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MEDICAL PROGRESS

THE GAMMA GLOBULINS AND THEIR CLINICAL SIGNIFICANCE (Continued)*

III. Hypergammaglobulinemia

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Hypergammaglobulinemia

The gamma globulins normally comprise 11 to 14 per cent of the total serum proteins, with a normal range of 600 to 1100 mg. per 100 ml. in older children and adults. American Negroes have slightly higher normal values than whites.[81,82] Although no classification could be complete at this time, many diseases in which hypergammaglobulinemia has been noted are listed in Table 1, with an indication of the diseases in which the most marked elevations are found. High globulin values may be diagnostic clues. In one large series about 50 per cent of patients with a serum total globulin of 5.0 gm. per 100 ml. or higher had multiple myeloma, sarcoidosis or a connective-tissue ("collagen") disease.[91]

Infection. Acute infections first cause a rise in alpha globulins and a fall in serum albumin.[92] It is only when the infection is sufficiently prolonged or produces a local lesion, such as an abscess or endocarditic focus from which antigenic material and breakdown products are absorbed, that a really significant rise in gamma-globulin levels occurs. Chronic granulomatous infections, such as tuberculosis, leprosy, lymphogranuloma venereum, kala-azar and visceral larva migrans, are most often associated with marked hypergammaglobulinemia. The rise may reflect the formation of specific antibody or nonspecific "inert" gamma globulin or both. In rheumatic fever the rise has been correlated in time with the appearance of antibody in the blood.[93] In most chronic purulent and granulomatous infections it seems likely that the increased gamma globulin contains both specific and nonspecific gamma globulins. However, this needs to be re-examined in the light of the suggestions of Najjar and Fisher[27] and Gajdusek[94] that complexes between antigen and antibody and antigen and tissues and antibody are formed and act as additional new antigens in the process of immunization resulting from infection.

Recently, a group of children have been recognized with extreme hypergammaglobulinemia, recurrent infections (especially of the lungs and skin with staphylococci, proteus and pseudomonas organisms) and, in some cases, hepatosplenomegaly and generalized lymphadenopathy, associated with neutropenia, eosinophilia and monocytosis.[95] Serum gamma-globulin levels were high, ranging from 1.9 to 4.5 gm. per 100 ml., and were reflected histologically by a diffuse infiltration of plasma cells in the bone marrow and other organs. Reports from a number of pediatric clinics have confirmed the existence of such a syndrome, but the evidence suggests that it has a number of different

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TABLE 1. *Conditions in Which Hypergammaglobulinemia Has Been Noted.**

I. INFECTIONS
- A. *Bacterial*
  1. Streptococcal, especially in subacute bacterial endocarditis, rheumatic fever & acute glomerulonephritis
  2. Severe staphylococcal infections
  3. Advanced tuberculosis, pulmonary and extrapulmonary
  4. Lepromatous leprosy
- B. *Spirochetal*
  1. Syphilis (all 3 stages)
- C. *Viral*
  1. Lymphogranuloma venereum†
  2. Infectious mononucleosis
  3. Psittacosis
- D. *Rickettsial*
  1. Typhus
- E. *Fungal*
  1. Histoplasmosis
- F. *Protozoal*
  1. Kala-azar†
  2. American mucocutaneous leishmaniasis
  3. Malaria
- G. *Helminthic*
  1. Visceral larva migrans (toxicara canis or catis)†
  2. Trichinosis
- H. *Chronic infection*† of nonspecific etiology

II. HYPERIMMUNIZATION†

III. LIVER DISEASE
- A. *Portal cirrhosis*†
  1. Laënnec's cirrhosis
  2. Postnecrotic cirrhosis
- B. *Acute viral hepatitis*
- C. *Toxic hepatitis (such as that from arsenic)*
- D. *Chronic liver disease in young women with extreme hypergammaglobulinemia ("lupoid hepatitis")*†
- E. *Cholangiolitic hepatitis*
- F. *Biliary cirrhosis (late)*

IV. SEVERE MALNUTRITION
- A. *Kwashiorkor*
- B. *Nutritional-recovery syndrome*†

V. NEOPLASMS
- A. *Multiple myeloma*†
- B. *Leukemia (monocytic, chronic myelogenous & chronic lymphatic)*
- C. *Lymphomas*
  1. Hodgkin's disease
  2. Lymphosarcoma
  3. Reticulum-cell sarcoma
- D. *Primary carcinoma & sarcoma, with or without metastases*

VI. PARAPROTEINEMIAS & DYSPROTEINEMIAS
- A. *Macroglobulinemia*†
- B. *Cryoglobulinemia*†
- C. *Benign hyperglobulinemic purpura*†
- D. *Amyloidosis*

VII. DISEASES POSSIBLY ASSOCIATED WITH HYPERSENSITIVITY
- A. *Connective-tissue diseases ("collagen" diseases)*
  1. Disseminated lupus erythematosus†
  2. Scleroderma†
  3. Rheumatic fever
  4. Rheumatoid arthritis
  5. Ankylosing spondylitis
  6. Periarteritis nodosa
  7. Sjögren's syndrome
- B. *Others*
  1. Serum sickness
  2. Acquired immune hemolytic anemia
  3. Autoimmune thyroiditis; Hashimoto's disease.
  4. Erythema nodosum

VIII. GRANULOMAS
- A. *Sarcoidosis*†
- B. *Chronic beryllium poisoning*

IX. DERMATOLOGIC DISORDERS
- A. *Pemphigus vulgaris (late)*
- B. *Extensive dermatitis (such as exfoliative dermatitis)*
- C. *Burns*

*Compiled mainly from reviews of electrophoretic alterations of plasma proteins in disease.[83-90]

†Often associated with striking elevations of gamma-globulin fraction.

causes, among which may be congenital neutropenia, the hypergammaglobulinemia being the result of prolonged and repeated infections.

Liver disease. An elevated serum gamma globulin is one of the most common abnormalities in liver disease. The rise occurs both in the $gamma_2$ and in the $gamma_1$ globulins[96] and seems to reflect the severity of the mesenchymal reaction, producing fibrosis more than parenchymal destruction in the liver.[97] Since the catabolism of gamma globulin is increased in cirrhosis[98] the high levels must be achieved by a marked increase in the rate of synthesis. The height of the gamma-globulin level can be directly correlated with the number of plasma cells in the bone marrow.[99] The highest levels occur in cirrhosis; values over 4.0 gm. per 100 ml. are highly suggestive of either the postnecrotic type or the "lupoid" type seen in young women, characterized by insidious onset, high fever, arthritis and plasma-cell infiltration of the liver.[100] Although the serum level usually returns to normal with the cessation of activity in cirrhosis, it may remain elevated without progression of the disease.[97] Moderate increases of serum gamma-globulin levels are seen in toxic and viral hepatitis. Small increases occur late in obstructive jaundice and in primary hepatic carcinoma. Elevations are unusual in metastatic, lymphomatous and leukemic infiltration of the liver. A progressive rise in gamma globulin after an attack of viral hepatitis may be the only indication of the development of postnecrotic cirrhosis. Jaundice in the absence of an elevated gamma globulin speaks against cirrhosis and favors a diagnosis of extrahepatic biliary obstruction, fatty change, metastatic carcinomatosis or lymphomatous infiltration.[97]

"Liver-function" tests are more the result of disproportion among the serum-protein fractions than of disturbed liver function per se. Positive tests of cephalin cholesterol and zinc sulfate flocculation reflect either the presence of abnormal gamma globulins, as in infectious mononucleosis and cryoglobulinemia, or the elevation of normal serum gamma globulins out of proportion to the stabilizing influence of albumin and a lipid-rich alpha globulin, as in cirrhosis.[101] The thymol turbidity test, on the other hand, reflects a rise in both the beta and the $gamma_2$ globulins predominantly.[102] Recent evidence points to the importance of the most slowly migrating (most basic) fraction of the $gamma_2$ globulins in causing abnormal results in both the cephalin-cholesterol and the thymol turbidity tests.[103]

Malnutrition. Severe malnutrition and kwashiorkor often produce high serum gamma-globulin levels.[104] Malnourished infants are susceptible to overwhelming infection and show an associated impairment of antibody response to antigenic stimulation.[105] Three to six weeks after a malnourished infant is started on proper nutritional therapy, the nutritional-recovery

syndrome may appear.[106] This syndrome is characterized by hepatomegaly, portal hypertension (with ascites in 50 per cent of cases), hypertrichosis of the shoulders, thighs and face, a progressively rising serum gamma globulin and an increasingly lower serum albumin. The total protein may be normal owing to the high serum gamma globulin. The signs and symptoms of the syndrome increase slightly during the two weeks after their onset, but disappear almost completely within two to four months after their onset.

"Collagen" diseases. Among these, systemic lupus erythematosus and scleroderma cause the greatest increase in serum gamma globulin.[107] In the former an elevated gamma globulin is found in about 60 per cent of patients[108] and may precede the onset of symptoms in certain familial cases.[109] The L.E. factor, an abnormal gamma globulin,[110] is found in most cases, and a biologic false-positive Wassermann test, also due to an abnormal gamma globulin, occur in about 40 per cent of cases.[107] A high gamma globulin favors a diagnosis of systemic lupus erythematosus over dermatomyositis, in which normal or only slightly elevated levels occur.[107] In rheumatoid arthritis considerably increased values appear late in the process, unless intercurrent infection or systemic organ involvement, as in Felty's syndrome and Sjögren's disease, causes an early rise.[111] Failure of treatment with cortisone, ACTH and prednisone to revert persistently high gamma-globulin levels toward normal suggests that control of the disease is unlikely.[112]

Abnormalities of the gamma globulins play a major part in the diagnostic tests used in rheumatoid arthritis. The rheumatoid factor, which causes the agglutination of gamma globulin and various particles coated with gamma globulin such as sheep red cells, polystyrene latex and bentonite, is itself both a euglobulin and a gamma globulin.[113] Recently, it has been further characterized as a protein of high molecular weight with a sedimentation constant of 22, which may be dissociated into gamma globulin of normal molecular weight (7 S) and a macroglobulin of a size found in normal serum (19 S).[114] Both the 22-S and 19-S protein fractions have serologic activity.[114] Although the 19-S component contains antibodies in other pathologic states, it is not yet known whether the rheumatoid factor is a true antibody.[113]

Neoplasms. In 3 of 4 cases of multiple myeloma, hyperglobulinemia is present; in 97 per cent of cases, electrophoretic analysis of serum and urine will reveal one or more abnormally increased globulin fractions.[115] In serum this myeloma globulin is usually found in the $gamma_2$ locus, but it may migrate with the $gamma_1$, the beta or the alpha globulins. The urinary globulin may have the same electrophoretic mobility as the abnormal serum globulin, but if it is a Bence-Jones protein, it usually has a different mobility.[116] In contrast to the normal globulin fractions and to most cases of hyperglobulinemia the myeloma globulin has a narrow base and a sharp peak when subjected to electrophoresis, indicating unusual electric homogeneity.[117] Myeloma globulin also often shows similar homogeneity on ultracentrifugal analysis, which, in most cases, gives a molecular weight, similar to that of normal gamma globulin, of 160,000.[118] Immunologically, the myeloma globulin of each patient seems to be related both to normal gamma globulin and to myeloma proteins from other patients; yet it also possesses certain physical, chemical or immunologic properties that make it unique.[119] The cell associated with the abnormal globulin is the plasma cell in most cases. However, similar globulins have been found in certain lymphomatous diseases such as lymphosarcoma and chronic lymphocytic leukemia, in which the lymphocyte predominates.[120]

When the abnormal globulin is in the $gamma_1$ or beta position, a striking deficiency of normal $gamma_2$ globulin is often seen.[121] The antibody response to antigenic challenge may be significantly diminished in myeloma, and isohemagglutinins may be absent.[122] These observations have been linked to the high susceptibility of patients with myeloma to recurrent bacterial infections, particularly those due to the pneumococcus. However, for reasons still unexplained, even the complete absence of gamma globulin in some patients with myeloma does not predispose to infection.[123] The rate of catabolism of the abnormal globulin is faster than normal, indicating a very high rate of synthesis to maintain the elevated serum concentration.[124] The rate of albumin catabolism is normal, so that a diminished rate of synthesis must account for the hypoalbuminemia frequently seen.[124] Whether the globulin formed excessively is one normally found in small amounts in the serum or an abnormal protein is not known. Presumably, the deficient synthesis of other serum protein fractions, including antibody, is a result of the diversion of available amino acids to the synthesis of the abnormal globulin.

Aside from myeloma, most neoplasms of the lymphoid system produce only a moderate increase in gamma globulin and rarely may even be associated with hypogammaglobulinemia. Hypergammaglobulinemia may occur in acute leukemia, subacute lymphocytic leukemia and about 25 per cent of cases of chronic lymphocytic leukemia,[125] usually in proportion to the severity and progress of the disease, or after prolonged urethane therapy.[126] It is also seen in over 25 per cent of cases of Hodgkin's disease but tends to fall markedly in the terminal phase.[127] It may also occur in mycosis fungoides and reticulum-cell sarcoma.[128]

The increased susceptibility to infection seen in leukemia, particularly of the lymphatic type, is more often correlated with severe neutropenia than with an antibody-deficiency syndrome. Likewise, there is no evidence that the tendency to bacteremic infections,

noted in children who have had splenectomy, is due to any change in gamma-globulin metabolism.

Macroglobulinemias

Like the myeloma globulins, the macroglobulins form a narrow, well defined band on electrophoresis and may migrate with the alpha$_2$, beta or gamma globulins, but most commonly migrate with the gamma globulins.[129,130] The macroglobulins may be dissociated into smaller units the size of normal gamma globulins by the addition of sulfhydryl groups (for example, mercaptoethanol), which presumably split the disulfide bonds binding these units together.[131] Whether these smaller 7-S gamma globulins are identical to normal 7-S gamma globulins, or different, is unknown.[131-134] In normal persons 3 to 5 per cent of the total proteins are macroglobulins with a sedimentation constant of 19 or more. When macroglobulins constitute 20 per cent or more of the total protein and when the clinical picture is characteristic, the diagnosis of Waldenström's macroglobulinemia can be made. A definite diagnosis can be made only by ultracentrifugal analysis, although the Sia–Brahmachari test, in which 1 volume of serum is diluted sixteen to twenty times with distilled water to precipitate the euglobulins, may sometimes be positive.[135] However, this test is not reliable, since false-positive and false-negative results are frequently observed. The bone marrow is often, but not always, infiltrated with atypical small lymphocytes, which are presumably the source of the macroglobulins. The erythrocyte sedimentation rate is rapid, and pancytopenia is common.

Clinically, macroglobulinemia tends to occur principally in elderly males who may present the following signs: dyspnea, edema, weakness and weight loss; petechiae, purpura and mucosal bleeding; and painless lymphadenopathy and hepatosplenomegaly.[129] It may be associated with other hypergammaglobulinemic diseases but is rarely, if ever, seen with multiple myeloma. As in myeloma, there may be a history of repeated infections[136] and an associated cryoglobulinemia.[135]

Cryoglobulins become insoluble in the cold and redissolve as the temperature is raised. Exposure to low temperature may result in intravascular precipitation, with Raynaud's phenomena at low concentrations, and secondary thrombosis and ischemia with necrosis of the tissues supplied at higher concentrations.[137] When cryoglobulins are present in significant concentration, the patient is most often suffering from multiple myeloma, but cryoglobulinemia may occur with a wide variety of other underlying diseases, or by itself.[138] Electrophoretically, it may be found in any globulin fraction from the gamma$_2$ to the alpha$_2$, but it is most commonly a gamma$_1$ globulin. Its molecular weight may vary from 160,000 (7 S) to 1,000,000 (19 S). It may have the property of cold agglutination.[139] Differentiation between cold agglutinins and cryoglobulins can often be made by determination of a sedimentation rate at 4°C.; the rate will be increased in the presence of cold agglutinins, owing to clumping of the red cells, and decreased if there is precipitation or jelling of the cryoglobulins.

Waldenström's hyperglobulinemic purpura is characterized by benign, recurrent, nonthrombocytopenic purpura, especially of the lower extremities, with a broad-based, diffuse elevation of the gamma globulin and a high erythrocyte sedimentation rate. Seventy-five per cent of cases occur in women. Diagnosis requires the exclusion of systemic diseases associated with hyperglobulinemia and purpura, such as systemic lupus erythematosus, cryoglobulinemia and macroglobulinemia.[140]

Primary acquired hemolytic anemia may be associated with hyperglobulinemia. Cold hemagglutinins associated with the syndrome of chronic hemolytic anemia and paroxysmal cold hemoglobinuria usually migrate on starch electrophoresis as gamma$_1$ globulins, but may migrate with the beta or gamma$_2$ globulins.[141] Cold agglutinins may not always be associated with the major fraction of the gamma globulins; the peak of the component may be in the gamma$_2$, and the hemagglutinin activity in the gamma$_1$ fraction. Cold agglutinins are macroglobulins (19 S) and may be antibodies.[141] The warm incomplete antibodies, on the other hand, appear to be gamma$_2$ globulins of normal gamma-globulin molecular weight (7 S).[141] Gamma-globulin levels are only moderately increased in the latter type unless it is secondary to some other cause, such as systemic lupus erythematosus.

Hashimoto's disease is thought to be due to the formation of autoantibodies against a component of the person's own thyroid gland, resulting in lymphadenoid goiter.[142] Serum gamma globulins may be slightly or moderately increased in some cases.[143] Levels may return to normal during the six months after resection of the goiter.

Approximately two thirds of the patients with *sarcoidosis* will have hypergammaglobulinemia, often of a marked degree.[144] Moreover, such patients show a hyperactive anamnestic serum-antibody response to secondary antigenic stimulation, although the response to primary immunization may be severely impaired.[145] Furthermore, there is often a cutaneous anergic reaction to a wide variety of antigens that normally induce a delayed type of skin hypersensitivity.[146] This has been correlated with a decrease in the amount of antibody within the lymphocytes producing a delayed type of response rather than a decrease in the number of lymphocytes.[147]

Primary "atypical" amyloidosis may cause a high, normal or low serum gamma globulin.[148] When amyloidosis complicates multiple myeloma, the hypergammaglobulinemia may return to normal levels.

(To be concluded)

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