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THE METABOLISM OF IgE

Studies in Normal Individuals and in a Patient with IgE Myeloma¹

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IgE metabolic turnover studies with purified radioiodinated IgE were performed in normal individuals and in a patient with IgE myeloma. The validity of the turnover studies was established in several ways, including comparisons of radioiodinated IgE turnover with the turnover of endogenously labeled ¹⁴C-IgE and with the turnover of infused unlabeled IgE in a patient with hypogammaglobulinemia.

The geometric mean serum IgE concentration in 73 normal adults was 96 ng/ml with a 68% confidence interval of 24 to 386 ng/ml. Metabolic turnover studies in 10 control individuals disclosed a geometric mean total circulating IgE of 4.1 μg/kg, a mean percentage of the total exchangeable IgE in the intravascular space of 41%, a mean half-time of survival of IgE of 2.7 days, a mean fractional catabolic rate of 94% of intravascular pool per day, and a geometric mean synthetic rate of 3.8 μg/kg/day. IgE has the lowest synthetic rate and highest fractional catabolic rate of the five major classes of immunoglobulin molecules.

In contrast to these normal values, a patient with IgE myeloma had a serum IgE concentration of 42 mg/ml, a total circulating IgE of 1.7 g/kg, and a synthetic rate of 270 mg/kg/day. Furthermore, although the synthetic rate was vastly increased, the survival time was prolonged and the fractional catabolic rate was decreased to 5.1 days and 16 to 22% of the intravascular pool per day, respectively.

These data are compatible with the concept that IgE is catabolized in part by a mechanism common to all immunoglobulin classes and in part by a unique mechanism not available to other immunoglobulins. At very high IgE serum concentrations, such as those encountered in patients with IgE myeloma, the unique mechanism would be saturated and only the catabolic pathways available to all immunoglobulins would be available to IgE.

In 1966 Ishizaka and co-workers (1) demonstrated that human reaginic antibody is associated with a distinct class of immunoglobulin, subsequently designated IgE. Independently, Johansson and Bennich (2) described a myeloma protein (ND) that was antigenically identical to IgE; later, a second IgE myeloma protein (PS) was detected by Ogawa and co-workers (3). The isolation of these myeloma proteins per-

mitted the definition of the chemical characteristics of IgE molecules and the development of a variety of radioimmunoassays for the quantitation of serum IgE levels.

Immunoglobulin E exists primarily as a monomer composed of two heavy and two light chains linked by covalent (disulfide) as well as by noncovalent bonds. Its molecular weight is approximately 200,000 of which 12% is accounted for by carbohydrate (4). IgE is produced by plasma cells in the mucus membranes and regional lymph nodes of the respiratory and gastrointestinal tracts (5). Autoradiographic studies have shown that IgE binds specifically to basophils and tissue mast cells (6-8). The interaction of antigen with cell-bound IgE antibody initiates a reaction which culminates in the degranulation of basophils and mast cells and in the liberation of histamine, slow reactive substance of anaphylaxis, and eosinophil chemotactic factor (8-10). These chemical mediators result in increased vascular permeability, contraction of bronchial smooth muscle, and the influx of eosinophils, events which give rise to the familiar manifestations of the immediate hypersensitivity reaction. It is, therefore, clear that IgE plays a major role in the pathogenesis of allergic diseases.

Metabolic turnover studies with purified radioiodinated IgG, IgA, IgM, and IgD have allowed definition of the metabolic characteristics of these immunoglobulins (11). With such studies it has been shown that each of the immunoglobulins has characteristic rates of synthesis and catabolism and, in some cases, unique pathways of transcellular transport. Such turnover studies have been of value in defining the physiologic factors that control immunoglobulin and antibody levels either through effects on rates of immunoglobulin synthesis or through effects on the rate of immunoglobulin breakdown (catabolism). Finally, turnover studies have also been of value in identifying pathophysiologic factors that are responsible for abnormalities of immunoglobulin levels and as a corollary have led to the discovery of a number of new types of immunodeficiency diseases.

The studies reported here were directed toward defining the metabolic parameters of IgE in individuals with normal IgE levels and in a patient producing an IgE myeloma protein. More specifically, they were directed toward answering the following questions: 1) What are the rates of synthesis and catabolism and patterns of distribution of IgE in individuals with normal levels of IgE? 2) Is the apparently short survival of IgE relative to other immunoglobulins caused by damage sustained by IgE during isolation and radioiodination or is it an intrinsic characteristic of this immunoglobulin class? 3) What is the effect of a high serum concentration of IgE such as that

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encountered in patients with IgE myeloma on the survival of this immunoglobulin?

PATIENTS AND METHODS

Preparation and labeling of purified IgE. Purified IgE for the majority of IgE turnover studies was prepared from the plasma of a patient with an IgE myeloma (PS). The plasma of this patient was dialyzed against 0.01 M Tris, pH 8.0, 0.02 M NaCl buffer and applied to a diethylaminoethyl (DEAE)² cellulose column equilibrated with the same buffer. A broad protein peak was then eluted from the column by using the starting buffer and then a second protein peak was obtained when the buffer was changed to 0.01 M Tris, pH 8.0, 0.06 M NaCl. This second peak was shown to consist only of IgE by Ouchterlony double diffusion by using goat antisera to human IgE, IgG, IgA, IgM, albumin, transferrin, and whole human serum. A number of studies were also performed with an IgE preparation purified by Drs. S.G.O. Johansson and H. Bennich from the serum of patient ND and kindly given to us. This preparation was also tested by Ouchterlony analysis and found to be immunochemically pure.

The purified IgE was labeled with ¹²⁵I or ¹³¹I by the iodine monochloride method of McFarlane (12). Unbound radioiodide was removed by dialysis against frequent changes of pyrogen-free 0.15 M NaCl. All preparations had a specific activity of approximately 2 mCi/mg. Following iodination, human serum albumin was added to the IgE preparations, which were then sterilized by passage through a 0.22- μ Millipore filter.

Measurement of IgE concentrations. Serum IgE concentrations were determined by a double antibody radioimmunoassay as previously described (13). The anti-IgE antiserum used in the assay was a rabbit antiserum to IgE myeloma protein (PS) absorbed with insolubilized bovine serum albumin, fetal bovine serum, human IgG, IgA, IgM, light chains from the IgE myeloma producing patients, and agammaglobulinemic plasma. The specificity of the antiserum thus obtained was confirmed by Ouchterlony double diffusion tests. The second antibody used in the assay was a goat anti-rabbit IgG absorbed with insolubilized human serum and human IgG. The ¹²⁵I IgE used in the assay was IgE myeloma protein ND labeled with a modification of the chloramine-T method (13). For each assay a standard curve was constructed by plotting the logit of the per cent specific counts bound to anti-IgE vs the log₁₀ nanograms of unlabeled IgE added to the reaction mixtures. These curves were linear from 0.4 to 28 ng of IgE in the reaction mixture. The IgE concentration of unknown serum samples was calculated from the coordinates of the least square regression analysis of the standard inhibition curve. As the technique was usually performed, the minimal detectable IgE value was 4 ng/ml.

Patients. Control patients in the IgE metabolic turnover studies consisted of 10 patients with neuromuscular or neoplastic diseases who were suitable for study because they had normal serum IgE concentrations and because groups of patients with comparable disorders had normal serum IgE concentrations. These patients included one patient with malignant melanoma, one patient with the adult Fanconi syndrome, and eight patients with various neuromuscular disorders (Table I). Their ages ranged from 11 to 63 years; 7 were male and 3 were female. None of the patients in these

groups had a history of allergic disorders, skin conditions, or evidence of parasitic infestation.

Metabolic turnover studies with radioiodinated preparations of both PS and ND proteins were also performed in patients PS who had myeloma with IgE paraprotein and a serum IgE level of 4.2 g/100 ml. The clinical aspects of this patient have been reported previously (3).

All of the patients gave informed consent to the performance of the IgE metabolic turnover studies.

Turnover study protocol. Patients were hospitalized at the Clinical Center of the National Institutes of Health during the period of study. Over this period they were clinically stable and their serum IgE concentration remained constant. Therefore, the patients were considered to be in a steady state with regard to IgE metabolism. Before study and throughout the study period the patients received 5 drops of saturated solution of potassium iodide three times a day to prevent thyroidal uptake of radioiodine. At the initiation of study five to 25 μ Ci of ¹²⁵I-IgE or ¹³¹I-IgE were administered i.v. from a calibrated syringe. Serum samples were then drawn at 10 min, 4 hr, and daily for 7 to 14 days. In addition, 24-hr urine collections were made for 7 to 10 days following labeled protein administration. Serum and urine samples thus obtained were counted along with dilutions of the injected dose in an automatic gamma ray well-type scintillation counter. Whole body decline of radioactivity was also measured in several patients utilizing the NIH whole body counter; in this procedure the patient was counted at 30 min and at daily intervals following administration of the radioiodinated ¹³¹I-IgE.

Endogenously labeled IgE protein turnover study. In one study IgE turnover in a patient with IgE myeloma was determined with the use of IgE labeled endogenously with ¹⁴C-arginine. In this study a single i.v. dose of 50 μ Ci of ¹⁴C-guanido-labeled arginine was administered and plasma samples were obtained at 4 hr, 18 hr, and then daily throughout the study period. The specific activity of IgE in each sample was then obtained by purification and counting of IgE contained therein. To this end the IgE myeloma protein was isolated from each of the serum samples as discussed above; 5 mg of the purified material were then completely precipitated and 10% trichloroacetic acid, dissolved in 0.5 ml of NCS tissue solubilizer (Amersham/Searle, Arlington Heights, Ill.), and mixed with 10 ml of a mixture of Liquifluor (New England Nuclear, Boston, Mass.) and toluene; finally, the mixture was counted in a liquid scintillation counter.

Analysis of the metabolic data. Whole body radioactivity was calculated by cumulative subtraction of radioactivity appearing in the urine from the injected dose. In addition, the whole body radioactivity was determined by whole body counter for those patients receiving ¹³¹I-IgE. The radioactivity in the serum and the radioactivity in the whole body were expressed as a fraction of the injected dose assuming that the radioactivity in the serum at 10 min and in the whole body at 30 min after administration was equal to the injected dose. The plasma volume was obtained by dividing the value for the amount of radioactivity in the injected dose by the value for the amount of radioactivity in 1 ml of plasma at zero time; the latter value was determined by extrapolation of the serum decay curve to the zero time point. Plasma and whole body die-away curves were constructed on semi-logarithmic paper and the biologic half-time ($t_{1/2}$) of each labeled protein was determined from the resultant graphs. The total circulating and total body protein pools, the fraction of the protein body

² Abbreviations used in this paper: DEAE, diethylaminoethyl; FCR, fractional catabolic rate.

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TABLE I
IgE metabolism in control individuals

Patient	Age	Sex ^a	Diagnosis	Serum IgE Concentration	Plasma Volume	Total Circulating IgE	Intra- vascular	Survival <i>t</i> _{1/2}	FCR	Synthetic rate	Serum Concentration		
											IgG	IgA	IgM
				ng/ml	ml/kg	μg/kg	%	days	<i>fraction of total intra- vascular IgE/day</i>	μg/kg/day	mg/ml	mg/ml	mg/ml
C.H.	60	F	Neuromuscular disease	18.0	29.9	0.54	21.1	4.5	1.17	0.63	8.4	2.6	1.7
W.J. ^b	36	M	Myotonic dystrophy	37.5	24.8	0.93	36.2	2.7	0.99	0.92	4.9	1.6	1.3
L.W.	60	M	Adult Fanconi's syndrome	61.0	36.0	2.20	32.0	1.8	0.97	2.14	6.5	1.5	2.0
J.C. ^b	43	M	Myotonic dystrophy	62.0	38.8	2.40	46.8	2.3	0.77	1.85	7.8	2.5	0.96
J.L.C.	33	M	Neuromuscular disease	64.2	41.0	2.63	33.5	3.0	1.01	2.66	6.5	1.7	1.4
S.C.	57	M	Malignant melanoma	170.0	40.1	6.82	56.8	1.9	0.75	5.09	10.0	3.3	0.65
J.W.	11	M	Cerebellar ataxia	250.0	48.7	12.2	39.6	3.1	1.09	13.33	9.6	2.7	0.76
M.D.	63	F	Neuropathy	253.0	34.0	8.60	57.1	3.0	0.63	5.45	13.7	3.4	0.91
E.R. ^b	53	M	Amyotrophic sclerosis	380.0	41.2	15.7	53.7	2.1	0.63	9.87	11.0	3.5	1.4
S.P.	15	F	Neuromuscular disease	422.0	44.1	18.6	29.5	2.9	1.42	26.32	6.3	2.2	0.88
Mean ^c				111	37.9	4.13	40.6	2.7	0.94	3.77	8.1	2.4	1.1
68% confidence interval				38.1-323	30.9-44.8	1.23-13.92	28.2-53.1	2.0-3.5	0.69-1.19	1.15-12.35	6.0-11.0	1.7-3.3	0.78-1.62

^a M, male; F, female.^b Turnover studies with two different IgE sources (PS and ND) were performed on these patients.^c The mean values of serum IgE concentration, total circulating IgE, synthetic rate, and serum concentrations of IgG, IgA, and IgM are expressed as geometric means.

pool remaining in the intravascular pool, the fraction of the intravascular pool catabolized per day (fractional catabolic rate or FCR), and the absolute metabolic rate (synthetic rate) were determined by the methods of Matthews (14) and Nosslin (15). In this analysis, the FCR was determined from the reciprocal of the area under the serum decay curve and the per cent of the exchangeable IgE in the intravascular pool was determined from the ratio of the area under the serum die-away curve to the area under the whole body die-away curve. The fitting of the curves to the data was performed with a digital computer (UNIVAC 1108).

Statistical analysis. Mean values for the serum IgE concentration, total circulating IgE pool, and the absolute metabolic rate for IgE were obtained as geometric means. Means values for the per cent intravascular, the ($t_{1/2}$) of survival, and the fractional catabolic rate were obtained as arithmetic means. Significance of the difference between means was evaluated by Welch's *t*-test.

RESULTS

The geometric mean serum IgE concentrations for 73 normal adults was 96 ng/ml with a 68% confidence interval of 24 to 386 ng/ml. The control patients participating in the IgE metabolic turnover studies had a similar mean IgE concentration of 111 ng/ml with a 68% confidence interval of 38 to 323 ng/ml (Table I). Metabolic turnover studies performed with ^{125}I -IgE (PS) disclosed that the serum IgE concentration was associated with a total circulating IgE pool of 4.1 $\mu\text{g/kg}$ with a 68% confidence interval of 1.2 to 13.9 $\mu\text{g/kg}$. The intravascular pool contained $41 \pm 12\%$ of the total exchangeable IgE in the body with the remainder distributed in the extravascular space. The whole body curve, estimated either by using the whole body counter or by cumulative subtraction of urinary radioactivity from the injected dose, declined as a single exponential with time to at least the point where only 10% of the injected IgE remained in the body. This indicates that no large extravascular depot of IgE exists which exchanges poorly with the circulating IgE pool.

The IgE serum survival was quite short when compared to that of other immunoglobulin classes with a mean half-life of 2.7 ± 0.8 days; this corresponded to a FCR of $94 \pm 25\%$ of the intravascular pool per day. The absolute amount of IgE catabolized per day was 3.8 $\mu\text{g/kg}$ with a 68% confidence interval of 1.2 to 12.4 $\mu\text{g/kg}$. Since the individuals studied were in the steady state, this is equal to the amount of IgE synthesized and delivered to the plasma compartment each day.

In the light of the very short survival of IgE and high FCR for this protein when compared to other classes of immunoglobulins, a series of studies were performed to ensure that these metabolic parameters were truly characteristic of this molecule and did not reflect alterations in the molecule that might occur during its purification and radiolabeling. 1) Three control patients indicated in Table I as well as five patients with various diseases were studied twice by using preparations of IgE obtained from both patient PS and patient ND; the metabolic values obtained with IgE_{PS} and IgE_{ND} were quite comparable in all of the individuals studied with both preparations and there was no statistically significant difference ($p > 0.1$) between the mean metabolic values obtained with either of these preparations in the patient group as a whole; in addition, isolation of PS protein performed on separate occasions and labeled separately gave comparable metabolic turnover values

when studied in different patients or when studied in the same patient at different times. 2) With all preparations the fraction of the circulating radioactivity excreted within the first 24-hr period was equal to or less than that excreted on subsequent days; this contrasts with the excessive early excretion of radioactivity commonly observed when damaged protein preparations are utilized. 3) The die-away of labeled IgE was compared with the die-away of unlabeled IgE in a patient with hypogammaglobulinemia who was receiving therapeutic plasma infusions; the patient with hypogammaglobulinemia had no detectable IgE in the serum before therapy whereas the donor plasma obtained from a normal individual had an IgE concentration of 1000 ng/ml; donor plasma was infused into the patient and, simultaneously, the patient was given an injection of ^{125}I -IgE (PS); the die-away of unlabeled IgE was followed by performing radioimmunoassay on serial serum samples and the die-away of radioiodinated IgE was followed by measuring radioactivity in serial serum samples; it was found that the die-aways of the two species of IgE in the serum were essentially identical (Fig. 1). 4) Finally, as indicated below, the survival of IgE myeloma protein (PS) was studied in the patient PS by using both radioiodinated purified PS protein as well as *in vivo* labeling of this protein with ^{14}C -guanido-arginine; 50 μCi of ^{14}C -guanido-L-arginine were administered i.v. and the specific activity in the purified serum IgE was determined at various times thereafter; as shown in Figure 2, the $t_{1/2}$ of survival of IgE labeled *in vivo* was 5.6 days, a figure quite comparable to the $t_{1/2}$ of 5.1 days obtained with IgE purified and radiolabeled *in vitro*. These various studies indicate

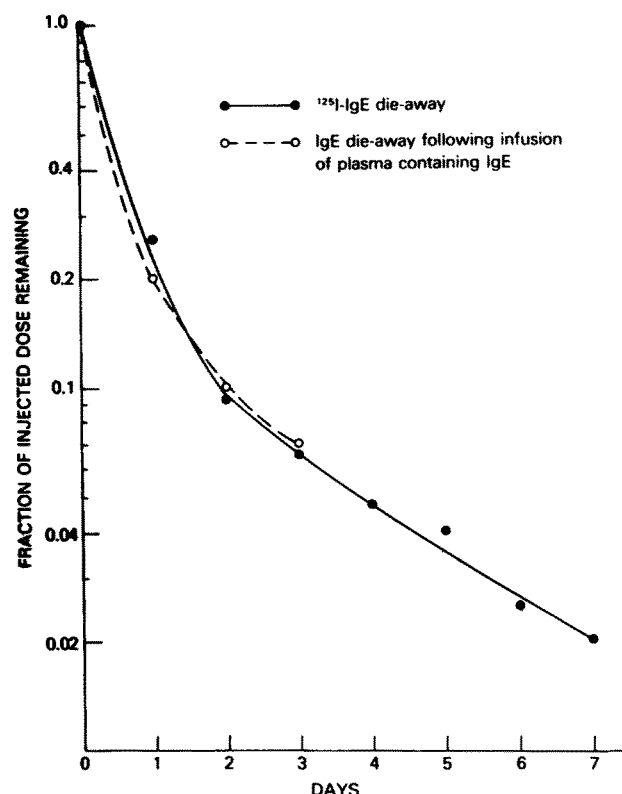


Figure 1. Serum decay curves of ^{125}I -IgE and of unlabeled IgE in a patient with hypogammaglobulinemia. ^{125}I -IgE (PS) and IgE-rich normal plasma were injected simultaneously into the vascular system. The serum die-away of labeled and unlabeled IgE was then followed by measuring the amount of these species in serial blood specimens. The serum die-aways of the radiolabeled IgE and of the unlabeled IgE were essentially identical.

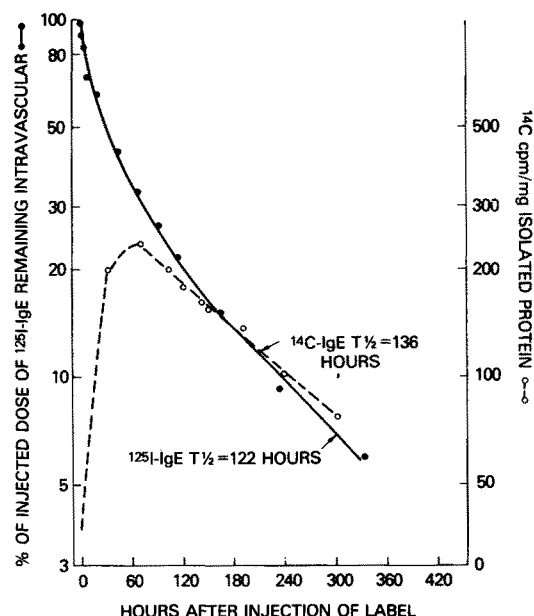


Figure 2. Serum disappearance curves of ^{125}I -IgE (PS) and ^{14}C -IgE in patient PS. The final slopes of the decay curves of both ^{125}I -IgE ($t_{1/2}$ 5.1 days) and ^{14}C -IgE ($t_{1/2}$ 5.6 days) were comparable.

that the survival of IgE as determined by radioiodinated IgE is an inherent property of the IgE molecule and the physiologic factors affecting its metabolism, rather than the result of denaturation occurring during purification and iodination.

One of the most important factors affecting the survival of an immunoglobulin is the serum concentration of the immunoglobulin itself. Accordingly, to define the effect of an exceedingly high IgE concentration on IgE survival, the metabolism of radioiodinated IgE was studied in patient PS who had IgE myeloma and a serum IgE concentration of 42 mg/ml. In this patient, the total circulating IgE pool size estimated from the serum concentration and metabolic studies with ^{125}I -IgE (PS) was 1.7 g/kg and the IgE synthetic rate was 270 mg/kg/day. These values were 70,000- to 400,000-fold greater than the mean values for these parameters in normal individuals. Of great interest is the fact that the survival of IgE was significantly longer in PS than in any of the control individuals: the survival $t_{1/2}$ of IgE was 5.1 days with radioiodinated IgE (PS) and 4.9 days with radioiodinated IgE (ND), values which correspond to fractional catabolic rates of 16 and 22% of the intravascular pool per day, respectively. Thus, in this patient, the exceedingly high serum IgE concentration is associated with, and partially caused by, a reduced fractional catabolic rate as well as an exceedingly high synthetic rate.

DISCUSSION

The results of studies of the metabolism of the five major classes of immunoglobulins in normal individuals are summarized in Table II. It can be seen that among the various classes there is a wide range in the serum concentration and in the synthetic rates and catabolic rates governing these concentrations. It can also be seen that the serum concentration of IgE in normal individuals, approximately 100 ng/ml, is markedly less than that of any of the other immunoglobulin classes and only $1/100,000$ that of IgG. This is primarily because of the fact that the synthetic rate of IgE, 0.0034 mg/kg/day, is only $1/100$ that of IgD, $1/1000$ that of IgM, and $1/10,000$ that of IgA and IgG. In addition, the low serum IgE concentration is caused by the fact that the FCR

of IgE, 94% of the i.v. pool per day, is markedly greater than that of the other immunoglobulin classes whose FCR's range from 6.7% of the i.v. pool per day for IgG to 37% of the i.v. pool per day for IgD (11, 16).

The catabolism of immunoglobulins is controlled in part by physiologic factors that affect all serum proteins such as the body metabolic rate and in part by factors that are specific for one or more of the immunoglobulin classes. A major example of this latter form of control is seen in the relationship between the serum immunoglobulin concentration and the FCR. In the first pattern governing this relationship, exemplified by IgM (17) and IgA (18), the FCR is independent of the serum concentration; that is, the FCR and the $t_{1/2}$ of survival of these classes are essentially the same in normal control individuals as in patients with hypogammaglobulinemia and markedly reduced concentrations of these immunoglobulins or in patients with greatly elevated concentrations of these immunoglobulins such as those with macroglobulinemia of Waldenström or with IgA myeloma.

In the second pattern, exemplified by IgG, the FCR varies with the concentration of IgG in the plasma (11, 19). In this case, as the concentration of IgG rises by endogenous production or by infusion, the FCR increases until a limiting concentration is reached. In man the fraction of the intravascular pool of IgG catabolized daily rises from 2% in patients with extreme hypogammaglobulinemia to a limit of 16 to 18% in patients with high concentrations of IgG such as those with IgG myeloma. The most attractive hypothesis so far suggested to account for this concentration-catabolism effect is that a saturable protection system specific for IgG is present. It is hypothesized that a fraction of the plasma pool is isolated from the circulating protein into the catabolic pool where a proportion of the IgG molecules become attached to a limited number of specific protective receptors. The molecules attached to the receptors are ultimately returned to the circulation whereas the remaining unattached IgG molecules are degraded. At a low concentration most IgG molecules are protected and returned to the circulation producing a long IgG survival, whereas at a high concentration the converse is true. Preliminary evidence in support of the existence of such protective receptors for IgG has been obtained (20).

The third pattern governing the relationship between serum concentration and FCR is seen with IgD where there is an inverse relationship between the IgD FCR and IgD concentration (21). Here, the FCR is low with high serum IgD levels and high in patients with low or normal serum IgD levels. The

TABLE II
Metabolic properties of human immunoglobulins^a

Immunoglobulin	Serum Concentration	Distribution (% Intra-vascular of Total Body Pool)	Total Circulating Pool	FCR	Half-life	Synthetic Rate
	mg/ml		mg/kg	% of intra-vascular pool/day	days	mg/kg/day
IgE	0.0001	41	0.004	94.3	2.7	0.0038
IgD	0.023	75	1.1	37.0	2.8	0.4
IgM	0.93	76	37.0	18.0	5.1	6.7
IgA	2.6	42	95.0	25.0	5.8	24.0
IgG	12.1	45	494.0	6.7	23.0	33.0

^a The data on IgD, IgM, IgA, and IgG have been described previously (11).

pattern of metabolism of IgE as reported in this study is similar to that previously seen with IgD in that the patient with IgE myeloma protein and a markedly elevated level of IgE in the serum had a low FCR for IgE as compared to patients with normal IgE levels. A similarly prolonged survival of radiolabeled IgE has been noted in patient ND (4).

The factors responsible for this relationship between serum concentration and FCR of IgE are likely to be related to one or another of the unique biologic properties of IgE (4, 22). In this regard we know that IgE can bind to cell surface receptors in a variety of tissues and it seems possible that such binding governs a pathway of catabolism that is specific for this molecule. With this in mind, one could explain the high FCR of IgE relative to other immunoglobulins by assuming that the catabolism of IgE is caused by two separate mechanisms acting additively, one mechanism common to all immunoglobulins and one mechanism specific for IgE and involving IgE-specific binding. One could also explain the reduced IgE FCR seen in the patient with IgE myeloma since, in this case, the cell surface receptors for IgE would be saturated by the excess IgE present and only the catabolic pathways available to all immunoglobulins would be available to IgE.

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