Hypercatabolism of Normal IgG; an Unexplained Immunoglobulin Abnormality in the Connective Tissue Diseases

R. DEAN WOCHNER

From the Washington University Medical Service, St. Louis City Hospital, and the Department of Medicine, Washington University School of Medicine, St. Louis, Missouri 63104

ABSTRACT The metabolism of radioiodinated IgG was studied in a series of 42 patients with connective tissue diseases (16 systemic lupus erythematosus, nine rheumatoid arthritis, five polymyositis, five vasculitis, and seven miscellaneous diagnoses). Fractional catabolic rates were increased and survival half-lives were shortened in all diagnostic categories indicating hypercatabolism of IgG. This hypercatabolism was masked by increased IgG synthesis, resulting in elevated serum concentrations of IgG in patients with systemic lupus erythematosus and rheumatoid arthritis and in generally normal concentrations in the others.

The metabolism of iodinated IgM was also studied in eight patients with systemic lupus erythematosus, in seven with rheumatoid arthritis, and in 12 controls. The fractional catabolic rates were normal in both groups of patients. Serum concentrations of both IgM and IgA were moderately elevated in all diagnostic categories. Serum albumin metabolism was entirely normal in the nine subjects studied who were not receiving corticosteroids; in three who were receiving them, moderate hypercatabolism was observed.

The hypercatabolism of IgG could not be accounted for by factors previously known to alter IgG metabolism. It was not observed in 15 patients with other chronic, inflammatory diseases and was not explained by concomitant administration of adrenal corticosteroids to some patients. Identical results were obtained whether the IgG was obtained from a patient himself or from a normal donor, demonstrating that the hypercatabolism is a host defect and not an abnormality of the protein. Thus, patients with connective tissue disease of several different diagnostic categories have been shown to have an unexplained immunoglobulin abnormality; they catabolize normal IgG at an accelerated rate.

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INTRODUCTION

Both qualitative and quantitative alterations in the circulating immune globulins have long been recognized to be associated with the puzzling group of illnesses commonly referred to as the connective tissue diseases. Qualitative abnormalities include the many serologic ("autoimmune") reactions entered into by the immune globulins in these patients. Quantitative measurements usually show hypergammaglobulinemia, especially in systemic lupus erythematosus. However, there is relatively little information available concerning the overall metabolism of the immune globulins in such patients, and it is not known whether the serologic abnormalities lead to alterations in metabolism of the patient's own immune globulins that might not be seen with normal immune globulins. In previous studies of the metabolism of immune globulins in these disorders, the results have been somewhat conflicting. Some workers have observed accelerated breakdown of IgG (1–3) while others have not (4, 5).

The current study was undertaken to examine immunoglobulin metabolism, especially that of IgG, in patients with connective tissue disorders and to determine whether a patient's own IgG is more susceptible to catabolism than normal IgG. The results demonstrate an unexplained immunoglobulin abnormality in these patients; namely, they catabolize normal IgG at an accelerated rate, a finding which is not accounted for by any of the factors previously known to accelerate IgG catabolism.

METHODS

Patients

Serum immunoglobulin concentrations were determined in 56 patients, and metabolic turnover studies of IgG were performed in 42 patients with connective tissue disease. The patients are subdivided as follows:

(*a*) *Systemic lupus erythematosus.* Serum immunoglobulin concentrations were measured in the sera of 23 patients, IgG metabolism was studied in 16 patients, and IgM metabolism in eight. All patients had typical symptoms and laboratory manifestations of the disease. Six were hospitalized only for the study while each of the others had entered for an exacerbation of symptoms and were then studied after the clinical status had returned to its usual level. Patients who entered with fever were not studied until they had become afebrile. In four patients, multiple studies were performed at various times through the course of the illness.

(*b*) *Rheumatoid arthritis.* Serum immunoglobulin concentrations were determined in sera from 15 patients, IgG metabolism was studied in nine patients, and IgM metabolism in seven. Each of the patients in whom metabolic studies were done had typical, progressive, deforming polyarthritis with positive tests for rheumatic factor, except for one subject whose test for rheumatoid factor was negative. All but two had subcutaneous nodules at some time during their course.

(*c*) *Polymyositis.* Serum immunoglobulin concentrations were measured in six subjects and IgG metabolism in five. All exhibited weakness and atrophy of proximal muscles, four had had skin manifestations, and 3 had polyarthritis. Four patients had active disease at the time of study, and two had had the onset of their disease and its most active phase 8 and 10 yr before study and subsequently were left with significant but only slowly progressive weakness.

(*d*) *Vasculitis.* Five patients were studied in whom the primary feature of the disease was vasculitis. Since this group may be heterogeneous, each patient is summarized separately in the Appendix.

(*e*) *Miscellaneous.* Seven subjects with miscellaneous connective tissue disease were studied including three in whom a specific diagnosis could not be made. These patients are also summarized individually in the Appendix.

(*f*) *Control subjects.* Metabolic turnover studies of IgG were performed in 38 control subjects, of IgM in 12, and of albumin in 20. Of these, 26 were normal volunteers and the remainder were hospitalized patients with illnesses not affecting serum protein metabolism (epilepsy, iron deficiency, hypertension, arteriosclerotic heart disease, elderly patients awaiting placement in nursing homes, etc.). IgG metabolism was also measured in 15 additional patients who were designated as "disease controls" because of the presence of a chronic, inflammatory, often debilitating illness which was not due to a connective tissue disease. These included three subjects with chronic gouty arthritis, three with amyotrophic lateral sclerosis, four with muscular dystrophy, two with chronic bronchitis and obstructive emphysema, two with pulmonary abscesses, and one with chronic alcoholic neuropathy and multiple infections.

Immunoglobulin concentration

Serum immunoglobulin concentrations were determined by radial immunodiffusion (6) using Hyland Immunoplates (Hyland Laboratories, Los Angeles, Calif.) and dilutions of a reference standard kindly provided by Dr. John Fahey. Concentrations obtained in the patients by this method were compared to those in 50 control sera. Total serum proteins were measured by a biuret reaction and albumin was measured by paper electrophoresis.

Preparation of labeled proteins

Purified IgG was prepared by DEAE cellulose chromatography using fresh serum from both normal donors and from patients, as previously described (7). IgM was obtained by block electrophoresis followed by gel filtration, also as previously described (8). Albumin was either purified from fresh serum by block electrophoresis (9, 10) or was obtained commercially.[1] Each of the purified proteins was labeled with ioidne 131 (^{131}I) or iodine 125 (^{125}I) by the iodine monochloride technique of McFarlane (11). All preparations contained less than 1% nonprecipitable radioactivity in the final product, and each had an average of one atom iodine or less per molecule of protein, except the preparation of IgM which had an average of three atoms of iodine per molecule of protein. Human albumin (Cohn fraction V) was then added to each preparation to minimize damage from irradiation and storage, and the mixture was sterilized by filtration.

Many different preparations of labeled IgG and albumin were used for these studies; both controls and patients were studied with the same preparations. Each preparation was shown to have a normal turnover in at least one control subject; and during the period of time in which these studies were obtained, none of the IgG preparations were found to be damaged, i.e., none had an abnormal metabolism in a control subject. One albumin preparation was found to be damaged by this criterion and the results obtained with that preparation were excluded from this study. All of the subjects studied with IgM, including the controls, were injected with a single preparation of ^{125}I-labeled IgM.

Study protocol

All of the subjects were hospitalized during the study except six patients and four controls who were studied as outpatients. Serum immunoglobulin and albumin concentrations were measured at intervals through the period of study to verify that the patients were in a steady state. From 10 to 30 μCi of iodinated proteins were administered intravenously from a calibrated syringe; serum samples were obtained 10 min later and daily thereafter. All urine was collected in 24-hr lots. Thyroidal uptake of released isotope was prevented by the administration of five drops of saturated solution of potassium iodide three times daily during the study period. Serum and urine aliquots were counted to within less than $\pm 3\%$ counting error in an automatic well-type scintillation counter with a thallium-activated sodium iodide crystal. When both isotopes were studied simultaneously, they were differentiated with a pulse height analyzer.

Calculation of data

The metabolism of the iodinated proteins was analyzed according to the methods of Pearson, Veall, and Vetter (12), Berson, Yalow, Schreiber, and Post (13), and Matthews (14). The plots of the serum radioactivity and the total body radioactivity (radioactivity administered minus cumulative radioactivity excreted) were constructed on semilogarithmic graph paper, and the survival half-lives of the proteins were determined graphically. The following equations summarize the calculations:

[1] Behring Diagnostics, Inc., Woodbury, N. Y.

$$\text{plasma volume (ml/kg)} = \frac{\text{radioactivity administered}}{\text{(radioactivity/ml serum per 10 min)} \times \text{body weight (kg)}} \quad (1)$$

$$\text{total circulating protein} = \text{(plasma volume)} \times \text{(plasma concentration of protein)} \quad (2)$$

fraction of circulating protein catabolized per day (fractional catabolic rate)

$$= \frac{\text{radioactivity excreted in 24 hr}}{\text{(plasma volume)} \times \text{(circulating radioactivity per milliliter at beginning of that day)}} \quad (3)$$

This fraction was determined for each day and the mean of values from days 4 to 14 was used in the following equation:

$$\text{catabolic rate of the protein (mg/kg per day)} = \text{fractional catabolic rate (\%/day)} \times \text{total circulating protein (mg/kg)} \quad (4)$$

Since the serum concentrations of the proteins studied were shown to be constant during the period of study, each of the subjects was presumed to be studied under steady-state conditions, in which the rates of synthesis and catabolism are equivalent. Therefore, the observed value for the catabolic rate was also taken to be that for the synthetic rate of the protein; this value is also referred to as the turnover rate.

In a few instances, the urine collections were judged to be incomplete by determination of 24 hr creatinine excretion in each specimen, and the fractional catabolic rate used in the above equation was calculated instead by the method of Matthews (14), using the serum curve alone.

If significant proteinuria were to occur unnoticed, the urinary excretion of intact radioactive protein could be mistaken for excretion of radioactive iodide and so could result in falsely high estimates of catabolism. Therefore, the urine specimens on each subject were examined for protein-bound radioactivity. After the addition of about 100 mg of albumin as carrier protein, aliquots of urine were precipitated with 10% trichloroacetic acid, and the precipitable radioactivity (if any) was compared to the total radioactivity. In only one case was significant excretion of intact IgG encountered; in this subject, 5% of the overall catabolism of IgG was accounted for by proteinuria, and the calculations were adjusted by this factor.

The significance of the difference between sample means was evaluated by the t test, with the aid of an Olivetti Underwood Programma 101 computer, according to the following formula:

$$t = (\bar{X}_1 - \bar{X}_2) \Big/ \left(s\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}\right),$$

where s^2 is the pooled variance.

RESULTS

The immunoglobulin concentrations in sera of 23 patients with systemic lupus erythematosus, 15 patients with rheumatoid arthritis, six patients with polymyositis, and five with vasculitis, are depicted in Fig. 1. The IgG concentrations were generally increased in systemic lupus, averaging 24.5 mg/ml, compared to 12.1 ±2.6 mg/ml in normals. IgG concentrations were also increased in rheumatoid arthritis (average 16.9 mg/ml) and were normal in the other groups. IgM concentrations were normal or moderately increased in each category, averaging 1.85 mg/ml in systemic lupus and 2.38 mg/ml in rheumatoid arthritis, compared to 1.45 ±0.6 in normals. IgA concentrations were commonly increased in each group averaging 6.86 mg/ml in systemic lupus and 6.10 mg/ml in rheumatoid arthritis, compared to 2.6 ±1.1 mg/ml in controls. The highest values for all three proteins were observed in patients with systemic lupus.

Metabolic studies were carried out using radioiodinated IgG, IgM, and albumin. Fig. 2 depicts the results of such studies in a single illustrative patient. This patient had systemic lupus erythematosus, manifested by arthritis, rash, and typical laboratory abnormalities. She was afebrile during these studies and was being treated only with analgesic agents except during the IgM study when she received corticosteroids as well. Fig. 2 illustrates that the breakdown of IgG in this patient was greatly accelerated while the studies of albumin and IgM were normal. There was no significant abnormality in the pattern of distribution for any of the three proteins. In spite of the greater than two-fold increase in her IgG fractional catabolic rate, her serum IgG concentration remained elevated; this was because her rate of IgG synthesis was elevated to five times the mean of normals.

The findings illustrated by this patient were observed throughout the entire series of patients with connective tissue diseases. A striking acceleration of IgG catabolism was seen with no significant differences observed among the different diagnostic categories (Fig. 3, Table I). The fractional catabolic rates averaged 11.5%/day in the entire series compared to the mean ±1 SD of 6.76 ±1.24%/day in 38 normals. The fractional catabolic rates were greater than 2 SD above the normal mean in 11 of 16 patients with systemic lupus erythematosus, eight of nine with rheumatoid arthritis, four of five with polymyositis, all of five with vasculitis, and six of seven in the miscellaneous group. Survival half-lives of the IgG were shortened in each group averaging 14.2 days in the entire series compared with an average of 22.7 days in controls. Since serial IgG concentrations confirmed that each of the patients was in a steady state of IgG metabolism, the observed catabolic rates (mass of IgG catabolized daily) can be assumed to be equivalent to the IgG synthetic rates. As seen in Fig. 4, the synthetic rates were markedly elevated in patients with

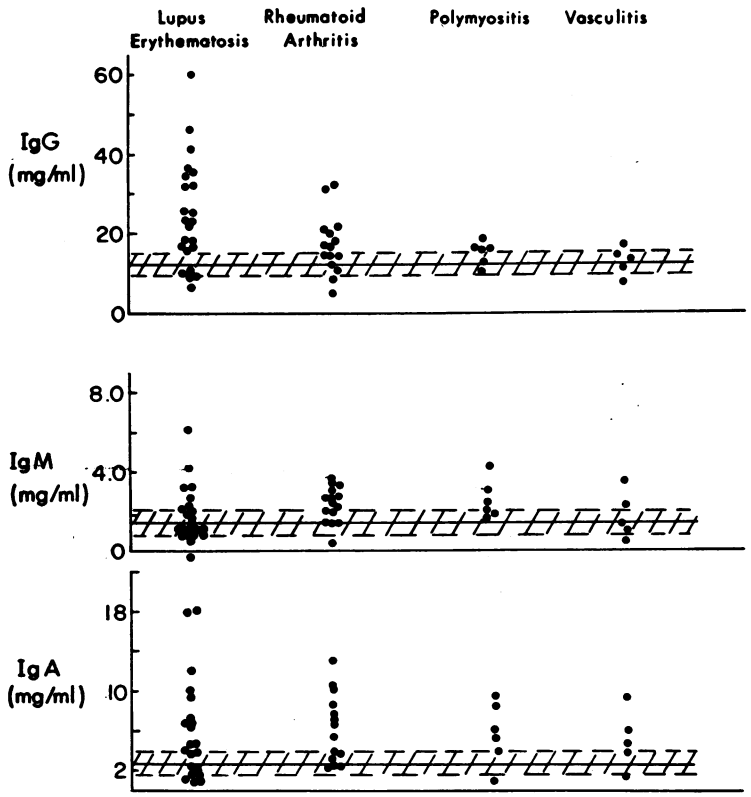

FIGURE 1 Serum concentrations of the major immune globulins in connective tissue diseases. The cross-hatched areas represent ±1 SD about the mean of 50 normal subjects.

systemic lupus averaging 114 mg/kg per day, and moderately elevated in the other categories averaging 78 mg/kg per day in rheumatoid arthritis, 57 mg/kg per day in polymyositis, 62 mg/kg per day in vasculitis, and 87 mg/kg per day in the miscellaneous group (normals 31 ±11 mg/kg per day). In the 15 "disease controls" (selected because of the presence of chronic inflammatory and/or debilitating disease) no hypercatabolism of IgG was observed (Table I). Their fractional catabolic rates averaged 7.07%/day while their synthetic rates were normal to moderately elevated.

The metabolic studies of IgM in eight patients with systemic lupus and seven with rheumatoid arthritis are summarized in Fig. 5 and Table II. The total circulating pools of IgM were normal or moderately elevated in both groups. The fractional catabolic rates were normal in both groups, with the exception of a single value of 25%/day in one patient with rheumatoid arthritis. They averaged 15.2%/day in the patients with systemic lupus, and 14.7%/day in those with rheumatoid arthritis, compared to 15.1 ±2.9%/day in the 12 control subjects. The survival half-lives for IgM averaged 8.5 days in patients with systemic lupus, and 8.1 days in those with rheumatoid arthritis, compared to 8.8 ±1.7 days in the controls. The IgM synthetic rates were slightly increased in both groups, but the increase was not statistically significant in either group.

Albumin metabolism was studied in 12 patients; 10 of the 12 had been shown to have abnormally elevated IgG fractional catabolic rates (more than 2 SD above the mean of normals). Three were receiving corticosteroids at the time of study and nine were not. In the latter group (four with rheumatoid arthritis, three with systemic lupus erythematosus, one with vasculitis, and one with chronic discoid lupus erythematosus), the metabolism of albumin was entirely normal (Table III). The patients receiving corticosteroids (two with systemic lupus erythematosus and one with polymyositis) demonstrated moderate hypoalbuminemia, increased fractional catabolic rates, and shortened half-lives for albumin, with normal rates of synthesis.

Autologous IgG was prepared from the serums of 16 patients and the metabolism compared to that of IgG derived from normal serum. No differences in metabolism were found between the two sets of IgG when these preparations were studied simultaneously in either the patients or in control subjects.

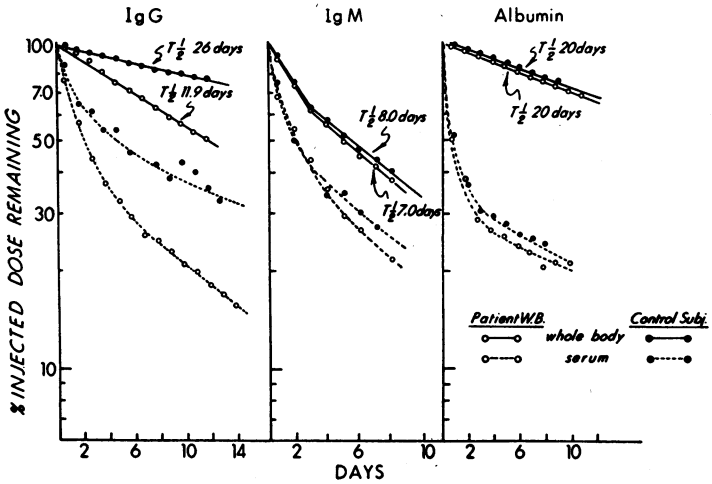

FIGURE 2 Metabolic studies of iodinated IgG, IgM, and albumin in a single illustrative patient with systemic lupus erythematosus. The patient and the controls received the same preparations of iodinated proteins. The patient catabolized IgG at an accelerated rate, while the IgM and albumin studies were normal.

12 of the 42 patients were receiving therapeutic doses of corticosteroids during their study and 23 were not receiving them at all. There was no significant difference seen in IgG fractional catabolic rates between these two groups. Three patients were studied both before and during the first 2 wk of steroid therapy; in two the fractional catabolic rate rose, and in one no significant change was seen. There was some tendency for patients with the most active disease to have the highest fractional catabolic rates. In addition, multiple IgG turnover studies were done at various times through the course of the illness in four patients with systemic lupus, and the height of the fractional catabolic rates roughly paralleled the degree of clinical activity at the time of study. However, it was also noted that a number of nearly asymptomatic patients had markedly elevated fractional catabolic rates and that three of the four patients whose fractional catabolic rates were within 1 SD of the mean of normals had active, advancing disease at the time of study.

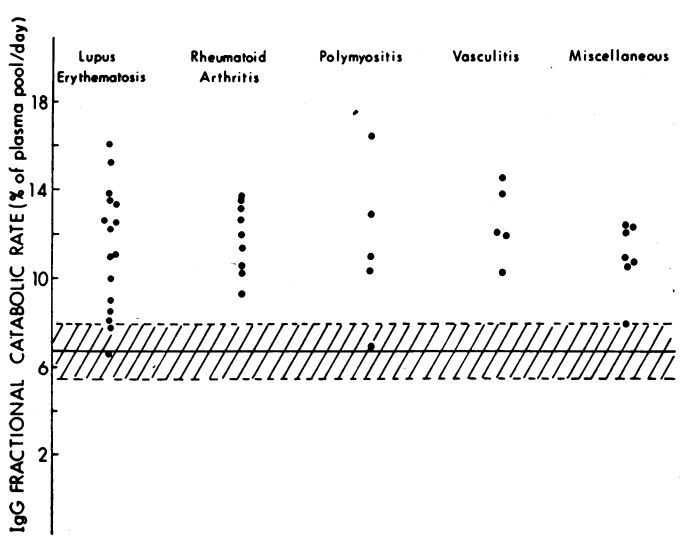

FIGURE 3 Fractional catabolic rates of IgG in patients with connective tissue diseases. The cross-hatched area represents the mean ±1 SD (6.76 ±1.24%/day) for 38 control subjects.

An unsuccessful search was made for serum factors that might react with IgG and render it susceptible to hypercatabolism. First, only 18 of the 42 patients had positive tests for rheumatoid factor, and there was no correlation between its titer and the fractional catabolic rate. Second, serums from eight patients (including two with rheumatoid factor activity) were incubated with IgG-^{125}I and passed over columns of Sephadex G 200 to determine whether the labeled-IgG was accelerated in its passage through the gel, indicating possible interaction with other proteins and formation of complexes of higher molecular weight. However, such a phenomenon could not be demonstrated. Third, IgG-^{125}I was incubated at 37°C for 3–6 hr in 5 ml of sterile serum freshly obtained from four of the patients with systemic lupus erythematosus. These mixtures were then injected into control patients, simultaneously with IgG-^{131}I that had not been so treated, and the metabolism of the two preparations of IgG were compared. No differences in fractional catabolic rates were observed, and no rapidly catabolized fraction was found in the incubated preparations. Finally, analytical ultracentrifugation was performed on serums from seven patients and failed to demonstrate complexes of either intermediate (7–19S) or high molecular weight (greater than 19S), except in two subjects with cryoproteins.

DISCUSSION

The normal metabolism of IgG is better defined than that of any other immune globulin, owing to its relative ease of purification. Normally, it has the longest survival half-life (average 23 days) of any of the serum proteins that have been studied; this is a major

TABLE I

*IgG Metabolism in Patients with Connective Tissue Disease and in Controls**

Patients and diagnosis	Serum IgG concentration	Plasma volume	Total circulating IgG	Intravascular	Survival $t_{1/2}$ (whole body)	Fractional catabolic rate	Turnover rate
	mg/ml	*ml/kg*	*mg/kg*	*%*	*days*	*% plasma pool/day*	*mg/kg per day*
Controls (38)							
Mean	11.0	41.2	455	47.3	22.7	6.76	30.5
±SD	±2.7	±6.0	±124	±5.8	±4.2	±1.24	±10.8
Disease controls (15)							
Mean	13.1	41.9	570	45.2	23.6	7.07	40.5
±SD	±5.6	±6.1	±293	±6.3	±3.7	±1.38	±21.5
	$P < 0.05$						$P < 0.05$
Systemic lupus erythematosus (16)							
Mean	22.8	40.9	975	44.1	14.7	11.3	114
±SD	±11.2	±9.1	±695	±7.2	±3.3	±2.8	±93
	$P < 0.01$		$P < 0.01$		$P < 0.001$	$P < 0.001$	$P < 0.001$
Rheumatoid arthritis (9)							
Mean	17.6	39.2	664	48.1	13.8	11.8	78
±SD	±6.7	±9.8	±234	±3.5	±1.7	±1.6	±28
	$P < 0.01$		$P < 0.01$		$P < 0.001$	$P < 0.001$	$P < 0.001$
Polymyositis (5)							
Mean	14.7	36.4	502	42.4	15.0	11.5	57
±SD	±2.9	±7.7	±111	±2.1	±4.0	±3.5	±20
	$P < 0.05$				$P < 0.001$	$P < 0.001$	$P < 0.01$
Vasculitis (5)							
Mean	12.2	39.1	482	43.8	13.5	12.5	62
±SD	±3.2	±8.8	±165	±7.1	±1.6	±1.6	±26
					$P < 0.001$	$P < 0.001$	$P < 0.01$
Miscellaneous (7)							
Mean	20.3	37.8	781	48.9	14.2	10.9	87
±SD	±11.6	±5.0	±481	±5.1	±2.4	±1.5	±54
	$P < 0.05$		$P < 0.05$		$P < 0.001$	$P < 0.001$	$P < 0.01$

* Only P values showing significant differences ($P < 0.05$) from controls listed.

factor in its relatively high serum concentration. Previous work indicates that IgG catabolism occurs in a compartment in rapid equilibrium with the intravascular space (15, 16). Thus, the most meaningful and reproducible measure of catabolism is the fractional catabolic rate, expressed as the percent of the plasma pool of protein catabolized per day; it is this measure of catabolism that is used in this report. It is important to keep in mind the difference between the fractional catabolic rate and the turnover rate. The latter is the product of the fractional catabolic rate and the total circulating pool of the protein, and measures the mass of protein catabolized per day. This value is expressed here in milligrams per kilogram body weight per day; in the steady state, it measures both the catabolic rate and the synthetic rate for the protein.

In the current study, a striking increase in IgG fractional catabolic rates has been observed in patients with systemic lupus erythematosus, rheumatoid arthritis, polymyositis, vasculitis, and a miscellany of other connective tissue disorders. This accelerated breakdown of IgG was compensated for and masked by increases in IgG synthetic rates. The resultant serum IgG concentrations were elevated in patients with systemic lupus erythematosus and rheumatoid arthritis and generally normal in the other categories.

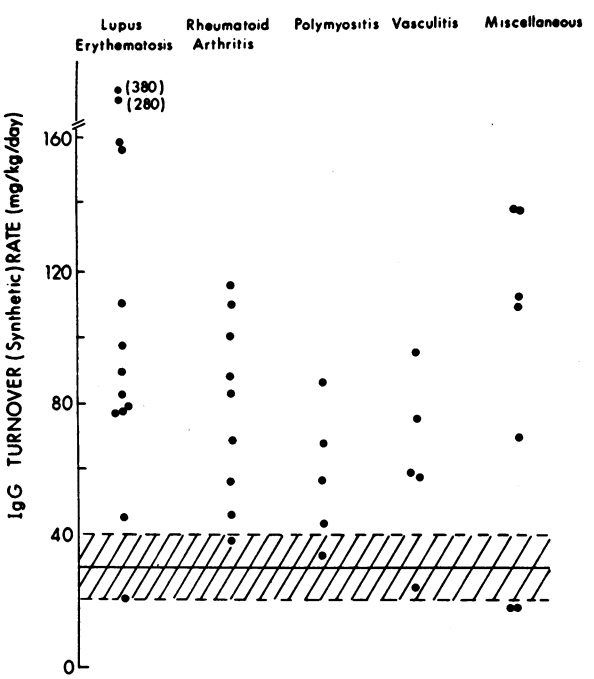

FIGURE 4 Rates of IgG turnover in patients with connective tissue diseases. The cross-hatched area represents the mean ±1 SD (30.5 ±10.8 mg/kg per day) for 38 control subjects.

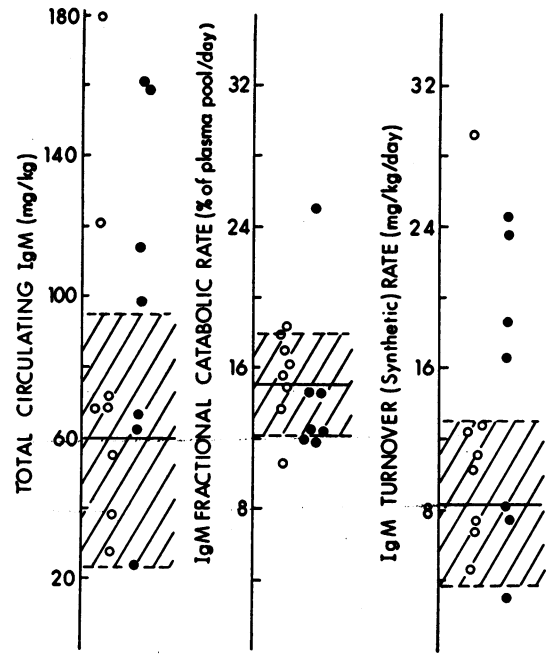

FIGURE 5 IgM metabolism in patients with systemic lupus erythematosus (○) and rheumatoid arthritis (●). The cross-hatched areas represent the mean ±1 SD of values obtained in 12 control subjects.

In contrast to these abnormal findings for IgG metabolism, the IgM fractional catabolic rates were normal in all of the eight patients studied with systemic lupus, and in six of the seven with rheumatoid arthritis. The IgM synthetic rates varied from normal to moderately increased in both groups. These observations fail to provide for the recent report that IgM survival is shortened in rheumatoid arthritis (3). Instead, they support another recent study in which autologous IgM was found to be metabolized normally in patients with rheumatoid arthritis (17).

The observed acceleration in IgG breakdown is not explained by any of the factors previously known to alter IgG catabolism. There was no loss of protein into the urine, and no evidence of loss into the gastrointestinal tract. Such bulk loss phenomenon should have affected albumin and IgM as well as IgG; such was not the case. Hypercatabolism of the IgG fraction alone has been observed previously in patients with myotonic dystrophy (7), and patients with the nephrotic syndrome (18), but neither of these phenomena explain the findings in the current series of patients. The IgG fractional catabolic rate may also be increased in patients with marked elevations in serum IgG, such as that seen in IgG myeloma (19, 20) or that induced in animals by infusion of IgG (21). However, no correlation was found between the serum IgG concentrations

TABLE II

IgM Metabolism in Patients with Connective Tissue Diseases and in Controls

Patients and diagnosis	Serum IgM concentration	Plasma volume	Total circulating IgM	Intravascular	Survival $t_{1/2}$ (whole body)	Fractional catabolic rate	Turnover rate
	mg/ml	*ml/kg*	*mg/kg*	*%*	*days*	*% plasma pool/day*	*mg/kg per day*
Controls (12)							
Mean	1.33	43.3	58.8	58.4	8.80	15.1	8.39
±SD	±0.73	±7.1	±36.0	±5.6	±1.65	±2.85	±2.67
Systemic lupus erythematosus (8)							
Mean	2.17	40.0	78.8	55.7	8.53	15.2	11.9
±SD	±1.71	±14.1	±49.5	±11.3	±2.81	±2.5	±7.6
Rheumatoid arthritis (7)							
Mean	2.40	40.8	97.2	63.7	8.07	14.7	14.5
±SD	±1.04	±9.0	±51.5	±10.3	±2.26	±4.7	±8.4

and fractional catabolic rates in either the entire group of patients (Fig. 6) or when the individual diagnostic categories were plotted separately. Indeed, many of the subjects with elevated IgG fractional catabolic rates had normal serum IgG concentrations; 23 of the 42 patients had serum IgG concentrations that were within 2 SD of the mean of normals. Nor could the hypercatabolism be explained by the presence of a chronic inflammatory disease or by corticosteroid therapy. Although administration of corticosteroids is known to induce hypercatabolism of albumin (22–24), a phenomenon observed again in this series, it did not explain the observed hypercatabolism of IgG; there was no difference between the IgG fractional catabolic rates of patients receiving therapeutic doses of corticosteroids and those not receiving them at all.

It should be emphasized that identical findings were observed whether the labeled IgG was derived from normal donors or from the patients themselves. Therefore, the abnormality observed is a host defect in the patients, and not a result of an abnormal IgG protein made by the patient. Thus, the IgG is not being catabolized rapidly because it is an antibody; however, this does not exclude the possibility that IgG is for these patients playing the role of the antigen. Indeed, such a postulated reaction between IgG and an "antiglobulin" factor would

TABLE III

Albumin Metabolism in Patients with Connective Tissue Diseases and in Controls

Patients	Serum albumin concentration	Plasma volume	Total circulating albumin	Intravascular	Survival $t_{1/2}$ (whole body)	Fractional catabolic rate	Turnover rate
	mg/100 ml	*ml/kg*	*mg/kg*	*%*	*days*	*% plasma pool/day*	*mg/kg per day*
Controls (20)							
Mean	3.89	37.5	1.55	37.5	18.4	10.2	0.168
±SD	±0.42	±5.6	±0.37	±5.6	±3.5	±2.1	±0.041
Connective tissue diseases not receiving corticosteroids (9)							
Mean	3.60	43.4	1.54	37.4	18.0	10.4	0.159
±SD	±0.40	±8.3	±0.23	±5.0	±1.8	±1.0	±0.025
Receiving corticosteroids (3)							
Mean	3.00	41.6	1.19	31.0	14.3	14.7	0.174
±SD	±0.66	±8.1	±0.05	±5.6	±2.2	±1.0	±0.005

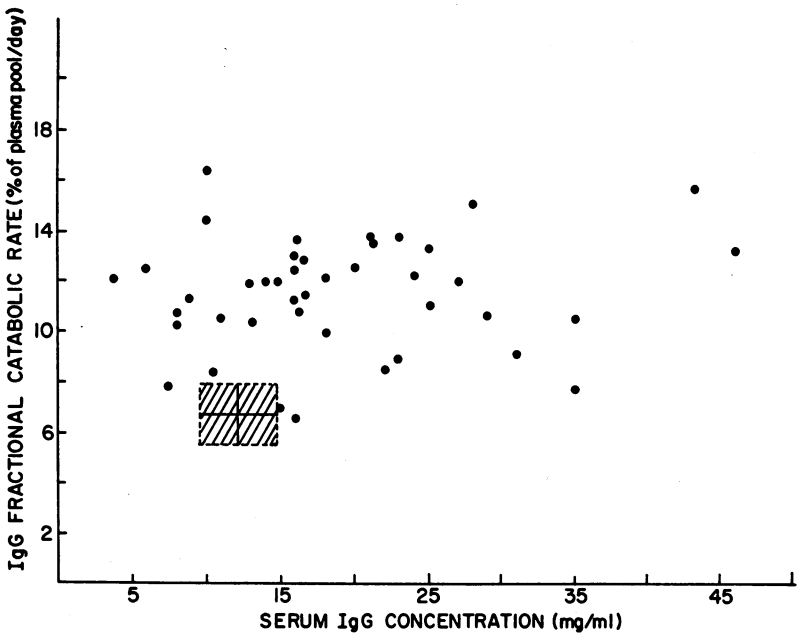

FIGURE 6 Relationship of IgG fractional catabolic rate to serum IgG concentration in connective tissue diseases. The fractional catabolic rate for each of the 42 patients is plotted against his serum concentration. No correlation is seen between the two parameters.

be an attractive hypothesis to explain the pathogenesis of vasculitis and other pathologic lesions seen in these patients. A great deal of evidence has been accumulated to suggest that circulating immune complexes may play an important role in the pathogenesis of these illnesses (25–27). However, the nature of the suspected antigens is largely unknown. Attempts to identify possible antigens have centered about a variety of drugs, especially in patients with vasculitis (28–30); DNA in lupus nephritis (31–33), and IgG especially in rheumatoid arthritis and in illnesses accompanied by "mixed" (IgM and IgG) cryoproteins (34–39). If IgG were playing such a role in these patients, either in its native, unaltered state or altered so as to react with rheumatoid factor, it would provide a mechanism whereby large quantities of potential antigen would be available to produce tissue damage. However, our efforts to demonstrate immune complexes in these patients have been unsuccessful so far.

Thus, the nature of the phenomenon leading to hypercatabolism of IgG in these patients remains unknown. It is not known whether the process is an acceleration of normal IgG catabolism or the addition of a new process since the normal mechanism of IgG catabolism remains undefined. Whatever the mechanism may be, hypercatabolism of IgG occurs in a broad spectrum of connective tissue disease categories implying an important relationship to the fundamental disease process.

APPENDIX

The summaries of individual patients in whom the primary feature of the disease was vasculitis are as follows:

1) J. W. was a 37 yr old woman with a history of chronic mild polyarthralgia, who suddenly developed fever, weakness, arthritis, and dependent purpuric lesions which showed vasculitis histologically. Tests for cryoproteins, antinuclear factor, rheumatoid factor, and lupus erythematosus (LE) cells were negative. The lesions subsided without specific therapy.

2) H. H. was a 60 yr old man with a previous history of mild polyarthralgia developed fever, prostration and acute, necrotizing, purpuric lesions of both legs which showed vasculitis by biopsy. He was treated with adrenocortical steroids and his symptoms gradually subsided.

3) D. K. was a 76 yr old man with a history of alcoholism being treated at a psychiatric hospital for depression and mental deterioration. He developed a dependent, purpuric rash, which had the gross and histologic features of vasculitis. All routine laboratory studies were negative. The eruption gradually cleared after all previous medications were stopped.

4) J. M. was a 56 yr old man who developed a generalized eruption, most marked in the dependent areas. He was otherwise asymptomatic. Histology of the skin showed vasculitis and some liquefaction degeneration of the basal layer. Laboratory studies showed cryoglobulins, positive tests for rheumatoid and antinuclear factors, and negative LE preparations. After study of his IgG and IgM metabolism, he was treated with adrenocortical steroids with improvement in his skin lesions.

5) P. G. was a 28 yr old woman who had chronic polyarthralgia, mild weakness of proximal muscles, and an intermittent purpuric rash which demonstrated vasculitis histo-

logically. All laboratory work was negative. Several months after the study of her IgG metabolism, she also developed abdominal pain and bloody diarrhea. No additional diagnoses could be made at that time.

The summaries of patients with miscellaneous connective tissue diseases are listed below. In the last three, no specific diagnosis could be made.

1) A. D. was a 33 yr old woman with typical features of scleroderma of 2 yr duration.

2) E. A. was a 74 yr old woman with Coombs positive hemolytic anemia of 2 yr duration, without other clinical or laboratory features of connective tissue disease, except for a palpable spleen and a positive antinuclear factor.

3) A. C. was a 26 yr old man with chronic discoid lupus erythematosus and alcoholism. There were no symptoms of systemic involvement and no abnormal laboratory findings except a positive test for antinuclear factor.

4) J. S. was a 28 yr old man with extensive chronic discoid lupus erythematosus. There were no symptoms of systemic activity and no laboratory abnormalities except a weakly reactive test for rheumatoid factor.

5) J. F. was a 61 yr old woman with 9 year history of Raynaud's phenomenon associated with ulceration of both fingers and feet, hypergammaglobulinemia, false positive serologic test for syphilis, positive antinuclear factor, trace quantities of cryoproteins, and negative LE preparations.

6) M. C. was an 18 yr old man with asymptomatic proteinuria, hematuria, and hypertension. Renal biopsy showed a severe focal glomerulonephritis with wire-loop formation, many adhesions, some fibrinoid necrosis of the glomerular tufts, and some glomerular hyalinization. There were no other clinical abnormalities and tests for antinuclear factor and LE cells were negative, as were all other laboratory studies.

7) W. K. was a 37 yr old man developed sore throat, fever, profound weakness (especially of proximal muscles), polyarthralgia, and pleuritic chest pain over a 2 wk period. Laboratory data included hematocrit 27%, blood urea nitrogen (BUN) 44, antistreptolysin titer (ASO) 1250 U, and negative tests for rheumatoid and antinuclear factors, negative LE preparations, and normal biopsies of liver, muscle, and skin. His symptoms all improved greatly on bedrest and salicylates and he was not given steroids.

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