Familial Hypercatabolic Hypoproteinemia

A Disorder of Endogenous Catabolism of Albumin and Immunoglobulin

Thomas A. Waldmann* and William D. Terry‡
**Metabolism Branch and ‡Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892*

Abstract

The metabolism of albumin and IgG was investigated in two siblings, products of a first-cousin marriage, a female aged 34 yr and a male aged 17, who had a marked reduction in their respective serum concentrations of IgG (1.3 and 3.1 mg/ml) and albumin (19 and 21 mg/ml). The metabolism of radioiodinated IgG and albumin was studied in the two patients. The total circulating and body pools of IgG were < 28% of normal. The IgG synthetic rates were within the normal range. However, the IgG survival was short, with their respective fractional catabolic rates increased fivefold to 31% and 36% of the intravenous pool per day (normal, 6.7±2%/d). Furthermore, the patients had reduced total body pools, normal synthetic rates, and increased fractional catabolic rates for albumin. There was no proteinuria or abnormality of renal or liver function. In addition, the patients did not have circulating antibodies directed toward IgG, IgA, or albumin. Furthermore, both patients had normal fecal ^{51}Cr-labeled albumin tests, thus excluding excessive gastrointestinal protein loss. We propose that these siblings have a previously unrecognized familial disorder characterized by reduced serum concentrations of IgG and albumin caused by a defect in endogenous catabolism, leading to a short survival of these proteins that is associated in this family with chemical diabetes and a skeletal deformity. (*J. Clin. Invest.* 1990. 86:2093–2098.) Key words: familial disorders • hypogammaglobulinemia • hypoproteinemia

Introduction

The study of immunoglobulin metabolism has been of value in elucidating the physiological factors controlling the rates of immunoglobulin synthesis, catabolism, and transport (1). These studies also have been of value in the study of the pathogenesis of abnormalities of immunoglobulin levels seen in disease. A number of new categories of immunoglobulin deficiency disease have been elucidated through the use of plasma protein turnover studies (1, 2). In the majority of cases, hypogammaglobulinemia has been shown to result from decreased synthesis of immunoglobulin (1–3). A second major pathophysiological mechanism resulting in hypogammaglobulinemia is excessive loss of serum proteins into the urinary or gastrointestinal tracts (4). Hypogammaglobulinemia may also result from a disorder of endogenous immunoglobulin degradation leading to a short immunoglobulin survival (1, 5–8). This hypercatabolism may be restricted to a single class of immunoglobulins, as in the isolated hypercatabolism of IgG in patients with myotonic dystrophy (5) or in some patients with abnormal immunoglobulin-immunoglobulin interactions, as in those with complex IgM-IgG cryogels (6). Hypercatabolism restricted to IgA occurs in patients with antibodies to this immunoglobulin class (7). Alternatively, hypercatabolism may involve different classes of serum proteins. For example, the survivals of IgG, IgA, and albumin are shortened in patients with the Wiskott-Aldrich syndrome; however, increased rates of synthesis mask the endogenous hypercatabolism in these cases (8).

We now report on two siblings with a marked reduction of their serum IgG and albumin concentrations. The synthetic rates of these proteins were essentially normal, whereas the fractional catabolic rates reflecting endogenous degradation were markedly increased. The patients did not have proteinuria, excessive gastrointestinal protein loss, or other known causes of a shortened protein survival. Thus, these siblings appear to have a previously unrecognized familial disorder characterized by reduced levels of serum IgG and albumin due to an abnormality of endogenous protein catabolism leading to a short survival of these proteins.

Methods

Patients. Two siblings (W.J., a female 34 yr of age, and D.W., a male 17 yr of age), the products of a first-cousin marriage (pedigree shown in Fig. 1), were studied because they displayed a marked reduction of their serum IgG and albumin concentrations. W.J. was in good health until age 21 when she had a miscarriage in the 7th mo of pregnancy. After the miscarriage, she developed purplish red spots over the left anterior aspect of her leg. 6 mo before admission, she developed multiple ulcerations of the left leg. A diagnosis of diabetes mellitus was made on the basis of glucose tolerance tests, and a biopsy of the leg was interpreted as necrobiosis lipoidica diabeticorum. A serum protein electrophoresis revealed decreased gammaglobulin and albumin concentrations. Quantitative studies of immunoglobulin on serum submitted to the National Institutes of Health (NIH) revealed an IgG of 1.3, an IgA of 4.6, and an IgM of 0.5 mg/ml (Table I). She was admitted to the Clinical Center of the NIH for further evaluation of her dysproteinemia. Physical examination was normal with the exception of short-appearing arms and confluent areas of old and encrusted healing skin ulcerations of the pretibial areas of both legs. On biopsy of the skin lesions there were a number of small nodules that were epithelioid, surrounded by lymphocyte infiltrations but no giant cells, consistent with livedo reticularis leading to ulceration. On x-ray examination of the short forearms and wrists, short ulnae with bilateral bowing of the radii were observed. The patient's hemoglobin was 14.4 g/dl, the platelet count was 143,000/mm^3, and white blood cell count was 4,500/

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Dr. Terry's present address is Damon Biotech, Needham Heights, MA 02194.

Address reprint requests to Dr. Waldmann, Metabolism Branch, Building 10, Room 4N115, National Cancer Institute, Bethesda, MD 20892.

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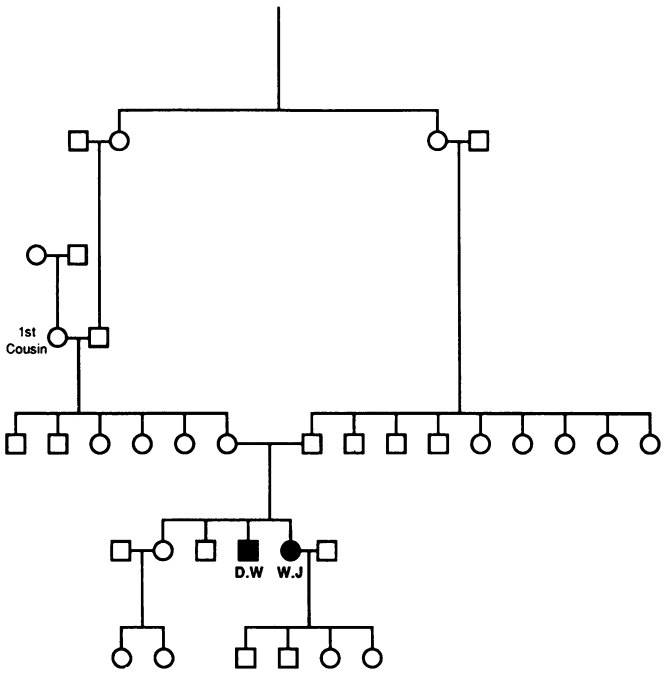

Figure 1. Pedigree of patients (W.J. and D.W.) with familial hypercatabolic hypoproteinemia. The affected individuals are indicated by the solid circles and squares, whereas individuals with essentially normal albumin and immunoglobulin levels are indicated by the outlined circles (females) and squares (males).

mm^3 with 65% polymorphonuclear leukocytes, 26% lymphocytes, and 9% monocytes. Renal and hepatic function tests were normal. On protein electrophoresis, the patient had a total protein of 5.0 with an albumin of 2.4, an α-1 of 0.3, an α-2 of 1.0, a β of 1.0, and a γ-globulin of 0.3 g/dl. The patient was nonreactive to the recall skin test antigens Brucellergen, second strength purified protein derivative, and histoplasmin and made only an equivocal response to dinitrochlorobenzene. On assessment of her ability to make antibodies after antigenic challenge, the patient, who was blood group A-positive, manifested a serum anti-B titer of 1:32 that did not increase on intramuscular stimulation with B blood group substance (normal host stimulation titer mean of 12 controls, 1:1,024). The patient responded to typhoid vaccine with a rise in H antibody titer from 0:1 to 1:320. There was no increase in the antibody titer to the Vi antigen of *Escherichia coli* from the 1:4 value present before immunization, and the titer to the tularemia antigen rose only to 1:4 after immunization, a value much lower than the mean of 13 normals of 1:64. Thyroid functions were essentially normal, with a protein-bound iodine measurement of 7.5 μg/dl and a triiodothyronine uptake of 23%. The 24-h urinary excretions of 17 ketosteroids and 17 OH steroids in the urine were 7.6 and 6.3 mg, respectively. 2 yr subsequently, the patient developed an abnormally low platelet count of 46,000/mm^3 with an associated white blood cell count of 3,600/mm^3. 4 yr after the initial admission, the platelet count declined to 3,000/mm^3 and the patient developed thrombocytopenic purpura, menometrorrhagia, and severe epistaxis. The lupus erythematosus test, monospot test, and anti-nuclear antibody test were negative. No pancreatic anti-islet or anti-parietal antibodies were demonstrated. At this time, the IgG was 2.6, the IgA 2.1, the IgM 5.3, and the IgD 0.007 mg/ml. The patient was thought to have idiopathic thrombocytopenic purpura that proved unresponsive to prednisone therapy, and a splenectomy was performed. The spleen had lipid histiocytosis of the red pulp, consistent with idiopathic thrombocytopenic purpura, as well as extramedullary thrombocytopoiesis, granulocytopoiesis, and erythropoiesis. After splenectomy, there was a gradual increase in the platelet count to the 40,000–50,000/mm^3 range. The patient developed recurrent fever during the weeks after the operation, and on subsequent laparotomy, an ovarian desmoid cyst of the right ovary was removed. The patient's fever gradually responded to antibiotic therapy, and the patient was discharged. 7 mo after discharge from the NIH the patient developed bilateral pneumonia, pulmonary and oral bleeding associated with thrombocytopenia, and septic shock and died at an outside hospital at 40 yr of age. No autopsy was performed.

D.W., the 17-yr-old brother of the patient, was shown to have reduced immunoglobulin levels on submitted serum samples, with an IgG of 3.1, an IgA of 3.5, an IgM of 0.46, and an IgD of 0.016 mg/ml (Table I). The remainder of the immediate family members had essentially normal immunoglobulin levels (Table I). Patient D.W. was admitted to the Clinical Center of the NIH for evaluation of his dysproteinemia. He was entirely well on admission, with the only physical abnormality being short arms. On x-ray examination of his forearms and wrists, he was shown to have shortened ulnae and bowing of the radii (Fig. 2). On chest x-ray, there were minute fibrocalcification densities in the right mid-lung field consistent with healed granulomas. The hemoglobin was 15.5 g/dl, the platelet count 156,000/mm^3, and the white blood cell count 7,800/mm^3 with 65% polymorphonuclear leukocytes, 22% lymphocytes, 12% monocytes, and 1% eosinophils. The total serum protein concentration was 4.4 g/dl with an albumin

Table I. Immunoglobulin Levels

Patient	Relationship to propositus	IgG	IgA	IgM	IgD	Type κ	Type λ
				ng/ml			
1 (W.J.)	propositus	1.3	4.6	0.50	0.054	1.5	0.2
2 (D.W.)	brother	3.1	3.5	0.46	0.016	2.7	1.6
3	father	8.4	3.5	0.60	0.030	6.3	2.5
4	mother	9.7	2.8	0.76	0.014	6.5	3.1
5	brother	10.5	3.0	0.64	0.017	6.8	3.5
6	sister	8.1	2.6	1.9	0.041	7.1	2.3
7	daughter	10.5	2.8	1.4	0.025	9.3	2.8
8	daughter	11.0	2.6	1.9	0.041	9.3	3.2
9	son	7.8	2.9	2.1	0.021	6.0	3.7
10	son	7.5	2.4	0.7	0.096	7.0	3.4
Normal (50) mean±SD		12.4±2.2	2.8±0.7	1.2±0.4	0–0.3	8.0±2.0	4.5±1.2

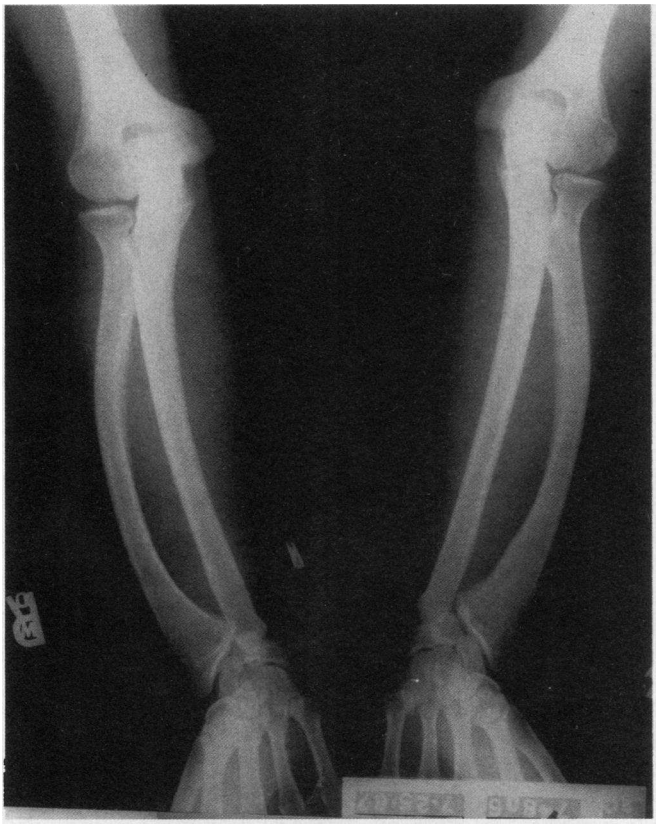

Figure 2. X-ray examination of the forearms of patient DW showing shortened ulnae and bowed radii. The patient's sister had the same abnormality.

concentration of 2.3 g/dl and a gammaglobulin concentration of 0.3 g/dl. The patient did not have proteinuria and had normal renal and hepatic function tests. The lupus erythematosus test was negative. No anti-pancreatic islet cell or anti-parietal antibodies were demonstrated. Thyroid function tests were normal, with a protein-bound iodine measurement of 6.8 μg/ml and a triiodothyronine uptake of 26%. On adrenal function studies, the patient excreted 8.6 mg/24 h of 17 OH steroids and 8.05 mg/24 h of 17 ketosteroids into the urine. On two of the three examinations, the patient manifested an abnormal diabetic type glucose tolerance test. The patient was nonreactive to challenge with recall skin test antigens Brucellergen, mumps, and dermatophyten 0 but had positive skin tests to histoplasmin and second strength purified protein derivative. The patient produced antibodies after antigenic challenge normally, with a normal rise in titer from 1:64 before immunization to 1:2048 after intramuscular administration of B blood group substance. Furthermore, on stimulation with typhoid vaccine, there was a rise in the titer of anti-H antibodies from 1:8 to 1:2560 and a rise in titer of anti-tularemia antibodies from 1:8 to 1:256 after immunization with the Foshay (tularemia) antigen.

The patient had no clinical symptoms throughout the 5-yr period of observation until age 22. The patient was lost to follow-up at that time.

Serum protein concentrations. Serum immunoglobulin concentrations were determined by an immunodiffusion technique (9). Samples were placed into wells of constant size, and agar plates were made with an antiserum specific for an individual immunoglobulin incorporated into the agar. The diameter of the precipitin ring formed by each serum sample was compared with the diameter obtained from dilutions of a reference standard. Immunoglobulin concentrations thus obtained were compared with those of a panel of 50 control sera.

Total serum proteins were determined by a biuret reaction, and albumin concentrations were determined by paper electrophoresis.

Preparation of labeled proteins. Preparations of IgG were obtained from normal sera by DEAE-cellulose chromatography using a technique previously described (5). The serum used in preparation of IgA and the details of preparation and characterization of the IgA are described elsewhere (7). Albumin was prepared from the serum of a normal individual utilizing Geon-Pevicon block (Geon Resin, B. F. Goodrich Co., Niagara Falls, NY; Pevicon, Superfosfat Fabrika, Aktiebolog, Stockholm, Sweden) electrophoresis as described previously (10). The immunoglobulin and albumin preparations were tested by Ouchterlony analysis and found to be immunochemically pure.

Iodination of each of the above preparations was performed with either ^{131}I or ^{125}I by the iodine monochloride technique of McFarlane (11). All preparations were calculated to have an average of less than one atom of iodine per molecule of protein in the final product. These products contained < 1% nonprecipitable radioactivity. Normal human albumin was added to each preparation to prevent damage to the protein by self-irradiation, and the mixture was sterilized by passage through a 0.22-μm Millipore filter. ^{51}Cr-albumin was prepared by a previously described technique (12).

Study protocol. All patients and controls were hospitalized at the Clinical Center of the NIH. 10 drops of Lugol's solution were administered orally three times daily throughout the study period to prevent thyroidal uptake of the released isotope. Serum immunoglobulin and albumin concentrations were obtained at intervals throughout the study period to verify that each patient was in a steady state. Turnover studies of different protein preparations were done either sequentially or simultaneously with one preparation labeled with ^{125}I and the other with ^{131}I. The dose of radioactivity administered ranged from 10 to 25 μCi/study. A 10-min blood sample was obtained for plasma volume determination. Additional blood samples were collected daily for 7–14 d after the administration of the labeled protein. Urine and stool specimens were collected in 24-h lots. Serum and urine samples were counted with appropriate standards in a γ-ray well-type scintillation counter with a thalium-activated sodium iodide crystal. When two isotopes were studied simultaneously, they were differentiated using a pulse height analyzer.

The patients were evaluated for abnormal gastrointestinal loss of protein with ^{51}Cr-labeled albumin according to methods previously described (12). 25 μCi of ^{51}Cr-labeled albumin were administered intravenously, and subsequent daily serum and stool collections were obtained. Stools were brought to a constant volume with saline, homogenized, and counted with appropriate standards in a γ-ray bulk counter employing two 2-in thalium-activated sodium iodide crystals.

Calculations of metabolic data. The time course of decline of radioactivity from the serum and whole body was plotted semilogarithmically (Fig. 3). Whole-body radioactivity was calculated by cumulative subtraction of the radioactivity appearing in the urine from the total injected dose. The biological $t_{1/2}$ of each labeled protein was determined graphically. The total circulating and total body pools, the fraction of the intravascular pool catabolized each day (fractional catabolic rate), and the synthetic rate (in the steady state equal to the absolute turnover rate) were determined according to the method of Nosslin (13) as discussed previously (1). The ^{51}Cr-labeled albumin results are expressed as the percentage of the intravenously injected isotope recovered in the feces during the 4 d after injection.

Evaluation of immune function. Naturally acquired delayed hypersensitivity to mumps, Brucellergen, dermatophyten 0, histoplasmin, and intermediate strength purified protein derivative was assessed using intradermal skin tests. To define the patients' ability to develop a delayed immune response to a new antigen, dinitrochlorobenzene (2,000 γ) dissolved in acetone was applied topically as a vesicant dose, and the ability to make a response 2 wk later to a 100-γ test dose placed topically was determined. Active immunization was performed with the following antigens: typhoid vaccine (Eli Lilly & Co., Indianapolis, IN) (0.3 ml subcutaneously weekly ×3), specific blood group substance B (Pfizer, Inc., New York) (0.5 ml subcutaneously daily ×2), and Foshay (tuleremia) antigen (provided by Dr. Paul Carbone, NIH) (1.0 ml intramuscularly) and *E. coli* Vi antigen (provided by Dr. N. E.

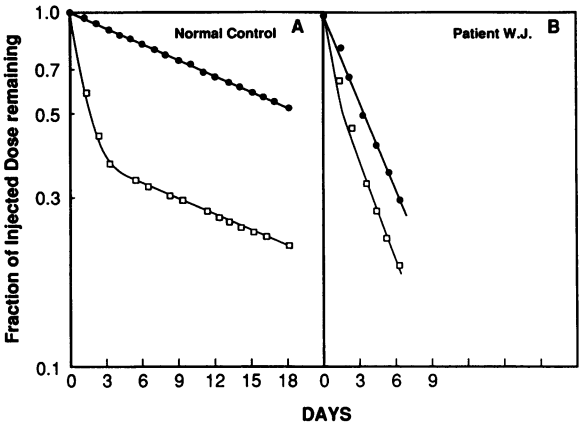

Figure 3. The metabolism of radiolabeled IgG in (*A*) a normal individual and (*B*) patient W.J. The fractions of the injected dose remaining in the serum are indicated by the square symbols and those remaining in the whole body are indicated by the circles. The survival of normal IgG in patient W.J. was markedly reduced ($t_{1/2}$ = 3.0 d) when compared with that in the normal individual ($t_{1/2}$ = 20 d).

Webster, NIH) (0.1 mg subcutaneously). The antibody titers from blood samples obtained before and 2 wk after completion of the immunizations were assayed as described previously (14). Antibodies to the blood group B antigen, Vi, and tularemia were measured by hemagglutination assays, whereas typhoid antibodies were measured by bacterial agglutination as described previously (14).

Search for circulating autoantibodies. The patients' sera were assessed for antibodies to IgG, IgA, and albumin using a conventional enzyme-linked immunoassay (ELISA). To determine the presence or absence of circulating human auto-antibodies to IgG, human IgG (Cappel Laboratories, Durham, NC) was used as the coating agent, PBS-1% normal rabbit or goat serum as the blocking agent and patient or control serum as the potential source of anti-IgG antibody. Rabbit anti-human IgM (Cappel Laboratories) and in independent studies goat anti-IgA peroxidase conjugates (Cappel Laboratories) were used as the detection antibodies to define IgM and IgA anti-IgG antibodies, respectively, in the patients' sera. Tetramethybenzidine/H_2O_2 (Kirkegaard & Perry Laboratories, Inc., Gaithersburg, MD) was used as the chromatogenic substrate. The presence or absence of IgM or IgG antibody to IgA was determined with a comparable procedure with the exception that human IgA was used as the coating agent and rabbit anti-human IgM or anti-IgG peroxide conjugates as the detection antibodies. Furthermore, the procedure was used to define the presence or absence of serum antibodies to albumin using human albumin as the coating agent, normal goat serum and ovalbumin (Sigma Chemical Co., St. Louis, MO) as the blocking agents, goat anti-human albumin as the positive control, and peroxide conjugates of anti-human Ig (Tago, Inc., Burlingame, CA) and swine anti-goat Ig (Tago, Inc.) as the detection antibodies.

Results

Two siblings, a woman aged 34 yr and a man aged 17, who were the products of a first-cousin marriage, had a marked reduction of serum IgG (1.3 and 3.1 mg/ml) and of albumin (19 and 21 mg/ml). The serum immunoglobulin concentrations of these two patients and their immediate family members are shown in Table I. The serum protein levels of the patients' parents, two normal siblings, and the four children of the female patient were essentially normal, as were the IgA and IgM concentrations of the patients. In Table II, we show the results of ^{131}I-albumin metabolic studies in the two patients and 10 normal individuals. The total circulating albumin pools determined from the product of the serum albumin concentrations and the plasma volumes expressed as grams per kilogram were 0.77 and 0.68 for the two patients, ~ 40% of the normal mean of 1.7 g/kg. The total body pools of albumin were similarly reduced to 1.5 and 1.3 g/kg when compared with the normal mean of 4.2 g/kg. The albumin survival was markedly shortened in both patients, with a survival $t_{1/2}$ of 6 d in each case compared with the normal mean of 16 d (range 13–20 d). The calculated fraction of the circulating (intravascular) pool of albumin catabolized per day for both patients was 0.22, twice the 0.11 mean value for albumin fractional catabolic rates in normal individuals. In contrast to these disorders of albumin survival, the synthetic rates for albumin were normal in the patients, with values (0.17 and 0.15 g/kg per d) that were within the normal range (0.13–0.22 g/kg per d). Thus, the reduced serum albumin concentrations and reduced circulating and total body pools of this protein were due to increased fractional catabolic rates (short survivals) of these proteins rather than abnormal albumin synthetic rates. The results of two independent metabolic studies with different preparations of radioiodinated IgG in patient W.J. and one study in patient D.W. paralleled those with radioiodinated albumin (Table III). The total circulating and total body pools of IgG of both patients were < 28% of normal. The IgG survival $t_{1/2}$s in the patients were 3.3, 3.0, and 2.8 d, markedly shorter than the mean 22.9 (±4) d in the normal individuals (Table III; Fig. 3). The fractions of the intravascular pool of IgG catabolized per day were increased fivefold to 31%, 34%, and 36% of the intravenous pool per day in the two siblings compared with the normal mean value of 6.7±2%/d. The IgG synthetic rates in the two studies of W.J. of 17 and 20 mg/kg/d were slightly lower than the mean of 34±11 mg/kg per d for normal controls, whereas the IgG synthetic rate of D.W., 51 mg/kg per d, was slightly higher than normal.

The survival $t_{1/2}$ of radioiodinated IgA in patient W.J. was reduced to 2.9 d compared with the normal mean of 6.4 d, and

Table II. Albumin Metabolism in Patients W.J. and D.W.

Patient	Serum albumin	Plasma volume	Total circulating albumin	Total exchangeable albumin	Albumin survival $t_{1/2}$	Fraction of circulating albumin degraded per day	Albumin synthetic rate	4-d fecal excretion of ^{51}Cr-albumin
	g/dl	*ml/kg*	*g/kg*	*g/kg*	*d*		*g/kg per d*	*% injected dose*
WJ	1.9	40.6	0.77	1.48	6.0	0.221	0.17	0.66, 0.72
DW	2.1	32.2	0.68	1.29	6.0	0.217	0.15	0.33
Normals (10)*	3.82±0.11	45.5±1.35	1.73±0.02	4.23±0.157	16.2±1	0.109±0.007	0.188±0.0146	0–0.7 (range)

* Number of individuals in group in parentheses; data expressed as mean±SEM.

Table III. IgG Metabolism in Patients W.J. and D.W.

Patient	Serum IgG	Plasma volume	Total circulating IgG	Total exchangeable IgG	IgG survival $t_{1/2}$	Fraction of circulating IgG degraded per day	IgG synthetic rate
	mg/ml	*ml/kg*	*g/kg*	*g/kg*	*d*		*mg/kg per d*
W.J., study 1	1.3	40.9	0.053	0.079	3.3	0.313	17
W.J., study 2	1.3	45.0	0.059	0.087	3.0	0.34	20
D.W.	4.4	32.0	0.141	0.207	2.8	0.36	51
Normals (23) mean±SD	12.1±2.6	42.0±5.8	0.494±0.116	1.090±0.263	22.9±4.0	0.067±0.015	34±11

the fraction of the intravascular pool catabolized per day was increased to 0.42 compared with the normal mean of 0.22 in the seven controls studied (Table IV). The serum IgA concentration was normal or slightly elevated in this patient, with an increased synthetic rate obscuring the short IgA survival.

The pattern of a reduced albumin and IgG concentration associated with a shortened survival of albumin, IgG, and IgA is comparable to that observed in patients with protein-losing enteropathy (15). Therefore, to determine whether excessive gastrointestinal protein loss was present in these patients, ^{51}Cr-labeled albumin clearance studies were performed on two occasions for patient W.J. and on one occasion for patient D.W. In each case, the ^{51}Cr-labeled albumin excreted in the 4 d after intravenous administration was normal, with 0.66 and 0.72% of the administered dose for patient W.J. and 0.33% for patient D.W., values within our normal range of 0–0.7% (12) (Table II). Patients with excessive gastrointestinal protein loss as the cause of the hypoproteinemia with comparable serum albumin and IgG concentrations excreted from 10% to 29% of the intravenously administered ^{51}Cr-labeled albumin dose within the 4-d collection period (T. A. Waldmann, unpublished observations). In accordance with these observations with ^{51}Cr-labeled albumin, both patients excreted < 0.3% of the radioiodinated albumin pool catabolized daily in the daily stool collections, a rate comparable to the proportion of the catabolized radioiodinated albumin excreted in the feces as radioiodine observed in nine control individuals (range 0.1–1.0%) and markedly lower than the mean value of 4.6% observed in 18 patients with protein-losing enteropathy due to intestinal disease (16). Thus, using radiolabeled albumin fecal excretion studies, we have eliminated excessive gastrointestinal protein loss as a possible cause of these patients' protein abnormality.

The patients' sera obtained during the period of radiolabeled protein turnover studies were assessed for the presence of autoantibodies to albumin, and IgM and IgA antibodies to IgG as well as for IgM or IgG antibodies to IgA using ELISA. Neither patient manifested autoantibodies to albumin or IgA. The serum of one of the patients (D.W.) did not contain measurable antibodies to IgG, whereas that of the other patient (W.J.) expressed equivocal anti-IgG antibodies of the IgA class in some but not all specimens. On the basis of these studies we have excluded autoantibodies to autologous serum proteins as the cause of the widespread serum protein hypercatabolism in these patients.

Discussion

In the present study, we report on two adult siblings who had marked reductions in their serum IgG and albumin concentrations that were due to an abnormally short survival of these serum proteins rather than a disorder in their rates of synthesis. This pattern can be easily distinguished from that of the most common genetic causes of hypogammaglobulinemia, in which a decreased rate of immunoglobulin synthesis is observed. Furthermore, in patients with a reduced IgG concentration due to decreased synthesis (hyposynthetic hypogammaglobulinemia) the survival of IgG is generally prolonged (fractional catabolic rate reduced). In such patients, the IgG survival $t_{1/2}$ usually ranges from 30 to 70 d owing to the concentration-catabolism effect, a physiological phenomenon affecting the metabolism of IgG in which there is a direct relationship between the serum IgG concentration and its fractional catabolic rate (1, 17, 18).

The pattern of protein metabolism observed in the present cases is much closer to that observed in patients with nephrotic syndrome or especially those with protein-losing enteropathy who develop hypogammaglobulinemia secondary to excessive loss of albumin and immunoglobulin (1, 2, 15). Both patients

Table IV. IgA Metabolism in Patient W.J.

Patient	Serum IgA	Plasma volume	Total circulating IgA	Total exchangeable IgA	IgA survival $t_{1/2}$	Fraction of circulating IgA catabolized per day	IgA synthetic rate
	mg/ml	*ml/kg*	*g/kg*	*g/kg*	*d*		*mg/kg per d*
W.J.	4.6	35.8	0.165	0.289	2.9	0.419	69
Normals (7)							
Mean	2.5	38.3	0.095	0.209	6.4	0.219	22
Range	0.2–5.0	32–44	0.008–0.190	0.020–0.400	5.4–8.2	0.180–0.245	2–44

with protein-losing enteropathy and the two cases in the present study have a reduced serum concentration predominantly affecting those proteins, albumin and IgG, that normally have the longest survival (4, 15). Furthermore, in both disorders, the reduced serum albumin and IgG concentrations reflect shortened survival of these proteins associated with near normal rates of synthesis. The rates of albumin synthesis are not meaningfully increased in these disorders, because the liver's capacity to increase albumin synthesis in response to a reduced concentration associated with a short survival is limited (10). The rates of immunoglobulin synthesis are usually relatively normal in these patients, because these rates are determined by the nature and magnitude of antigenic stimuli impinging on the host rather than on the serum immunoglobulin concentration. All patients with protein-losing enteropathy studied have an increased rate of excretion of radioactivity into the stool after the intravenous administration of ^{51}Cr-labeled albumin (12). In contrast, both of the patients in the present study had normal fecal ^{51}Cr-labeled albumin excretion tests, thus excluding excessive gastrointestinal protein loss. Furthermore, they had no weeping skin lesions or proteinuria, thus excluding external protein loss as the cause of their shortened protein survival.

The patients in the present study have a third major pathophysiological mechanism resulting in hypoalbuminemia and hypogammaglobulinemia, that is, a disorder in the endogenous catabolic pathways for these serum proteins. The pattern in these cases can be distinguished from one in which hypercatabolism is restricted to one class of proteins, since the patients have hypercatabolism of both albumin and immunoglobulins. Specifically, the pattern in these patients can be distinguished from the pattern observed in three other groups of patients: those with myotonic dystrophy, where there is a selective hypercatabolism of IgG (5), those with complex cryogels who have an abnormal IgM–IgG interaction leading to hypercatabolism of IgG (6), and those with selective IgA deficiency and an associated antibody to IgA, who have a short protein survival that is limited to this class (7).

An increased fractional catabolic rate affecting multiple serum proteins, including albumin and immunoglobulins, has been observed in a number of different disease states. These include hyperadrenal corticoidism (19), increased metabolic rates due to fever or hyperthyroidism (20), the Wiskott-Aldrich syndrome (8) or, in select cases, collagen vascular diseases (21). In these disorders, in contrast to the patients in the present study, the reduction in albumin and immunoglobulin survival and the increases in fractional catabolic rates of these proteins are modest. Furthermore, in contrast to the patients in the present study, there is an associated increase in the rate of immunoglobulin synthesis that leads to normal or increased immunoglobulin levels, thus masking the increases in the fractional rates of protein catabolism. The patients in the present study did not have abnormalities of thyroid or adrenal function nor did they have circulating antibodies to albumin, IgG, or IgA, thus excluding these known factors that cause modest decreases in immunoglobulin and albumin survival. Thus, the siblings in the present study appear to have a previously unrecognized familial disorder characterized by reduced levels of serum IgG and albumin due to a decreased survival of these proteins, associated in this family with a skeletal deformity.

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