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## Immunoglobulin Changes in Disease: Quantitation on the Basis of Heavy Polypeptide Chains, IgG ( $\gamma$ G), IgA ( $\gamma$ A), and IgM ( $\gamma$ M), and of Light Polypeptide Chains, Type K (I) and Type L (II) \*

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The immunoglobulins are made up of heavy and light polypeptide chains (1, 2). There are three major classes of immunoglobulin (gamma globulins) that are commonly identified in normal human serum: the IgG ( $\gamma$ G-, or 7 S  $\gamma_2$ -globulin), the IgA ( $\gamma$ A-,  $\gamma_{1A}$ -, or  $\beta_{2A}$ -globulin), and the IgM ( $\gamma$ M-,  $\gamma_{1M}$ -,  $\beta_{2M}$ -, or 18 S  $\gamma_1$ -macroglobulin).<sup>1</sup> These classes are distinguished on the basis of heavy polypeptide chain differences.

A separate subdivision of human immunoglobulin is made on the basis of differences in the light polypeptide chains (3-6). Two forms of light chains are recognized and are identified as kappa and lambda chains. Immunoglobulin molecules with kappa chains are Type K (formerly Type I). Molecules with lambda chains are Type L (formerly Type II). The features that distinguish Type K (Type I) and Type L (Type II) molecules are independent of the features that identify IgG, IgA, and IgM. Therefore, some of the IgG molecules are Type K and some are Type L. Similarly, IgA and IgM molecules are either Type K or Type L on the basis of their particular light polypeptide chain characteristics.

Each class of human immunoglobulin can be identified by specific antisera (Figure 1). These antisera, which react with specific antigenic determinants, also permit quantitative immunochemical determination of each form of immunoglobulin. We have used an isotopic im-

mune inhibition test (7) and a diffusion plate technic with specific antibody incorporated into the agar (8) for the quantitative measurement of IgA, IgG, and IgM as well as Type K (I) and Type L (II) proteins.

The present study was undertaken to determine the quantitative changes that occur among the three classes and two types of human immunoglobulin during various disease states in man.

### Methods

Sera from adults with various diseases were obtained from the clinical services of the National Institutes of Health, the National Naval Medical Center, and Walter Reed Army Hospital. These patients were predominantly Caucasian males. In addition, sera from six children with agammaglobulinemia were tested. Twelve sera of patients with trypanosomiasis,<sup>2</sup> five sera from patients with ataxia telangiectasia,<sup>3</sup> and sera from patients with protein-losing enteropathy and from additional cases of ataxia telangiectasia<sup>4</sup> were generously made available.

The diagnosis was substantiated in each case by appropriate tissue examination and by bacterial or fungal cultures for infectious disease. Only sera drawn at the time of active disease were tested.

Quantitation of the respective immunoglobulins was carried out by the isotopic immune inhibition test (7) and the antibody-agar plate technic (8). Normal values are given in Table I. The probable error of measurement is  $\pm 10\%$ , and levels as low as 0.003 mg per ml may be quantitated. Recent determinations have been made with the antibody-agar plate technic because it is better suited to screening large numbers of samples. Both methods give comparable serum values for IgG and IgM (8). The measurement of serum IgA concentration by the antibody-agar plates, however, gives values approximately 25% lower than those determined by the isotopic im-

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<sup>1</sup> The immunoglobulin (gamma globulin) nomenclature used in this paper follows that recommended by an international committee (Bulletin of the World Health Organization 1964, 30, 447).

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<sup>4</sup> From Dr. Thomas Waldmann, Metabolism Service, National Cancer Institute.

mune inhibition technics. This is because of molecular size heterogeneity within the IgA group (8). The Type K and Type L immunoglobulins are similarly composed of proteins of varying molecular size. Therefore, serum levels of Type K and Type L determined on antibody-agar plates also are lower than levels determined by the isotopic immune inhibition technics (8). However, there is no statistically significant difference between the ratios of Type K and Type L as determined by the two methods. The Type K and L values and ratios reported herein were all determined by the antibody-agar plate tests, which reflect predominantly the Type K and L content of the 7 S (i.e., largely IgG) immunoglobulins.

The IgG, IgA, and IgM levels in disease are expressed as the ratio of the mean disease levels to the mean normal level for each protein class (Table I). The tabulated figure represents the observed protein concentration di-

vided by the normal adult mean protein concentration for that component. Thus a normal serum value is 1.0. Ratios of IgA/IgG and IgM/IgG are expressed similarly. The data for Type K and Type L immunoglobulins, however, are expressed as simple ratios of their respective serum levels: K/L (I/II). Data are presented in this way to facilitate the recognition of relative changes among the various immunoglobulin categories.

Results

The immunoglobulin levels in normal subjects and in 224 patients with a variety of diseases are recorded in Table I. Representative immunoelectrophoretic findings are shown in Figure 1. Antibody-agar plate results for five disease sera are

TABLE I  
Serum immunoglobulin changes in disease

	IgG		IgA		IgM		IgA/ IgG	IgM/ IgG	Type K/ Type L	Range
Normal	1.00*	0.18†	1.00*	0.25†	1.00*	0.29†	1.00*	1.00*	1.86	1.3-2.4
Infectious diseases										
Miscellaneous (6)‡	2.1	0.7	1.2	0.6	0.74	0.4	0.7	0.56	2.43	1.5-4.2
Trypanosomiasis (12)	1.6	0.6	1.5	0.6	4.7	1.8	0.94	3.0	1.81	1.3-2.3
Leprosy (3)	2.0	1.3	1.2	0.3	1.7	1.2	0.81	0.71	1.99	1.8-2.2
Kala-azar (2)	3.8	2.0	0.9	0.4	1.2	0.6	0.27	0.62		
Coccidioidomycosis (6)	1.5	0.5	1.6	0.7	1.2	0.5	1.1	0.80		
Cryptococcosis (10)	0.7	0.1	0.7	0.3	0.9	0.4	1.0	1.29	2.14	2.1-2.2
Histoplasmosis (15)	1.1	0.3	1.2	0.5	1.0	0.5	0.88	0.85	1.96	1.4-2.7
Blastomycosis (14)	1.0	0.2	1.2	0.5	1.1	0.4	1.2	1.10	2.32	1.9-2.7
Liver diseases										
Hepatic cirrhosis (7)	2.8	1.0	3.6	1.8	1.1	0.5	1.4	0.5	1.90	1.5-2.6
Biliary cirrhosis (2)	1.0	0.1	1.3	0.7	2.1	1.3	1.3	2.5		
Hepatoma (6)	1.3	0.7	1.0	0.5	0.53	0.2	1.0	0.52		
Wilson's disease (3)	0.8	0.2	0.7	0.3	0.8	0.1	0.88	1.1	2.31	2.0-2.7
Protein-losing diseases										
Nephrotic syndrome (5)	0.57	0.2	0.68	0.4	1.3	0.7	1.2	2.3	1.49	1.2-1.7
Enteric enteropathy (12)	0.35	0.1	0.39	0.07	0.49	0.3	1.1	1.4	1.90	1.3-2.4
Other diseases										
Agammaglobulinemia (6)	0.11	0.08	<0.01	0.01	<0.04	0.01				
Ataxia telangiectasia (7)§	0.84		<0.003		1.49			1.77	1.82	1.2-3.2
Lupus erythematosus (7)	1.5	0.6	1.3	0.4	1.2	0.6	0.87	0.8	2.87	1.9-4.2
Nephritis (1)	3.6		1.9		2.0		0.53	0.56	1.84	
Leukemia, plasmocytic, and related malignancy										
Hodgkin's disease (11)	1.2	0.2	0.78	0.3	1.0	0.5	0.6	0.86	2.18	1.6-3.9
Chronic lymphocytic leukemia (14)	0.8	0.2	0.44	0.2	0.25	0.1	0.7	0.44	1.9	1.5-2.0
Chronic myelogenous leukemia (10)	1.0	0.2	0.63	0.2	1.0	0.2	0.7	1.0	1.8	1.2-2.1
Acute lymphocytic leukemia (9)	1.0	0.2	0.60	0.3	1.0	0.5	0.74	1.1	1.7	1.4-1.9
Acute myelogenous leukemia (10)	1.4	0.3	1.0	0.3	0.9	0.4	0.77	0.76	1.7	1.5-1.9
G(γ) myeloma (16)	3.9	1.9	0.17	0.1	0.10	0.01				
A(β <sub>2</sub> A) myeloma (11)	0.3	0.07	19.0	6.4	0.10	0.01				
M-macroglobulinemia (18)	0.66	0.2	0.8	0.4	24.0	11.6				
Normal value, mg/ml	12.4	2.2	2.8	0.7	1.2	0.35				

\* Expressed as the ratio of mean disease value/mean normal value.  
 † Standard deviation.  
 ‡ The number of samples tested is indicated in parentheses.  
 § An eighth patient with ataxia telangiectasia had an IgA level twice normal.  
 || Normal value is 3.9 mg per ml when tested by isotopic immune inhibition test (7).

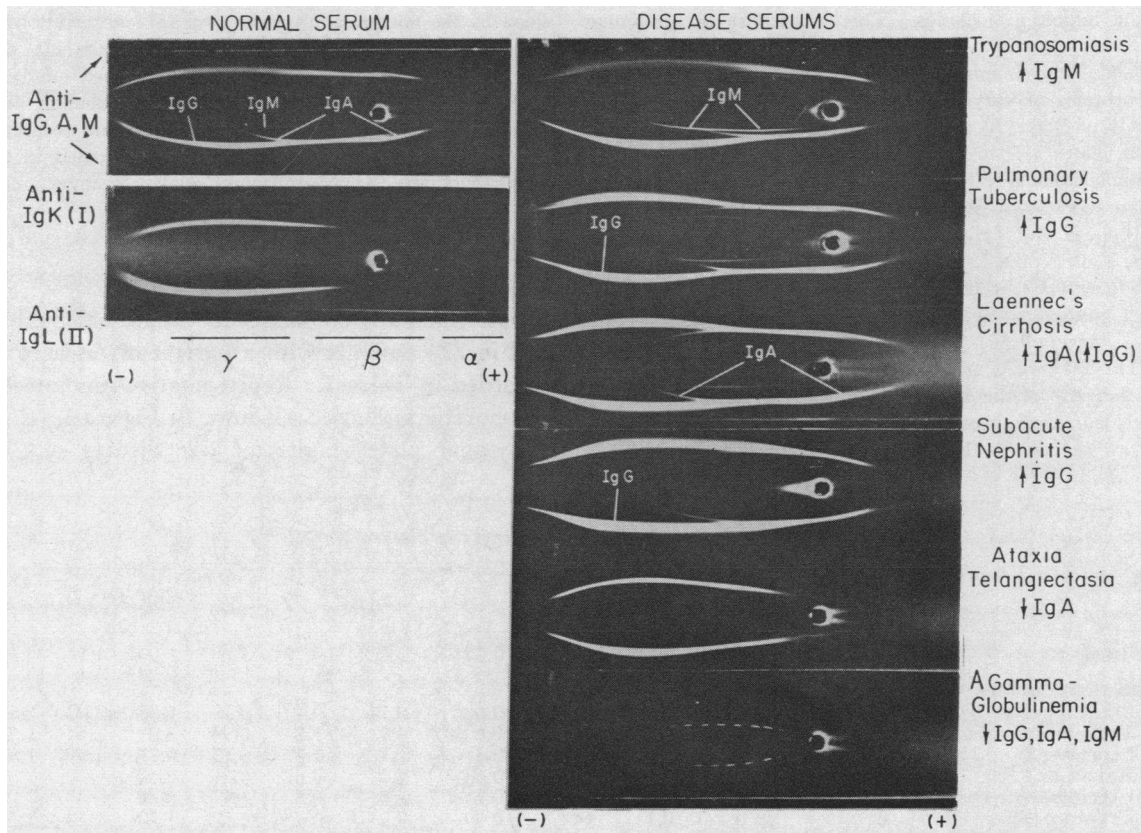


FIG. 1. IMMUNOELECTROPHORETIC ANALYSIS OF NORMAL AND DISEASE SERUM. A polyvalent antiserum reacting with IgG, IgA, and IgM was used for most serum analyses. Specific anti-IgK (Type I) and anti-IgL (Type II) were used to demonstrate these components in normal serum.

shown in Figure 2. The diameter of the precipitin rings in the agar reflects the concentration of IgG, IgA, and IgM in the sera.

**Infectious disease.** This group included sera from patients with leprosy, kala-azar, and pulmonary tuberculosis. An increase of serum IgG was characteristic of this group (Table I). The IgA, however, was only slightly increased. Analyses of 11 individual sera from patients with infectious disease are recorded in Figure 3. The sera are arranged on the basis of IgG level. The data on the ratio of IgA/IgG and IgM/IgG indicate that the increase of IgG usually occurred without any corresponding increase in IgA or IgM.

A marked IgM (macroglobulin) increase was found in patients with *T. gambiense* trypanosomiasis and set this disease apart from the others (Table I). This finding has already been noted by Mattern, Masseyeff, Michel, and Peretti (9).

An IgM increase was found in all but one of the samples studied (Figure 3). The IgG was increased in some sera (Figure 3) but IgA in only one. The IgM increase, however, was not directly related to IgG or IgA levels (Figure 3).

**Fungus disease.** A generalized increase in serum globulins was found with coccidioidomycosis (Table I). This correlates well with clinical observations of leukocytosis, fever, and other aspects of inflammatory host response characteristic of coccidioidomycosis infections. The inflammatory changes are not prominent in cryptococcosis. In this disease, all three classes of immunoglobulin tended to be decreased.

Essentially normal serum concentrations of all three immunoglobulins were found in 15 patients with histoplasmosis and 14 patients with blastomycosis. Only a slight elevation in IgA level was noted with normal values of IgG and IgM.

**Laennec's cirrhosis.** Marked elevations of

serum IgA and IgG were noted in hepatic cirrhosis. IgM levels were usually normal (Figure 3). The serum IgA concentration was greater in hepatic cirrhosis than in the other diseases studied, with the exception of IgA myeloma, and indicates that serum immune globulin measurements may be a useful diagnostic procedure in this disease. The changes in immune globulin levels with cirrhosis differ from those observed in chronic infection. Thus, chronic antigenic stimulation is not the only factor affecting the various serum globulin concentrations in hepatic cirrhosis.

*Biliary cirrhosis.* The only alteration of serum immune globulin in the two patients with biliary cirrhosis was an increase in the IgM globulin concentration. This differs notably from the changes observed in hepatic cirrhosis as outlined above. Although more cases are needed to adequately evaluate the immune globulin changes, these find-

ings are consistent with the demonstration of macroglobulin by cytofluorescent studies in biliary cirrhosis (10) and indicate that the immunoglobulin response of the host with biliary cirrhosis differs from that observed in other hepatic diseases.

*Hepatoma.* Six patients with hepatoma had serum IgM levels that were reduced to about 50% of the normal adult value. A slight increase was noted in serum IgG without change in IgA. The increase in IgG was relatively minor, not to the extent seen in infection or Laennec's cirrhosis. Thus, the major change in the hepatoma sera was the fall in macroglobulin concentration. IgM decreases of this degree were seen only in neoplastic diseases, protein-losing enteropathy, and agammaglobulinemia.

*Wilson's disease.* Although the three patients with Wilson's disease exhibited slight decreases in all three immunoglobulins, the deficiency was most pronounced for IgA. This is distinct from

## IMMUNOGLOBULIN DIFFUSION PATTERNS IN DISEASE

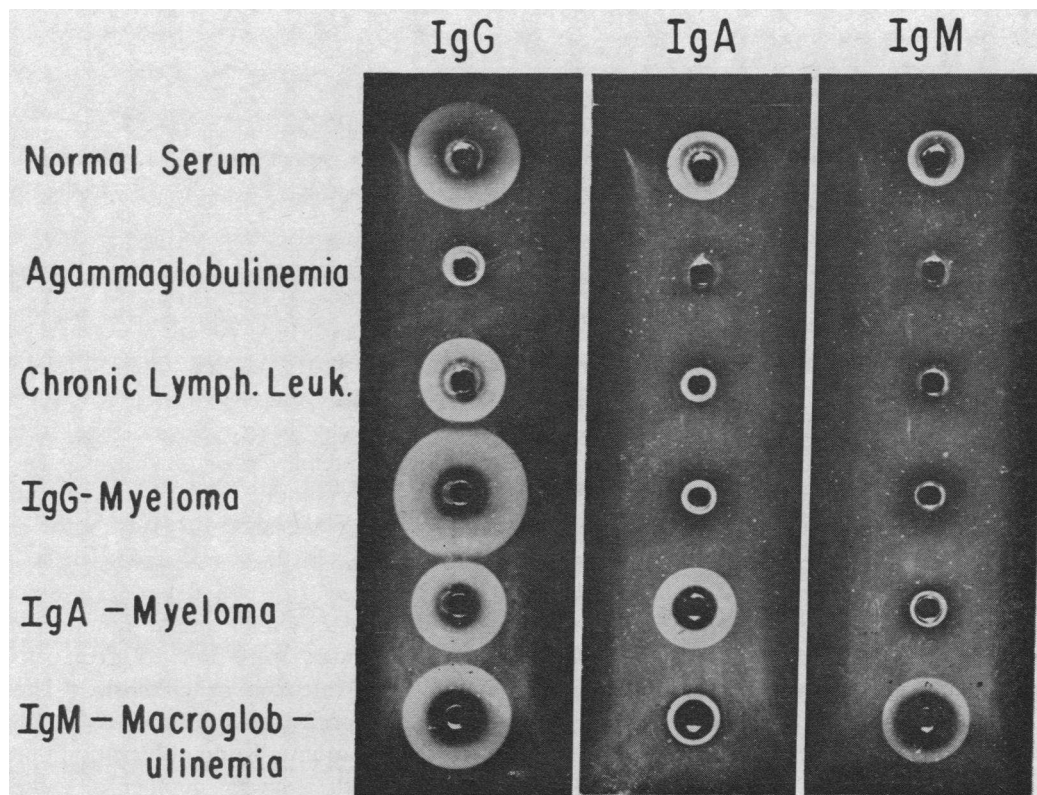


FIG. 2. IMMUNOGLOBULIN DIFFUSION PATTERNS IN DISEASE. Precipitin rings reflecting concentration of IgG, IgA, and IgM are shown in specific antibody-agar plates.

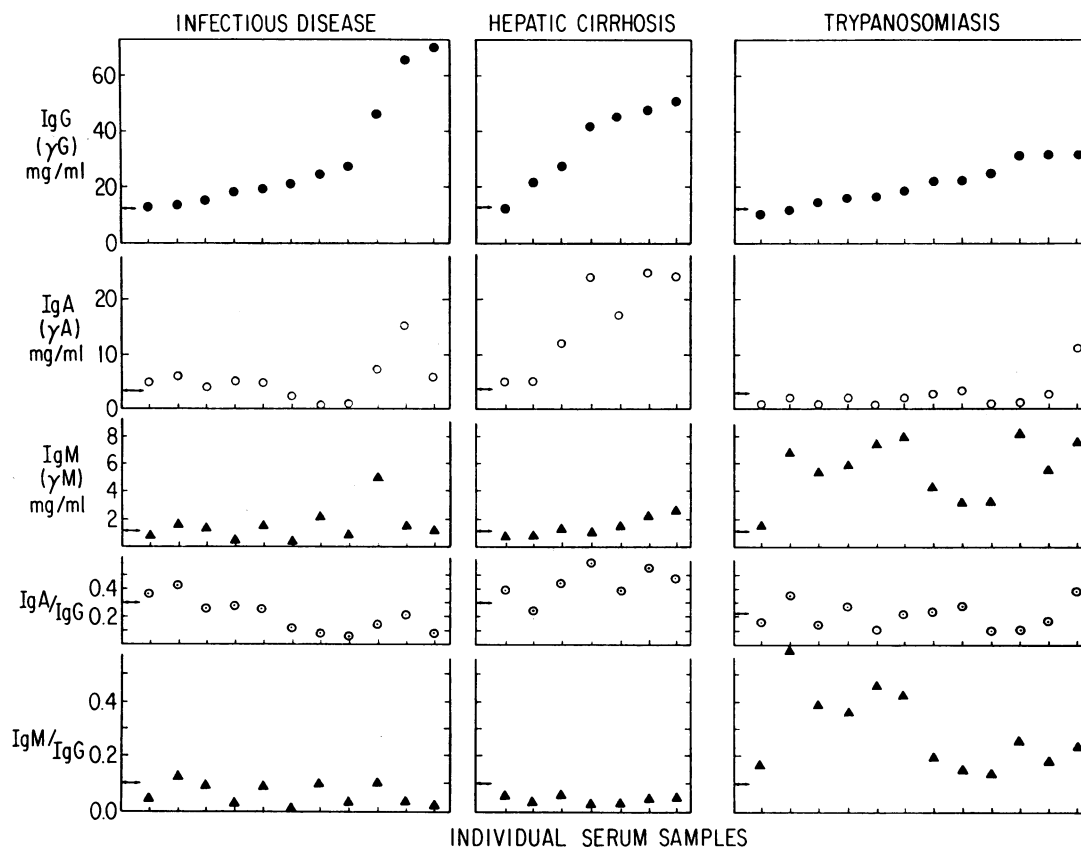


FIG. 3. SERUM IMMUNOGLOBULIN CHANGES IN DISEASE. Immunoglobulin levels for individual serum samples in three disease categories are shown. Arrows ( $\leftrightarrow$ ) indicate mean normal level. The values for infectious disease and hepatic cirrhosis were determined by the isotopic immune inhibition technic and the values for trypanosomiasis by the antibody-agar plate technic.

the pattern of normal or increased serum IgA found in hepatic cirrhosis.

*Nephrotic syndrome.* In five patients with nephrosis, the average serum levels of IgG and IgA were low, whereas the IgM was slightly increased. IgM macroglobulins are not usually found in the urine of patients with the nephrotic syndrome, although 7 S IgG and IgA globulins are characteristically present (11). The 18 S IgM macroglobulins do not escape into the urine because of their large molecular size. Thus, the observed serum protein concentrations are consistent with loss of IgG and IgA via the damaged kidney without loss of serum IgM macroglobulins.

*Protein-losing enteropathy.* Among the 12 patients with protein-losing enteropathy, marked decreases were apparent in all three serum immunoglobulin concentrations. These levels reflect the

generalized serum protein loss into the gastrointestinal tract seen in this disease (12, 13). The levels of IgG and IgA globulins were relatively lower than the IgM globulin values. This is not statistically significant.

*Lupus erythematosus.* Seven sera from patients with systemic lupus erythematosus were analyzed. All immune globulins were affected equally. Slight increases in IgG were accompanied by rises in IgA and IgM levels. This pattern indicates that this disorder is associated with a diffuse stimulation of the immune system, although increases were not so great as those observed with infection or cirrhosis. The finding of a predominance of Type K to Type L molecules was an interesting observation that must be checked with a larger number of samples to determine whether this is truly characteristic of the disease.

*Subacute nephritis.* Analyses on one patient with progressive, fatal nephritis are reported because the total serum immunoglobulin level exceeded 5 g per 100 ml. Most of this increase was in the IgG fraction and was normally divided between Type K and L (I and II) molecules.

*Agammaglobulinemia.* Six male children with congenital agammaglobulinemia were tested for serum IgG, IgA, and IgM. The serum levels of all three components were very low in these patients. The IgA and IgM were both less than 5% of the normal adult value. The IgG levels were more variable (1 to 25% of normal), perhaps due to differences in productive capacity of individuals and differences in gamma globulin replacement therapy.

*Ataxia telangiectasia.* Quantitative analysis of eight sera revealed undetectably low levels of IgA in seven patients and a high level (twice normal) in one patient. The IgG and IgM levels in all patients were normal. The abnormality in five of these patients has already been reported by Young, Austen, and Moser (14). The present data put such observations on a quantitative basis. Our measurements, however, do not clarify the nature of the association between the neurological disorder and the serum IgA aberrations (14-16). Thymic malfunction has been proposed as a possible factor in ataxia telangiectasia (15). Semiquantitative (17, 18) and quantitative (19) measurements of serum immunoglobulins in neonatally thymectomized mice and rats, however, failed to reveal any deficiency of IgA (or other immunoglobulin), although neonatal thymectomy produced lymphopenia, wasting, and death. Thus, there is no correlation between the serum protein changes of ataxia telangiectasia in man and of neonatal thymectomy in rodents.

*Hodgkin's disease and leukemia.* Sera from 11 patients with Hodgkin's disease were evaluated. A 20% increase in IgG was noted. IgA was decreased. These changes are not pronounced, and no change was apparent in serum IgM level. The findings are compatible with the evidence that patients with Hodgkin's disease do not have significant impairment of serum antibody production (20).

The sera of 14 patients with chronic lymphocytic leukemia had decreased levels of all three immunoglobulins. These findings are in accord

with the decrease of electrophoretically determined gamma globulin in such patients (21-26). This also correlates well with decreased antibody production and increased incidence of infection reported in chronic lymphocytic leukemia (21-26). The finding of relatively lower levels in the IgM and IgA groups is examined further in the Discussion.

Analysis of sera from ten patients with chronic myelogenous leukemia revealed only a decreased IgA level (about 70%) with normal IgG and IgM concentrations. Cells of the myelogenous series are not thought to be involved in antibody production, and patients with chronic myelogenous leukemia generally have normal antibody production (27).

Similarly, among patients with acute lymphocytic leukemia, the only abnormality was a decrease in IgA. The basis for the lowered level of IgA is not clear. It does not seem to be associated with any immune deficit. Indeed, marked deficiency of the serum IgA has been found in otherwise normal individuals (28, 29).

Analysis of sera from ten patients with acute myelogenous leukemia revealed an increased serum IgG. No change was noted in the other immune globulin groups. Normal or slightly elevated gamma globulin on paper electrophoresis has been observed in patients with acute myelocytic leukemia (30).

*Multiple myeloma and macroglobulinemia.* Quantitative studies in these diseases confirmed the well-known elevation of anomalous serum protein—G( $\gamma$ ) myeloma protein, A ( $\beta_{2A}$ ) myeloma protein, or M (Waldenström's) macroglobulin (Table I). The greatest increase over normal values was observed with macroglobulinemia where the serum IgM concentration averaged 24 times greater than normal.

The serum levels of normal immunoglobulins were decreased in these diseases. With G( $\gamma$ ) myeloma, the serum IgA and IgM levels were less than 20% of normal. The decreases in IgG and IgA, however, were less marked in macroglobulinemia (Table I).

Quantitative measurement of normal immunoglobulins of the same class as the anomalous protein, i.e., of the normal IgG in the presence of G( $\gamma$ ) myeloma protein, has been difficult. Immunoelectrophoretic technics have revealed a de-

TABLE II  
*Type K and L immunoglobulin  
 levels in myeloma sera*

Anomalous protein in serum*	Type K (I)	Type L (II)	K/L(I/ II) ratio†
	<i>mg/ml</i>	<i>mg/ml</i>	
G MP—Type K	50.0	0.4	167.0
A MP—Type K	35.0	2.0	70.0
M-macro—Type K	Increase	1.8	
G MP—Type L	0.8	68.0	0.01
A MP—Type L	2.7	80.0	0.03
M-macro—Type L	3.5	Increase	

\* G MP = G myeloma protein; A MP = A myeloma protein; M-macro = M-macroglobulin.

† Normal ratio = 1.86 (see Table I).

crease in the normal IgG components (31–33). Analysis by serum chromatography, with DEAE-cellulose columns, can also be used to measure the normal IgG in some sera containing G myeloma proteins (34). In such studies the normal IgG component was again found to be decreased.

Measurements of the levels of Types K and L (Types I and II) showed a marked abnormality in the ratio of Type K:L (I:II) immunoglobulins in myeloma serums (Table II). This abnormal ratio is caused by the large amounts of myeloma protein that are either Type K (I) or Type L (II) (35–38) and by the reduced amounts of normal immunoglobulin. The remaining immunoglobulins of the type not represented in the myeloma protein are found to be reduced (Table II). In the first serum listed in Table II, the total amount of type L was 0.4 mg per ml, i.e., about 10% of the normal value obtained by this test (8). Since this figure includes whatever normal IgG is Type L, the low serum level clearly indicates that the normal IgG of Type L is markedly reduced in the serum containing large amounts of G myeloma protein of Type K.

### Discussion

Normal serum immunoglobulin levels represent a balance between immunoglobulin synthesis and catabolism. Studies in germfree animals indicate that very low immunoglobulin levels are compatible with normal life and immune function (39). Immunoglobulin synthesis increases (40) and serum levels rise after exposure to the normal, nonsterile environment that contains bacteria, other organisms, and food products that are antigenic. Thus in the adult animal and, pre-

sumably, in man the antigenic experience of a nonsterile environment plus metabolic factors in the host determine the level of each serum immunoglobulin.

Disease may disturb both the environmental and metabolic factors in the immunoglobulin balance. Elevated protein concentrations are found in infections with increased antigenic stimulation. Inadequate synthesis of all immunoglobulins results in the agammaglobulinemia syndrome. Impaired synthesis of only part of the immunoglobulin population results in selective immunoglobulin deficiencies (dysgammaglobulinemia). Gross loss and catabolism of serum protein in protein-losing enteropathy cause a reduction in all immunoglobulins. The selective loss of smaller proteins in the nephrotic syndrome, however, causes a lowering of serum IgG and IgA, whereas serum IgM is normal or increased.

Reduced rates of normal immunoglobulin synthesis (13, 41) and lowered serum levels characteristically occur with plasmocytic and some lymphocytic malignancies. This defect does not depend on the type or amount of anomalous protein and is found in chronic lymphocytic leukemia (42) in the absence of any myeloma protein. The marked hypogammaglobulinemia is a specific manifestation of certain types of malignant disease and is not found with most malignancies. The means by which plasmacytic malignancy reduces normal immunoglobulin synthesis, however, is obscure. The effect does not seem to be mediated by myeloma protein.

Our studies in chronic lymphocytic leukemia indicated that the serum IgM and IgA levels were more markedly reduced (to about 25% and 45% of normal) than were the IgG globulins (about 80% of normal). Although this could reflect a differential effect of the disease on synthesis of specific immunoglobulin components, the differences can be explained on the basis of catabolic differences between these proteins. The IgM (13) and IgA (43) proteins are catabolized at a fairly rapid rate (i.e., about 10 to 15% of the total body pool each day), and the rate of catabolism is not affected by the serum level of these proteins. The IgG proteins are catabolized at a slower rate (about 3% per day) (41, 44), and the rate of catabolism depends on the serum IgG level. At high serum IgG levels, catabolism



is rapid; at low serum levels, catabolism is reduced (41, 45). In chronic lymphocytic leukemia, the rate of synthesis of all immunoglobulins falls, but the lowering of the serum level of IgG is partly compensated by a reduced rate of IgG catabolism (i.e., 1 to 2% per day), whereas IgA and IgM continue to be catabolized rapidly. Thus serum measurements in chronic lymphocytic leukemia show a more profound reduction in IgM and IgA than in IgG levels.

The marked increase of IgM in trypanosomiasis is of diagnostic (9) and immunologic significance. Particulate antigens may excite more IgM than IgG antibody response. Also some antigenic substances, such as the somatic O antigens of *Salmonella*, excite 18 S antibody response, in contrast to the 7 S antibody induced by H flagellar antigens (46, 47). It remains to be determined whether IgM antibody is increased because of the size, chemical composition, anatomic distribution, metabolic fate, or some other feature of the antigen. Further investigations of the antigens of the organism and of the immune response in trypanosomiasis may help to clarify this.

Less is known about the functional role of serum IgA than of IgG and IgM. Study of the aberrations of disease, however, may help to explain the role of this immunoglobulin. The marked increase with Laennec's cirrhosis and the severe deficiency (or considerable increase) in ataxia telangiectasia (14-16) are provocative but unexplained observations.

Survey studies can only detect the most obvious immunoglobulin disorder. More subtle and, perhaps, more meaningful observations can be made by serial studies in individual patients with immunoglobulin disorders where careful clinical observations permit more precise evaluation of the role of disease, therapy, and complications.

A quantitative study of serum immunoglobulins in acute leukemia has been carried out in 37 patients followed throughout treatment with intensive combination chemotherapy (48). The IgA levels tended to be low, but the IgG and IgM levels were normal in the untreated patients, as noted here. Within 2 to 4 weeks after the onset of chemotherapy, the IgG level fell to approximately two-thirds of the normal level and then remained at the new lower level. IgA levels were not changed, and IgM levels varied but

tended to increase. These observations indicate that immunoglobulin synthesis continues under circumstances where primary antibody response may be markedly reduced.

Many serum protein changes in disease have been described by zone electrophoresis (49) on supporting substances such as filter paper and cellulose acetate. Paper electrophoresis, however, does not reveal the changes in specific immunoglobulins that can be detected by immunochemical technics. Immunoelectrophoretic studies of the IgG, IgA, and IgM components in a variety of diseases have been reviewed by Burtin (31). Immunoelectrophoretic analyses shown in Figure 1 illustrate some of the principal changes recorded in the present paper. Since immunoelectrophoresis is a semiquantitative technic, the quantitative immunochemical methods, used in this and other studies (50-52), have provided more specific knowledge of the serum immunoglobulin changes in disease.

### Summary

Quantitative IgG ( $\gamma$ G-, 7 S  $\gamma$ <sub>2</sub>-globulin), IgA ( $\gamma$ A-,  $\beta$ <sub>2A</sub>-globulin), and IgM ( $\gamma$ M-, 18 S  $\gamma$ <sub>1</sub>-macroglobulin) measurements were made in serum from 224 patients. The levels of Type K (Type I) and Type L (Type II) immunoglobulins were also determined.

Increases of one or more immunoglobulins were noted in many disorders. Chronic infections characteristically showed increased IgG. Trypanosomiasis showed a remarkable increase of IgM. In Laennec's cirrhosis IgA increases were especially notable. Quantitative abnormalities of serum IgA (both high and low levels) were confirmed in ataxia telangiectasia.

The nephrotic syndrome usually showed low serum IgG and IgA levels with normal or slightly elevated IgM. This difference is presumed to relate to the differential loss of the smaller immunoglobulins via the kidney and urine. In protein-losing enteropathy, however, all serum immunoglobulins (IgG, IgA, and IgM) were low, indicating that all immunoglobulins were lost at the same rate.

The lowest serum immunoglobulin concentrations were found in agammaglobulinemia. All immunoglobulins were reduced in many sera of

chronic lymphocytic leukemia, but the serum IgM was relatively lower than the IgG. This difference is compatible with differences in the catabolism of the separate classes of immunoglobulin.

The anomalous proteins of multiple myeloma and Waldenström's macroglobulinemia were class specific (IgG, A, or M) and type specific, i.e., Type K (I) or Type L (II). The remaining immunoglobulins in the serum of these patients were decreased.

Type K (Type I) and Type L (Type II) immunoglobulins were identified in all sera. In multiple myeloma and macroglobulinemia the normal ratio of Type K:Type L immunoglobulins was markedly altered by the myeloma protein or macroglobulin.

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