence of defective synthesis of

gamma globulin. Gamma globulin is produced in plasma cells, and its synthesis was depressed in our patients as a result of either a decrease in the number of plasma cells or a qualitative impairment of the synthetic capacity of plasma cells. Albumin, however, is produced in the liver. Why, then, was its synthesis impaired? Liver damage or lack of albumin precursors, due either to deficient intake or to malabsorption, are two possible explanations.

Liver damage does not appear to be a major factor, since liver function tests were essentially normal in all six patients when their albumin metabolism was studied (Table I). A reduced intake of calories and amino acids, or malabsorption, may have played a significant role in the defective albumin synthesis, since the six patients had steatorrhea. Four had weight loss before this study, and all but one were underweight. Finally, other as yet undefined factors may be responsible for the defective albumin synthesis of the patients studied, since defective albumin synthesis is a common feature of chronic inflammatory diseases even when evidence of malabsorption or liver damage is lacking (24, 25).

Minor loss of protein into the gastrointestinal tract occurs in normal subjects and appears to be a factor in the normal catabolism of the serum proteins (26). Excessive enteric protein loss has been shown to be of significance in the hypoalbuminemia associated with a variety of disorders, including Whipple's intestinal lipodystrophy (27), gastric rugal hypertrophy (28), gastric carcinoma (29), sprue (30), regional enteritis, ulcerative colitis (31), constrictive pericarditis (32), and intestinal lymphangiectasia (6, 23). Holman, Nickel, and Sleisenger (6) described a patient with hypogammaglobulinemia, excessive enteric protein loss, and a localized granulomatous lesion of the small bowel. After resection of this lesion, the abnormal gastrointestinal protein loss stopped, but the serum gamma-globulin concentration fell to an even lower level. Vesin and co-workers (33) described a patient with hypogammaglobulinemia, protein-losing gastroenteropathy, and malabsorption, who responded to treatment with a gluten-free diet with reversal of the steatorrhea and hypoalbuminemia, but with persistence of the extreme hypogammaglobulinemia. In the present study, three of the six patients had

gastrointestinal protein loss as a major factor in their hypoalbuminemia as demonstrated by the use of I^{131} albumin and I^{131} PVP. One of these three patients had unexplained diarrhea and steatorrhea (P.M.), one had ileocolitis (M.Q.), and the third had chronic salmonellosis (I.T.). In each case appropriate therapy resulted in reversal of the abnormal enteric protein loss and of the hypoalbuminemia (Table II). However, the hypogammaglobulinemia and the defect in gammaglobulin synthesis persisted.

The pathological physiology. in these patients appears to be a primary disturbance of plasma cell development or function with a consequent defect in the synthesis of gamma globulins that leads to disorders of the gastrointestinal tract and consequent excessive enteric protein loss and hypoalbuminemia. This entity should be distinguished from excessive enteric protein loss due to primary bowel disease in which the hypoalbuminemia and the hypogammaglobulinemia are due solely to the exudative enteropathy, but in which the synthesis of gamma globulin is normal. In the latter entity, reversal of the abnormal enteric protein loss restores the serum concentrations of both albumin and gamma globulin to normal (10).

The ability to differentiate those patients with hyposynthetic hypogammaglobulinemia whose hypoalbuminemia is due to excessive enteric loss from those whose hypoalbuminemia is due to impaired synthesis of albumin is clinically important, since excessive loss may be reversed by appropriate therapy. This was demonstrated in the cases reported by Holman and co-workers (6) and Vesin and associates (33) and in the three cases described in the present paper. Unfortunately, the differentiation cannot be made on the basis of routine clinical studies. All six of the patients described in the present study, both those with excessive gastrointestinal albumin loss and those with defective albumin synthesis, had a low or low-normal serum cholesterol concentration, essentially normal liver function studies, significant diarrhea, and variable steatorrhea. Two patients from both the enteric loss and defective albumin synthesis groups had abnormalities of the X-ray examination of the intestine, ranging from coarsening of the mucosal folds, interpreted as mucosal edema, to significant ulceration of the ileocecal mucosa. Peroral biopsy of the jejunal mucosa

showed abnormalities in patients in each of the groups. Thus, to detect those patients with hyposynthetic hypogammaglobulinemia and associated excessive intestinal protein loss, one must use techniques such as the I^{131} albumin and I^{131} PVP tests that directly measure the metabolism of the proteins.

The reason for the 20 to 50% incidence of gastrointestinal tract disturbances in patients with impaired synthesis of gamma globulins is not entirely clear. Undoubtedly, in a certain number of these patients antibody deficiency predisposes them to enteric infections which are the immediate causes of the gastrointestinal tract pathology. This was true in six of the 12 patients with gastrointestinal disorders in the present study. I.T., who had enteric infection with *Salmonella newport,* is a typical example of this problem. Other patients, however, such as M.Q., whose clinical picture was that of ileocolitis, and A. J., who had features possibly suggestive of sprue, do not have problems obviously attributable to infection. In considering possible explanations for these disorders, we note that patients with hypogammaglobulinemia are also prone to chronic sinusitis and bronchitis, inflammations of other mucosal barriers to the external environment. This apparent general vulnerability of mucosal surfaces may in some way be related to the reduction in ability to form antibodies and to the absence of plasma cells from these tissues.

Summary

1) The serum albumin concentration was determined in 24 patients with defective gamma-globulin synthesis, including groups with congenital hypogammaglobulinemia, idiopathic acquired hypogammaglobulinemia, and hypogammaglobulinemia secondary to neoplastic disease.

2) The serum albumin concentration was below the lower limit of normal of 3.6 g per 100 ml in 20 of the 24 patients.

3) Each of the eight patients with a serum albumin concentration below 3 g per 100 ml had significant gastrointestinal symptoms.

4) The albumin metabolism of six of the patients with hypoalbuminemia and diarrhea was studied with I^{131}-labeled albumin and I^{131}-labeled polyvinylpyrrolidone.

5) The total body albumin pool was reduced in each of these patients. In four of the patients there was defective albumin synthesis, and in two of the patients the albumin synthetic rate was within normal range.

6) In three of the patients excessive loss of albumin into the gastrointestinal tract was a significant factor in the hypoalbuminemia. After treatment of these patients with antibiotics, gluten-free diet, or corticosteroids, there was a marked diminution in, or complete cessation of the abnormal enteric loss of albumin, with a return to normal serum and total body albumin levels. However, the primary defect in gamma-globulin synthesis was not affected by the therapy.

7) It is felt that the primary disorder in all these patients is defective gamma-globulin synthesis. However, an associated secondary disorder of the intestinal mucosa may be seen with consequent general enteric loss of the serum proteins.

Acknowledgment

Appendix

Case summaries

Patient E.R.—hypogammaglobulinemia; Hodgkin's sarcoma type of malignant lymphoma; malabsorption. This 46-year-old white male entered in March 1960, with anasarca which began in 1958 as pedal edema. Four months before admission the edema became generalized and associated with weakness and weight loss. There was no past history of recurrent infections, arthritis, diarrhea, jaundice, or renal or cardiac disease.

He had edema extending to the mid-thigh level and fluid in his abdomen and right chest. The heart, liver, and spleen did not seem enlarged. His leukocyte count was 2,100 cells per mm^3 with 44% polymorphonuclear leukocytes, 14% band cells, 40% lymphocytes, 2% monocytes, and 4 nucleated erythrocytes per 100 leukocytes. Roentgen studies revealed a right pleural effusion, widespread osteolytic lesions, and areas of mucosal swelling and irregularity in the mid-duodenum. A rib biopsy showed undifferentiated malignant tumor. Mucosal bi-

opsies from the proximal jejunum revealed short, broad villi and plasma cell infiltration of the lamina propria. The intestinal pathology in this and in the following cases will be described in detail elsewhere (34).

The patient suffered from progressive weakness and weight loss with preterminal marked hypoglycemia and death in May 1960. Post-mortem examination revealed widespread lymphomatous involvement, severe bone marrow hypoplasia, severe fatty metamorphosis of the liver, and acute necrotizing bronchopneumonia.

Patient A.J.—hypogammaglobulinemia; malabsorption; recurrent tetany. This 52-year-old white male entered in July 1960, with moderate diarrhea and tetany. At age 20 he developed diarrhea that persisted without weight loss until he was 44 when his stools became bulky, watery, and foul-smelling, and his weight fell gradually from 140 to 118 pounds. At age 49 he developed recurrent hypocalcemic tetany, anemia, and multiple infections including acute pyelonephritis, bronchopneumonia, and furunculosis. At age 51 his hypogammaglobulinemia was discovered.

On admission he was extremely thin and had bilateral hypocalcemic cataracts and ridged fingernails, but no edema or enlargement of liver or spleen. His serum calcium was 6.5 mg per 100 ml. Roentgen studies revealed coarsened mucosal folds in the stomach and proximal small bowel. In some areas of a jejunal mucosal biopsy the villi were shortened and even absent, but in other areas they were almost normal. The number of plasma cells in the lamina propria appeared normal.

On a gluten-free diet his daily fecal fat ouput fell to 25 g per day from an average value of 80. After discharge from the hospital his fat excretion rose to 50 g per day despite his efforts to stay on a gluten-free diet.

Patient A.H.—hypogammaglobulinemia; pernicious anemia; giardiasis; mild, variable malabsorption; arrested tuberculosis. This Negro female entered in May 1960, at age 36. She had many mild childhood upper respiratory infections. During her college years these were accompanied by purulent nasal discharge and cough. At age 30 she developed miliary tuberculosis which responded to a year of treatment but left her with a chronic cough productive of purulent sputum. In 1959 she developed anemia, and a bone marrow aspiration, performed shortly after treatment with iron, vitamins, and liver injections, revealed a decreased number of plasma cells and changes suggestive of megaloblastic erythropoiesis. She had hypoalbuminemia and hypogammaglobulinemia. Ten months before admission she developed recurrent upper abdominal cramps and watery diarrhea.

On admission, she was thin with a chronic cough, basilar rales bilaterally, and no detectable enlargement of her liver, spleen, or lymph nodes. Her leukocyte count fluctuated between 2,500 and 9,000 cells per mm³. Roentgen studies revealed bilateral maxillary sinusitis, diffuse punctate pulmonary calcifications, and a normal gastrointestinal tract. Her jejunal mucosa showed generally normal morphology with a marked decrease in the num-

ber, or actual absence, of plasma cells of the lamina propria. Bone marrow aspirate showed no stainable iron, only rare plasma cells and questionable megaloblastic erythropoiesis.

Her stools were freed of *Giardia lamblia* by treatment with Atabrine and her mild steatorrhea subsided. In January 1963, when she had been off medication for some time, she was found to have pernicious anemia. After intramuscular administration of vitamin B_{12}, her anemia subsided, and in addition, her serum albumin concentration rose from 2.6 to 4.0 g per 100 ml without any significant change in her serum gamma-globulin concentration.

Patient I.T.—hypogammaglobulinemia, enteric infection with Salmonella newport; cholelithiasis; malabsorption. This 53-year-old white male entered in January 1960, with prolonged diarrhea. Having had eczema and asthma in childhood, at puberty he developed a chronic cough, with recurrent episodes of pneumonia that continue to the present. Bronchiectasis was demonstrated in 1949, and from 1950 to 1958 he received 1 g of chlortetracycline daily. In 1952, he developed mild nausea and vomiting and sporadic episodes of mild diarrhea. A solitary large gallstone was discovered. In 1959, he developed periumbilical pain, his diarrhea became continuous and more severe, his weight fell from 135 to 95 pounds, and he developed pedal edema. One month before admission, in another hospital, he was found to have anemia with abnormal Schilling tests with or without added intrinsic factor, hypoalbuminemia, and hypogammaglobulinemia. Xylose-tolerance test results and serum carotenoid concentration were normal. Roentgen study revealed small bowel mucosal edema.

On admission, he was debilitated and had emphysema, with coarse, sticky rales in the left lower lobe, and a liver edge three finger-breadths below the right costal margin. The leukocyte count varied between 3,500 and 7,600 cells per mm³. Agglutination studies for *Salmonella* were negative. A jejunal mucosal biopsy revealed short, wide villi, consistent with partial atrophy, and hypocellularity of the lamina propria with virtual absence of plasma cells. Bone marrow aspiration showed myeloid hypoplasia and no plasma cells.

He developed recurrent septicemias and pulmonary infections and severe watery diarrhea, with malabsorption, weight loss, and peripheral edema. *Salmonella newport* was isolated from his stools and *Escherichia coli* from his blood. Treatment with gamma globulin and several broad spectrum antibiotics and a gluten-free diet failed to improve him. After intramuscular administration of colistimethate sodium (Coly-Mycin), his blood became sterile, the *Salmonella* disappeared from his stools, his diarrhea and edema subsided, and his weight rose from 40 to 62 kg. All tests of intestinal absorption (except for the Schilling and xylose-tolerance tests), the roentgen appearance of the small intestine, and the morphological abnormalities of the jejunal mucosa, with the exception of the absence of plasma cells, returned toward normal.

Patient P.M.—hypogammaglobulinemia; chronic lung

disease; intermittent malabsorption. This 35-year-old white housewife entered in January 1960, with hypogammaglobulinemia. Starting at age 16 she had numerous ear and lung infections, and at age 22 she had a left lower lobectomy. At age 26 she developed recurrent episodes of severe diarrhea with foul, green, fatty stools. At age 29 her hypogammaglobulinemia was detected. No plasma cells were seen in her bone marrow, her oral glucose tolerance test suggested poor absorption, and roentgen studies revealed coarsened mucosal folds in the small intestine and extremely rapid transit of contrast material. She improved after receiving antibiotics, cortisone, and gamma globulin, remained relatively well until age 31 when her pulmonary symptoms returned, and again responded to treatment. Her diarrhea, however, recurred and persisted.

On admission she was thin and chronically ill, and had diffuse expiratory wheezing, a distended abdomen, and no peripheral edema. Roentgen studies revealed emphysema, chronic fibrocystic disease of the lungs, and hepatosplenomegaly, but no abnormalities of the upper gastrointestinal tract. The jejunal mucosa contained almost no plasma cells.

On February 18, 1960, she developed an *Escherichia coli* urinary tract infection and was treated with 2 g of tetracycline daily by mouth. On February 21, she was placed on a gluten-free diet. By February 29, her diarrhea had subsided, and it did not return. After her discharge in March she remained on a gluten-free diet for several months and then changed to a normal diet, but had no recurrence of her diarrhea. She was readmitted in September 1961, and there was no laboratory evidence of malabsorption. Except for the paucity of plasma cells, her jejunal biopsy did not appear abnormal.

Patient M.Q.—hypogammaglobulinemia; enterocolitis. This 12-year-old white male entered in March 1960. Starting at age 1, after a perianal infection, he had numerous infections of the ears, nose, throat, lungs, and skin and episodes of hip and elbow arthritis. At age 7, hypogammaglobulinemia was detected and treated with periodic gamma-globulin injections. Because of recurrent sinusitis and lung infections he received tetracycline from age 9 to 11½ and did well. Then a rectal abscess was incised and drained, and penicillin was substituted for tetracycline. A week later he developed crampy abdominal pain and diarrhea. No pathogenic bacteria or parasites were found in the stools. His rectal mucosa appeared edematous and inflamed, but a biopsy was interpreted as normal. He responded to blood transfusions, ACTH, and steroids by rectum and remained relatively well until age 12 when the diarrhea and abdominal pain recurred and he lost 14 pounds.

On admission, his height and weight were strikingly below normal, he had thickened ear drums, scattered pulmonary rales and rhonchi, and perirectal tabs. His leukocyte count was 15,000 per mm³. Roentgen studies revealed extensive bronchiectasis, coarse mucosal folds in the entire small intestine, fixation of several ileal loops, and an area of constant narrowing near the large

intestine's splenic flexure, with mucosal spiculation in the narrowed area. Jejunal and rectal mucosal biopsies and bone marrow aspiration were abnormal only for the absence of plasma cells.

Because of progressive weight loss, fever, increasing diarrhea, rapid decline in serum albumin and cholesterol concentrations, and progressive anemia, he received blood transfusions, ACTH intravenously, and prednisolone, and he improved generally and significantly. The area of large-bowel narrowing also disappeared.

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