

Altered Immunoglobulin Metabolism in Systemic Lupus Erythematosus and Rheumatoid Arthritis

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ABSTRACT IgG and IgM metabolism was evaluated in 10 patients with systemic lupus erythematosus (SLE), 10 patients with rheumatoid arthritis (RA), and in seven normal volunteers. The biological half-lives of purified IgG and IgM, labeled with ^{131}I and ^{125}I , respectively, were determined by serial measurements of radioactivity in the blood and urine with a gamma well counter, and by serial counts of total body radioactivity in a total body counting chamber.

The mean survival half-life for IgG in patients with SLE was 8.2 days as compared to an average of 18 days in normal controls. An average of 10.1% of total body IgG was catabolized daily compared to a mean of 3.9% in normal controls. Turnover of IgM in patients with SLE was, with very few exceptions, normal. In contrast, patients with rheumatoid arthritis revealed a milder abnormality of IgG metabolism, but markedly abnormal IgM catabolism with a mean half-life averaging 5.9 days as compared to 9.3 days in control subjects. An average of 14.2% of total body IgM was catabolized daily in patients with RA as compared to 8.1% in normal controls.

Our data suggest that there are basic differences between patients with RA and SLE in the synthesis and catabolism of IgG and IgM not readily apparent from serum IgG and IgM concentration. Abnormal IgG and IgM metabolism may be related to underlying immunological mechanisms in these diseases. Immunoglobulin turnover studies appear to be an additional means for the characterization of rheumatic diseases.

INTRODUCTION

Alterations in the type and quantity of serum immunoglobulins in rheumatic diseases have been well appreciated (1-6). The participation of these globulins in the formation of immune complexes has given them a pos-

sible pathogenetic role in diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) (1, 2). Gammaglobulin serum concentrations appear to have little diagnostic or prognostic significance in any single patient and do not differ significantly in these two diseases. Studies in patients with SLE (3) and RA (4-6) suggest that there is a significant mean increase of serum IgG levels in both these disorders. Elevations in serum IgG levels, however, are not uniform and many values fall within the normal range. Elevation of serum IgM levels even in patients with high titers of rheumatoid factor were found to be inconstant (5).

Serum immunoglobulin concentration is a static determination and gives only a partial understanding of the dynamic nature of these proteins. Turnover studies, utilizing radioiodinated globulins, measure their catabolism and indirectly their synthesis and thus more closely reflect the activity of these proteins in disease. IgG catabolism has been found to be markedly prolonged in congenital and acquired hypogammaglobulinemia (7) and accelerated in myotonic dystrophy (8) and in hypergammaglobulinemic states such as hyperimmunization, chronic infection, and multiple myeloma (9-11). Relatively few gammaglobulin turnover studies have been reported in rheumatic diseases and these have described primarily IgG metabolism. Studies in RA and SLE have revealed frequent acceleration of IgG catabolism. Vaughan, Armato, Goldthwait, Brachman, Favour, and Bayles (12) have reported a shorter survival of an ^{131}I -labeled gammaglobulin in four patients with RA than in four normal controls. Their globulin preparation, however, showed a half-life in normals of 6 days suggesting marked denaturation. The authors concluded that patients with RA may possess enhanced immunologic or other mechanisms for removal of aggregated or precipitated proteins from the circulation. Mills, Calkins, and Cohen (13)

Received for publication 28 July 1969.

found an increased IgG catabolic rate in one of four patients studied with RA. Accelerated IgG synthetic and catabolic rates in patients with RA and SLE despite normal serum IgG concentration, have also been noted by Olhagen, Birke, Plantin, and Ahlinder (14) and by Andersen and Jensen (15). A recent report by Wochner (16) has described accelerated IgG fractional catabolic rates in 6 of 11 patients with SLE. In the present study synthetic and catabolic rates for both IgG and IgM are evaluated in patients with RA and SLE.

METHODS

Subjects. Immunoglobulin turnover studies were performed in 10 patients with RA, 10 with SLE, and 7 normal controls. Normal controls were healthy volunteers with normal serum immunoglobulins and negative tests for rheumatoid factor and antinuclear antibodies. All patients with RA had positive tests for rheumatoid factor and had either classical or definite RA according to ARA criteria. 3 of the 10, in addition, demonstrated positive antinuclear antibodies. Patients with SLE were judged to have active disease by clinical, serologic, and histologic criteria. 8 of the 10 patients with SLE had active renal disease. All patients with SLE, with the exception of B. V. and D. J., demonstrated positive antinuclear antibodies at time of study. One patient (F. E.) displayed a low titer positive rheumatoid factor. Treatment programs varied and included salicylates, indomethacin, and corticosteroids. Drug therapy was not interrupted during the course of study. Patients on immunosuppressive therapy with azathioprine, 6-mercaptopurine, amethopterin, or cyclophosphamide were not included in this series.

Preparation of IgM and IgG fractions for turnover studies. Pure IgM was separated from the serum of a patient with Waldenström's macroglobulinemia by ammonium sulfate precipitation followed by DEAE-cellulose chromatography and gel filtration on Sephadex G-200 and Separose 4B. The IgM fraction was determined to be homogeneous and to lack any 7S components by ultracentrifuge analysis. In addition, immunochemical techniques of Ouchterlony gel diffusion and immunoelectrophoresis revealed single precipitin lines with no contaminating proteins. The IgM preparation was found to lack any rheumatoid factor serologic activity by latex fixation (17) and sensitized sheep cell (18) tests.

Purified IgG was obtained from Merck, Sharp & Dohme as Gamma Gee, lot No. 0973J. The preparation was found by radial immunodiffusion (19) to contain greater than 99% IgG and with DEAE-cellulose column chromatography, greater than 97% of the protein fraction was eluted in a single homogenous peak with a 0.01 M phosphate buffer of pH 8.0. The preparation was found to lack antinuclear antibody activity as determined by an immunofluorescent technique using human leukocytes as a substrate (20).

The IgG and IgM preparations were labeled with ^{125}I and ^{131}I respectively, by the iodine monochloride method of McFarlane (21). The labeled fractions were calculated to have 1-2 moles of iodine per molecule of protein. Free ^{125}I and ^{131}I were removed by passage through an anion exchange column (Bio-Rad AG 1-x4) so that greater than 97% of the product's radioactivity was precipitable. 70 mg of sterile human albumin was added per ml to prevent damage due to self radiation and the preparation was sterilized by passage through a 0.22 μ Millipore filter.

After radioiodine labeling lack of denaturation of the labeled protein was demonstrated by adding trace amounts of ^{131}I -labeled IgG to an excess of fresh normal serum and chromatographing the mixture on DEAE-cellulose with a constant phosphate gradient (22). Radioiodine elution was identical with and limited to the first effluent peak representing native IgG.

Study protocol. Patients received 10 drops of Lugol's solution twice daily for 3 days before and during the entire study period to prevent thyroidal uptake of released radioiodine. Approximately 10 μCi of each labeled immunoglobulin was injected intravenously and the biological half-lives were calculated over a 21 day period by 8-10 serial determinations of radioactivity in the blood and urine in a gamma well counter, Nuclear Chicago, model No. 42-33 and by serial counts of total body radioactivity for ^{131}I by use of a total body counting chamber.

The total body counter consists of four uncollimated NaI scintillation detectors each 5 \times 4 inches in diameter, arranged in pairs above and below a cot upon which the subject rests in the supine position. The cot is placed in the center of a room having walls, ceiling, floor, and doors all of 6 inch steel with a $\frac{1}{8}$ inch thick inner lining of lead.

Plasma volumes were calculated by evaluation of 10-min IgM- ^{125}I samples. Patients with proteinuria were studied with quantitative immunoglobulin determinations on their urine and those patients found to have significant amounts of IgG or IgM had urine analyzed for protein-bound radioactivity. In no patients was significant urinary protein-bound radioactivity found.

Serial immunoglobulin concentrations were determined using the radial immunodiffusion assay (19) to establish the steady state in all our patients. Rheumatoid factor was evaluated and titers quantitated by tube dilution techniques using both latex particles coated with human gammaglobulin (17) and sensitized sheep cells coated with rabbit gammaglobulin (18). All patients were studied for antinuclear antibodies by the method of immunofluorescent staining of human leukocytes (20).

Analysis of data. IgG serum and total body radioactivity were plotted on semilogarithmic paper against time and their biological half-lives were determined graphically.

Fractional catabolic rate defined as the fraction of total body IgG catabolized per day was derived from the equation for exponential decay. Fractional catabolic rate (%) = $\text{Ln}2/t_{\frac{1}{2}}$ (half-life) = 0.693/ $t_{\frac{1}{2}}$.

Absolute synthetic rate was defined as the daily quantity of IgG catabolized, expressed as milligrams per kilogram per day. In the steady state, this rate also describes the daily quantity of IgG synthesized. Absolute synthetic rate was derived from the total body fractional catabolic rate according to the method of Berson, Yalow, Schreiber, and Post (23), and the method of Sterling (24). Absolute synthetic rate (mg/kg/day) = total body globulin pool (mg) \times fractional catabolic rate (%/day)/body weight (kg). Total body globulin pool (g) = plasma volume \times serum immunoglobulin concentration \times 100/per cent of total body globulin pool that is intravascular. Plasma volume (ml) = radioactivity administered/activity per ml of plasma at zero time (10-min samples). Per cent of body pool intravascular was computed by the graphic extrapolation method of Sterling, per cent intravascular = 100 \times extrapolation to zero time of the linear portion of the plasma radioactivity curve/activity administered, and by modification of the method of Berson et al., utilizing total body radioactivity, both by direct measurement of total body counts and by subtraction of cumulative urinary

radioiodine excretion. Per cent intravascular = $100 \times$ the total plasma radioactivity/radioactivity retained in body. Calculations by both these methods yielded comparable results.

IgG absolute synthetic rate was also calculated according to the U/P method of Pearson, Veall, and Vetter (25) by deriving the fraction of intravascular IgG catabolized per day. Absolute synthetic rate (mg/kg/day) = fraction intravascular globulin pool catabolized per day \times total intravascular pool/body weight. Fraction of the intravascular globulin pool catabolized per day = radioactivity lost daily (urine or total body counts)/mean intravascular radioactivity during that day. Total intravascular globulin pool = plasma volume \times serum immunoglobulin concentration. Synthetic rates calculated by this method yielded values within 10% of the previous method.

IgM turnover data was calculated by analysis of serum curves alone. This is due to the low energy level of ^{125}I making it unsuitable for total body counting. Objections to Sterling's method of calculation based on theoretical differences of protein activity in different body compartments are minimized in the case of IgM because of the primary intravascular site of this protein. Synthetic rates calculated by this method were confirmed by the U/P method in six patients.

RESULTS

Our data in 20 patients with SLE and RA and in 7 normal controls are summarized for IgG metabolism in Table I and for IgM metabolism in Table II.

TABLE I
IgG Metabolism in Systemic Lupus Erythematosus and Rheumatoid Arthritis

Patient and diagnosis	Serum IgG concentration <i>mg/100 ml</i>	Anti-nuclear antibody <i>titer</i>	Rheumatoid factor latex fixation <i>titer</i>	Weight <i>kg</i>	Plasma volume <i>liters</i>	IgG survival $t_{1/2}$ <i>days</i>	Per cent of total body IgG catabolized per day <i>%</i>	IgG absolute synthetic rate <i>mg/kg per day</i>
Normal controls (7)								
Mean	1070	Neg	Neg	69.0	2.6	18.0	3.9	34.5
\pm SE	\pm 180			\pm 3.2	\pm 0.8	\pm 1.4	\pm 0.4	\pm 5.7
Systemic lupus erythematosus								
F. E.	4100	+1:16	+1:160	72.0	2.3	5.0	13.8	484.0
L. S.	630	+Undil	Neg	89.5	3.1	9.1	7.6	30.4
B. V.	2200	Neg	Neg	82.5	2.6	11.5	6.0	49.8
S. M.	920	+Undil	Neg	62.0	2.3	2.7	25.7	113.0
Y. L.	1350	+1:64	Neg	56.0	2.2	7.5	9.2	95.4
D. J.	670	Neg	Neg	55.0	2.2	11.8	5.9	31.6
D. T.	2000	+1:64	Neg	64.0	2.6	13.0	5.3	82.9
M. B.	3000	+Undil	Neg	70.0	2.4	8.0	8.7	151.0
I. G.	2100	+1:256	Neg	50.0	1.7	8.8	7.8	115.0
G. T.	1250	+1:16	Neg	61.0	1.9	4.2	16.5	122.0
Mean	1830			66.0	2.3	8.2	10.7	127.5
\pm SE	\pm 347			\pm 3.9	\pm 0.1	\pm 1.1	\pm 1.6	\pm 41.6
						($P < 0.001$)	($P < 0.01$)	($P < 0.05$)
Rheumatoid arthritis								
F. M.	1570	Neg	+1:160	63.0	2.9	5.2	13.3	164.0
P. J.	1650	Neg	+1:2560	54.7	2.7	14.3	4.8	60.1
Y. M.	4000	Neg	+1:1250	44.0	1.8	10.8	6.4	216.0
D. C.	1100	Neg	+1:160	62.5	3.8	15.6	4.4	62.0
D. M.	1000	+Undil	+1:2560	45.0	3.1	14.3	4.8	58.0
W. M.	920	+1:16	+1:2560	70.3	3.4	11.0	6.3	58.0
T. N.	2000	Neg	+1:1280	72.0	3.8	11.3	6.1	124.0
H. B.	1450	Neg	+1:2560	56.0	2.7	15.2	4.5	62.9
M. R.	850	+Undil	+1:2560	82.0	3.9	11.7	5.9	48.9
E. M.	1650	Neg	+1:1280	61.0	2.8	14.5	4.8	72.7
Mean	1630			61.0	3.1	12.4	6.2	92.6
\pm SE	\pm 289			\pm 3.7	\pm 0.2	\pm 1.0	\pm 0.8	\pm 17.9
						($P < 0.02$)	($P < 0.02$)	($P < 0.01$)

Mean determinations for each group when found to differ significantly from normal by *t* test analysis are indicated by their appropriate *P* values.

Normal controls. In seven normal volunteers metabolic studies of our IgG preparation revealed a half-life ranging from 13 to 25 days with a mean half-life of 18.0 days, a fractional catabolic rate ranging from 2 to 5%/day with a mean of 3.9%/day and an absolute synthetic rate ranging from 15 to 50 mg/kg per day with a mean of 35 mg/kg per day. Mean serum IgG concentration was 1070 mg/100 ml. Metabolic studies of our IgM preparation in normals showed it to have a half-life ranging from 6 to 13 days with a mean of 9.3

days, a fractional catabolic rate ranging from 5 to 12%/day with a mean of 8.1%/day, and an absolute synthetic rate ranging from 2 to 10 mg/kg per day with a mean of 6.0 mg/kg per day. Mean IgM serum concentration was 95 mg/100 ml.

Systemic lupus erythematosus. Studies in 10 patients with SLE revealed a marked acceleration in turnover of IgG as compared to normals, with a mean half-life of 8.2 ± 1.1 days ($P < 0.001$), a mean catabolic rate of $10.1 \pm 1.6\%$ /day ($P < 0.01$), and a mean synthetic rate of 127.5 ± 41.6 mg/kg per day ($P < 0.05$). Turnover of IgM, however, was with few exceptions, normal. IgG serum concentration was elevated in five patients

TABLE II
IgM Metabolism in Systemic Lupus Erythematosus and Rheumatoid Arthritis

Patient and diagnosis	Serum IgM concentration mg/100 ml	Anti-nuclear antibody titer	Rheumatoid factor latex fixation titer	Weight kg	Plasma volume liters	IgM survival $t_{1/2}$ days	Per cent of total body IgM catabolized per day %	IgM absolute synthetic rate mg/kg per day
Normal Controls (7)								
Mean	95	Neg	Neg	69.0	2.6	9.3	8.1	6.0
±SE	±5			±3.2	±0.82	±0.96	±1.0	±1.3
Systemic lupus erythematosus								
F. E.	138	+1:16	+1:160	72.0	2.3	6.5	10.6	8.7
L. S.	65	+Undil	Neg	89.5	3.1	12.1	5.7	1.5
B. V.	97	Neg	Neg	82.5	2.6	8.2	8.5	2.7
S. M.	150	+Undil	Neg	62.0	2.3	5.0	13.9	11.0
Y. L.	120	+1:64	Neg	56.0	2.2	3.8	18.2	11.4
D. J.	60	Neg	Neg	55.0	2.2	11.1	6.3	1.9
D. T.	120	+1:64	Neg	64.0	2.6	10.0	6.9	4.1
M. B.	75	+Undil	Neg	70.0	2.4	8.8	7.8	2.5
I. G.	210	+1:256	Neg	50.0	1.7	7.0	9.9	8.7
G. T.	210	+1:16	Neg	61.0	1.9	3.4	20.4	16.1
Mean	124			66.0	2.3	7.6	10.9	7.0
±SE	±17			±3.9	±0.1	±0.9	±1.6	±1.5
Rheumatoid arthritis								
F. M.	64	Neg	+1:160	63.0	2.9	4.5	15.4	7.0
P. J.	215	Neg	+1:2560	54.7	2.7	6.2	11.1	14.1
Y. M.	170	Neg	+1:1250	44.0	1.8	3.5	19.8	17.8
D. C.	200	Neg	+1:160	62.5	3.8	4.2	16.5	40.0
D. M.	267	+Undil	+1:2560	45.0	3.1	3.2	21.7	51.2
W. M.	400	+1:16	+1:2560	70.3	3.4	5.0	15.1	34.0
T. N.	92	Neg	+1:1280	72.0	3.8	11.0	6.2	3.7
H. B.	500	Neg	+1:2560	56.0	2.7	5.6	12.4	37.6
M. R.	115	+Undil	+1:2560	82.0	3.9	4.0	17.3	12.1
E. M.	92	Neg	+1:1280	61.0	2.8	10.5	6.6	3.5
Mean	211			61.0	3.1	5.9	14.2	22.0
±SE	±45			±3.7	±0.2	±0.9	±1.7	±5.4
						($P < 0.05$)	($P < 0.01$)	($P < 0.02$)

and decreased in two. IgM serum concentration was slightly elevated in two patients. No correlation was evident between IgG serum concentration and catabolic rate (Fig. 1). A significant correlation coefficient ($P < 0.05$), however, was demonstrated in SLE between IgM hypercatabolism and IgM serum concentration (Fig. 2). IgG hypercatabolism did not correlate with antinuclear antibody titer. The two SLE patients with negative antinuclear antibody tests, however, had less acceleration in IgG turnover.

Rheumatoid arthritis. In contrast to patients with SLE, patients with RA had an accelerated turnover of IgM, but only a moderate increase in turnover of IgG. IgM catabolism was significantly increased above normal, with a mean half-life of 5.9 ± 0.9 days ($P < 0.05$), mean catabolic rate of $14.2 \pm 1.7\%/day$ ($P < 0.01$), and mean absolute synthetic rate of 22.0 ± 5.4 mg/kg per day ($P < 0.02$). IgG catabolism was increased to a moderate degree with a mean half-life of 12.4 ± 1.0 days ($P < 0.02$); fractional catabolic rate of $6.2 \pm 0.8\%/day$ ($P < 0.02$), and absolute synthetic rate of 92.6 ± 17.9 mg/kg per day ($P < 0.01$). No correlation of IgG or IgM hypercatabolism with titers of rheumatoid factor was noted. IgM serum concentration was significantly elevated in six patients and elevated IgG serum levels were found in three patients. There was no correlation between serum immunoglobulin levels and IgG or IgM catabolism in RA as is shown in Figs. 1 and 2.

Effect of corticosteroid therapy on metabolism. Accelerated IgG catabolism in two patients with systemic

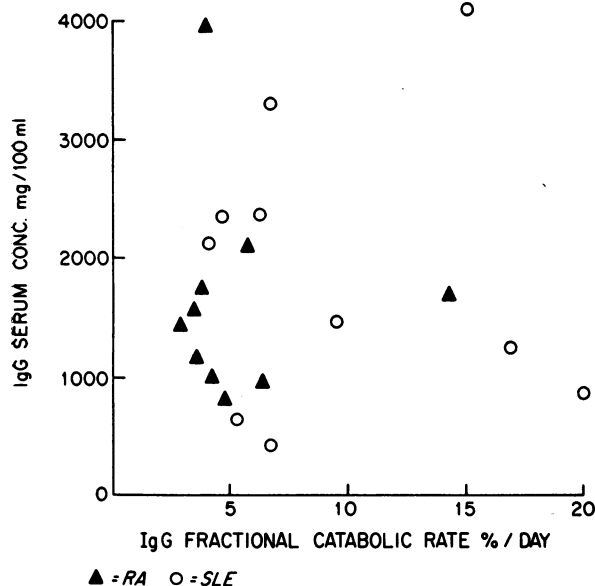


FIGURE 1 Relationship of IgG fractional catabolic rate and serum IgG concentration in subjects with RA (▲) and SLE (○).

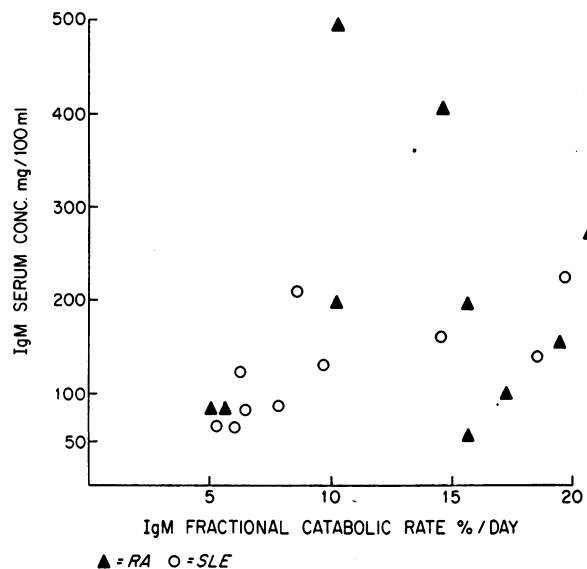


FIGURE 2 Relationship of IgM fractional catabolic rate and serum IgM concentration in subjects with RA (▲) and SLE (○).

lupus erythematosus and in three patients with rheumatoid arthritis not receiving corticosteroids would suggest that such treatment, although hypercatabolic in some circumstances (26), is itself not responsible for the observed abnormalities in immunoglobulin metabolism. Normal IgM turnovers in patients with systemic lupus erythematosus receiving high dose corticosteroids further confirm this conclusion. The failure of corticosteroids to affect IgG catabolism in rheumatic diseases has also been noted by Andersen and Jensen (15).

DISCUSSION

Hyperactivity of immunologic mechanisms can be suspected when an increase in gammaglobulin serum concentration is observed. Serum concentration, however, is not a reliable indicator of immunoglobulin activity since an increase in synthesis may be accompanied by an increase in catabolism with no net change in serum concentration. Turnover studies with radioiodinated gammaglobulins measure the synthetic and catabolic rates of these globulins and better describe the activity of the immune system.

With appropriate preparation of materials it has been well established that radioiodinated globulins are metabolized in the same manner as their native proteins and are suitable for turnover studies (27, 28). Lack of denaturation of our purified radioiodinated globulins was demonstrated by both in vitro and in vivo methods. The proteins were shown to be homogeneous by immunochemical and physical chemical means as well as identical in molecular size to their native proteins by

ultracentrifuge analysis and gel filtration. Electrical charge was shown to be identical with the native proteins by anion exchange column chromatography. In vivo evidence for lack of denaturation included a constant urinary excretion of radioiodine and linearity of the total body count decay. Marked prolongation of tracer IgG survival in two patients with acquired hypogammaglobulinemia ($t_{1/2}$ = 45 and 60 days) further evidenced the native state of our radioiodinated globulins.

In SLE, turnover studies demonstrated hypermetabolism primarily of the IgG class of immunoglobulins. Despite normal serum IgG concentrations patients with SLE showed synthetic rates as much as four to five times normal, revealing far greater IgG antibody production in SLE than suggested by serum concentration. IgM catabolism in these patients with SLE was, with very few exceptions, normal. In at least two patients with SLE an increased catabolic rate of IgG was revealed in the presence of a low serum IgG concentration giving a fractional catabolic rate increased disproportionately to synthetic rate. The low serum IgG concentration, therefore, was not due to a decreased synthesis, but an increased catabolism. Having excluded secondary causes of increased catabolism such as a generalized hypercatabolic state and gastrointestinal or renal loss of intact IgG, these results suggest a primary intrinsic acceleration of IgG catabolism. Known primary abnormalities of gammaglobulin catabolism include the hereditary IgG metabolic defect described in myotonic dystrophy (8) and the immune clearance of IgA found in some patients with ataxia telangiectasia (29). The determinants of IgG catabolism in SLE are probably multiple and may involve both known as well as yet undefined mechanisms.

Animal studies (30-32) and human disease states characterized by different IgG serum concentrations have both demonstrated a dependency of IgG catabolism on serum concentration. Diseases with a reduced IgG serum concentration secondary to decreased synthesis such as congenital or acquired hypogammaglobulinemia and lymphoproliferative malignancies have demonstrated a decreased fractional catabolic rate of IgG (7, 11, 33). Conditions marked by an increase in IgG serum concentration such as cirrhosis of the liver, chronic infections, and multiple myeloma have been associated with an increased catabolic rate (34, 35).

Other factors which may contribute to a primary IgG hypercatabolism may involve changes at the site of IgG catabolism. Work by Truax and McCoy (36) in the rat strongly suggests that the kidney is the major site of IgG catabolism. In the mouse, the kidney has been shown to be the primary site for the catabolism of some immunoglobulin fragments (37). The findings that increased IgG catabolism in nephrosis is only partly ex-

plained by loss of intact IgG globulin into the urine (10) suggest that when diseased, the kidney may increase its normal catabolic function. The presence of active nephritis in eight of the 10 patients with SLE may have contributed to an increased catabolism of IgG.

In RA a striking increase in IgM catabolism was noted in eight of the 10 patients. Accelerated IgM turnover has not been reported previously in any circumstance nor have we observed this abnormality in over 50 patients with a variety of diagnoses, studied with the same IgM preparation, except in patients with RA and in an occasional patient with SLE.

The interpretation of turnover studies of IgM is complicated by lack of agreement among authors as to whether the normal catabolic rate of IgM approximates 10%/day (38-41) or 20%/day (42-44). The use of homologous and autologous IgM in different studies does not explain the short half-life of some IgM preparations. Olesen (39) using both autologous and homologous IgM preparations in turnover studies in six subjects found IgM catabolic rates of both 8% and 20%. An analysis of his data suggests that the different catabolic rates reported for IgM are dependent on the type of preparation used and not on the choice of subjects. Catabolic heterogeneity of IgM is supported by the findings of two serologically distinguishable macroglobulin subclasses in patients with macroglobulinemia (45-48) and the precedent for catabolic differences among subclasses of immunoglobulins obtained from the finding of different catabolic rates for IgG subclasses (49, 50).

The observed differences in catabolism of IgM preparations make the interpretation of studies with autologous IgM difficult and make evaluation of patients studied with an IgM preparation, not evaluated in normals, hazardous. The findings of Bradley, Normansell, and Rowe (44) of autologous IgM half-lives of 3.7-6.5 days in patients with RA would lead to different interpretations if these patients' IgM preparations had half-lives of 9 or 4 days, when studied in normals. In our study an IgM preparation found to have a half-life of approximately 9 days in over 50 subjects was found to have a significantly increased catabolism in patients with RA.

The mechanisms for this IgM hypercatabolism can only be speculated at this time. A normal IgG synthetic and catabolic rate demonstrated simultaneously in many with abnormal IgM turnovers would appear to exclude a generalized hypercatabolic state, as has been suggested by Andersen and Jensen (15) and Vaughan et al. (12).

Increased IgM serum concentration in patients with RA may play some role in catabolism. Previous observations of the independence of catabolism of IgM from

serum IgM concentration based on studies in patients with Waldenström's macroglobulinemia (43) and cold agglutinin disease may not be relevant to studies in RA. Broad band polyclonal serum IgM elevations, as high as 500 mg/100 ml, as seen in our patients with RA, may have an effect on catabolic rate which differs from the effect of a narrow band homogeneous IgM elevation. The variability of the catabolic response to paraproteins has been well demonstrated in the case of IgG paraproteins in multiple myeloma where only some IgG paraproteins appear able to increase the catabolic rate (11). A similar mechanism may explain the failure of increased macroglobulin paraprotein in some patients with macroglobulinemia to influence their IgM catabolic rates.

Patients with RA in our study had a twice normal mean IgM serum concentration. Although no direct correlation between the degree of hypercatabolism and serum IgM concentration is evident (Fig. 1), the two patients with RA who demonstrated normal serum IgM concentration exhibited normal turnover. The remaining eight patients showed increased IgM catabolism and generally an elevated IgM serum concentration. An apparent influence of IgM serum concentration on IgM catabolism is suggested by the positive correlation ($P < 0.05$) between serum concentration and fractional catabolic rate in 10 patients with SLE (Fig. 2).

An additional primary mechanism which may be acting to increase IgM catabolism in RA may be related to increased blood clearance secondary to anti-IgM globulins if present, or to an enhanced ability in RA for removal of aggregated or precipitated proteins from the circulation, first postulated by Vaughan et al. (12). Increased reticuloendothelial clearance which has been described in RA (51) could preferentially clear denatured or complexed IgM before phagocytosis of smaller proteins such as IgG. Further work to investigate these hypotheses is presently being pursued in this laboratory.

ACKNOWLEDGMENTS

The technical assistance of L. Gingras, M. Cragen, I. Ban, and A. M. Flesher is gratefully acknowledged.

This work was supported in part by a Southern California Arthritis Foundation grant, U. S. Public Health Service Grants GM 15759 and RR-00238 and Contract AT-04-GEN12 between the U. S. Atomic Energy Commission and the University of California, Los Angeles, Calif.

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