Auto-Immunity Against IgG

Study of a Girl who had Undue Susceptibility to Infection
and an IgM-IgG Euglobulin Complex in her Serum

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Extract

A girl who had had severe recurrent infections from the seventh year of life and who died from the sequelae of extensive bronchiectasis at 18 years of age was studied. The serum of the patient contained a large amount of protein that could be isolated because of the character of the euglobulin. Ultracentrifugation showed that the serum consisted of two fractions with sedimentation constants of 17.4 S and 26 S, respectively. When this euglobulin had been removed, IgM and IgG were no longer identifiable in the serum, although increased concentrations of IgA were present. The macroglobulin was found to contain IgM and IgG determinants that showed antirabbit and antihuman IgG antibody characteristics. Specificity against a particular type of IgG was absent. The two components could not be dissociated in an acid medium or by 6 M urea. Separation by 0.1 M mercaptoethanol, however, yielded two fractions, an 11 S fraction containing both IgM and IgG determinants and a 7 S fraction containing IgM determinants only. It was concluded that the presence of IgM and IgG determinants in the euglobulin was caused by antibody activity of the IgM directed against the IgG of the patient.

Speculation

Excessive susceptibility to bacterial infection is usually due to deficient antibody production. The present study, however, showed that symptoms of the antibody deficiency syndrome may also occur when antibody production is at least partly unimpaired. The macroglobulin present in serum displays antibody activity against IgG. It is speculated that auto-immunization against the IgG of the patient had occurred and that the macroglobulin would bind any IgG antibodies produced during infection. A clinical picture of the antibody deficiency syndrome thus results. The question of whether this auto-immunization is an uncommon feature should be explored. It is probable that production of auto-antibodies could have been a factor in various cases of dysimmunoglobulinemia reported previously.

Introduction

Since 1952, when BRUTON [2] described a clinical picture of congenital agammaglobulinemia in a child with recurrent infections, several causes of the antibody

deficiency syndrome have been identified. Impairment of the defense mechanism present in every case may have been congenital or acquired. If it had been caused by inadequate production of lymphocytes, hypoplasia of the thymus and lymphopenia would usually have

been present [18]. There also may have been an inability to produce a sufficient number of immunoglobulins or specific antibodies in the presence of a normal lymphocyte count (hypogammaglobulinemia and dysimmunoglobulinemia) [8, 18, 21]. KRETSCHMER *et al.* [9] recently reported the case of a girl in whom recurrent infections were caused by the presence of an auto-antibody, a lymphocytotoxic antibody, and in whom lymphopenia constantly recurred.

The present study concerns a child showing an antibody deficiency syndrome in which a large amount of macroglobulin containing IgM and IgG determinants was present in the serum. No free IgG was identifiable. This macroglobulin was found to show antirabbit and antihuman IgG antibody characteristics. It is believed that the recurrent infections in this child were also caused by an auto-antibody that was, however, directed against the IgG of the patient. The present investigation, in conjunction with that by KRETSCHMER *et al.* [9], shows that auto-immunization may also be the cause of an impaired defense mechanism.

Case Report

The patient was born on March 14, 1945, and was the eldest of five children. Delivery was normal; birth weight was 4 kg. For a few days when she was eleven months of age, she showed symptoms of tetany, which disappeared after treatment with calcium. In 1952, bronchitis was followed by pneumococcal meningitis and suppurative otitis media, from which pyogenic streptococci were isolated. She developed impetigo during convalescence. The erythrocyte sedimentation rate showed a marked increase throughout this period.

In 1953, the patient twice had pneumonia and otitis media, followed by pneumococcal meningitis. She was surgically treated for sinusitis and a mastoidectomy was performed. The cause of the extremely high rate of erythrocyte sedimentation (126–136 mm/h) was investigated in 1954. Liver and kidney functions were unimpaired. Total serum protein was 7.55 g/100 ml; albumin 2.67, α -globulin 0.6, β -globulin 0.73 and γ -globulin 3.55 g/100 ml. The fibrinogen level was 0.47 g/100 ml. L.E. cells were absent; the ASO titer was 640 U, and the titer of the Rose-Waaler test was 1:128. Bronchiectasis was shown to be present in the left lower lobe in 1955, and this lobe was removed in October of that year. Healing was delayed by purulent wound infection.

The patient had several severe pulmonary infections during the period 1955 to 1961; she became cyanotic and clubbed fingers developed. Bronchiectasis was found to have recurred in both lungs. *Haemophilus influenzae* were isolated from the sputum several times. She was seen by the present investigators for the first time in

May 1960. Height was 145 cm and weight was 35.8 kg. She showed dyspnea and mild cyanosis, thoracic kyphosis, and clubbed fingers. Prurigo acne necroticans were present on the trunk and face, and indurated lymph nodes the size of cherries were palpable below the mandible, in the axillae, and in the groin. X-ray examination revealed extensive infiltration in the lungs, particularly in the right middle lobe. The other organs did not show any changes. The spleen was not enlarged. A large quantity of sputum (100 ml daily) was expectorated; *Haemophilus influenzae* and pneumococci were isolated from the sputum.

Laboratory Studies

The erythrocyte sedimentation rate was 92–95 mm/h; Hb 1.11 g/100 ml; hematocrit 35%; leucocyte count 11,000, including 10% of stab cells, 45% of polymorphonuclears, 35% of lymphocytes, 2% of eosinophils, and 8% of monocytes.

Serum electrolytes, like liver and kidney functions, were normal. Serum iron was 20 μ g/100 ml; saturation rate was 8%. Duodenal juice contained enzymes in normal quantities. Concentration of sodium in sweat was 43 mEq/l; fat absorption coefficient was 95%.

Total serum protein was 6.38 g/100 ml; albumin 1.2, α_1 -globulin 0.55, α_2 -globulin 0.97, β -globulin 0.72, and γ -globulin 2.94 g/100 ml. Pulmonary function tests showed that tidal air was only 430 ml, vital capacity was 730 ml, and FEV₁ (forced expiratory volume in first second) was 50%. Arterial oxygenation was 90%.

In view of the clinical condition of the child, the antibody-producing capacity could be studied only to a limited extent. The results are listed in table I. A striking feature was the high Forsmann antibody titer.

Treatment and Course of the Disease

The undue susceptibility to infection was accompanied by marked changes of the immunoglobulins. Although the nature of these changes was not understood at the time, treatment with γ -globulins was believed to be essential. The patient was treated with antibiotics and physical therapy for the bronchiectasis and was given 15 ml of a 16% preparation of γ -globulin monthly. Initially, this treatment produced some improvement, but pulmonary infections increased rapidly and cor pulmonale resulted. She died from pulmonary lesions and heart failure on February 9, 1963.

Morbid Anatomy

Resected left lower lobe (1955). There was extensive bronchiectasis and suppurative inflammation of the walls of the bronchi. A large number of plasma cells and Russell bodies were found to be present in the mucosa; these contained PAS-positive material. There

were many normal reaction centers in the peribronchial lymph nodes. A large number of plasma cells were observed at the margins of these centers, as well as in the lymph sinuses of the medulla.

Sputum (1962). Plasma cells were also observed several times among the large numbers of polynuclear leucocytes.

Bone marrow (1962). This presented a normal appearance. A very large number of plasma cells were observed, occasionally arranged in groups or nests. Most plasma cells were abnormally large because of an increase in protoplasm. The nuclei showed normal radial structure, and binuclear cells were observed. The presence of a granular substance in the protoplasm suggested that some material was being stored in several cells. Electron microscopic studies showed that a large number of ribosome-bearing cisterns of the endoplasmic reticulum were situated about the eccentrically placed nucleus; these cisterns were markedly dilated. The spaces within the membranes were filled with a large amount of fairly osmiophilic substance. The other structures were normal.

Necropsy (1963). The findings resembled features observed in heart failure; the heart was enlarged and dilated. The kidneys did not show any marked changes. Both lungs showed extensive bronchiectasis in all regions and infiltration in several areas of atelectasis. Microscopic examination again revealed the presence of a large number of infiltrations consisting of lymphocytes and plasma cells. The tracheal submucosa also contained similar infiltrations. The thymus was in a state of total regression and was not studied in great detail. The spleen was enlarged. The white pulp was relatively small in size and not clearly demarcated from the red pulp. Small reaction centers with marked disintegration of the nuclei of the lymphocytes were observed; the central arteries showed hyaline degeneration of the walls. The red pulp contained few lymphocytes. A large number of plasma cells were observed.

The lymph nodes were invariably surrounded by a broad fibrous capsule. The few follicles were groups of lymphocytes that were not clearly defined and were without distinct germinal centers. The subcapsular and medullary sinuses contained a very large number of plasma and plasmocellular reticulum cells, and a large number of Russell bodies. A few polynuclear giant cells were observed in some lymph nodes. At this time, the lymph nodes contained less lymph follicles than in 1955 and were not clearly defined. The lymphocyte count showed a marked decrease.

Family History

The family included no other members with an antibody deficiency syndrome or symptoms of autoimmune disease.

Methods

Agar electrophoresis was carried out by use of the method of WIEME [23], and immunoelectrophoresis by use of the micro-method of SCHEIDEGGER [20]. Equine antihuman antiserum (AHS), as well as anti-IgG and anti-IgM antisera, was obtained from the Central Laboratory of the Blood Transfusion Service, Amsterdam; sheep anti-IgA and rabbit antiserum to the macroglobulin complex were prepared in the laboratory of the present authors; rabbit anti- κ and anti- λ sera were received from Dr. R. E. Ballieux, Utrecht. Ultracentrifugation was carried out in a Model E Spinco Beckman centrifuge. The concentration of IgA was estimated by radial diffusion using the method suggested by MANCINI *et al.* [13] as modified by VAN MUNSTER and STOELINGA [15].

Isolation of the Macroglobulin

Sia's test showed that the serum contained a large amount of euglobulin. Two ml of serum were slowly poured into 80 ml of distilled water, centrifugation ($2500 \times g$) being performed within fifteen minutes, for a period of fifteen minutes. The sediment was dissolved in 1.3 ml of saline solution. This procedure was repeated twice.

Precipitin Activity

When normal serum or a preparation of IgG was added to the macroglobulin solution, turbidity appeared. Increasing quantities of fresh normal human serum were added to 0.05 ml of macroglobulin solution (20 mg/ml), the final volume being made up to 0.30 ml with 0.01 M phosphate-buffered saline, pH 7.4. Turbidity was constant and maximal within 26 minutes and was read in a Beckman spinco-microspectrophotometer at $550 \mu\text{m}$. The values recorded were adjusted to the turbidity of the two solutions and represented graphically.

Dissociation of the Macroglobulin

With 6 M urea. The following solutions were compared by gel filtration on Sephadex G 200, equilibrated with 6 M urea (height of column 39 cm, surface area 5.7 cm^2 , elution rate 12.5 ml/h) and by ultracentrifugation:

4 mg of macroglobulin dissolved in 0.7 ml 6 M urea;
3.2 mg of IgG was added to 4 mg of macroglobulin in 0.5 ml of saline; a gel was formed and was cleared after addition of 250 mg of urea (final volume, 0.7 ml in 6 M urea).

In an acid medium. The following solutions were compared with each other in the ultracentrifuge:

4 mg of macroglobulin in 1 ml of saline;

4 mg of macroglobulin in 1 ml of 0.1 M glycine hydrochloride, pH 3.3;

4 mg of macroglobulin and 3.2 mg of IgG in saline; a gel was formed and was dissolved by adding 0.1 ml of 1 M glycine hydrochloride, pH 3.3 (final volume 1 ml).

Dissociation into monomers with 2-mercapto-ethanol, using the method of DEUTSCH and MORTON [3].

Dissociation into H and L chains using the method suggested by FLEISCHMAN *et al.* [4] as modified by ROWE and FAHEY [19].

Results

Whole Serum

Paper electrophoresis revealed that the serum was low in albumin (1.5–2.5 g/100 ml) and high in γ -globulin (2.5–3.0 g/100 ml). A large amount of protein remained at the site of application on agar electrophoresis (fig. 1). The γ band was considerably shortened on the cathodal side and this fraction was stained deeply with PAS. Immunoelectrophoresis produced a striking pattern (fig. 2). When the euglobulin had been removed, the IgM and IgG determinants were found to have disappeared, although IgA continued to be present. The concentration of IgA had increased (440 mg/100 ml). The pattern resulting from ultracentrifugation (fig. 3) showed a high sharp M peak, the G peak being barely visible.

Isolated Euglobulin (Macroglobulin)

Physico-chemical properties. The euglobulin isolated from the serum was devoid of cryoglobulin properties. The sialic acid content was 1.4%. The amino acid composition was approximately identical with that of IgG and IgM as found by LIMBOSCH and CHRISTOPHE [12].

Two peaks were observed on ultracentrifugation (fig. 3d); 85% of the protein was present at the M_1 peak ($S_{20,W}^{\circ} = 17.4$) and 15% at the M_2 peak ($S_{20,W}^{\circ} = 26.0$).

The A and G peaks were no longer present.

Fig. 1. Agar electrophoresis of patient's serum (bottom) as compared with normal serum (top). The γ band is shortened on the cathodal side.

Immunochemical properties. Two lines showing no reaction of identity were observed on immunoelectrophoresis of the isolated macroglobulin with antihuman serum (fig. 4a), indicating that two different macroglobulins diffused independently of one another. The protein precipitated nearest the trough contained only IgM determinants (figs. 4a and b). The fraction precipitated farthest from the trough undoubtedly contained IgG determinants (fig. 4a) and may have contained IgM determinants also. The failure to demonstrate this finding with anti-IgM antiserum resulted because all anti-IgM antibodies had previously precipitated the precipitation line situated in front and could no longer reach the fraction behind it (fig. 4b). This macroglobulin did not contain any IgA determinants.

Antibody character. The macroglobulin showed precipitating anti-IgG antibody properties. When fresh, normal human serum was added to the isolated macroglobulin, turbidity appeared, and the mixture was dissolved again by excess normal human serum (fig. 5). The curve produced was typical of a precipitating antibody. Addition of a solution of IgG at a relatively high concentration to the isolated macroglobulin initially resulted in the appearance of a gel that was also dissolved by excess IgG. When this reaction was carried out in a highly dilute medium, however, the insoluble precipitate that was formed could not be dissolved with antigen in excess (fig. 6). IgM apparently precipitates to a much higher degree with aggregated IgG than with native IgG. The isolated macroglobulin precipitated with the IgG of any human serum studied. There was no specificity against Gm or Inv. factors since all erythrocytes sensitized by incomplete anti-D were agglutinated by the macroglobulin. This agglutination was inhibited by native IgG; therefore, the macroglobulin, like MÜLGROM's factors [14], also showed anti-antibody activity. When macroglobulin was added to normal human serum, ultracentrifugation showed that, compared with a similar concentration of macroglobulin in saline, the 17.4 S fraction decreased and the 26 S fraction increased; a third fraction appeared, the sedimentation constant of which was 21.7 S.

The macroglobulin also showed antibody activity against rabbit serum but not against sheep or horse serum (fig. 7); the macroglobulin was not directed against human IgA or other serum proteins.

Dissociation in 6 M urea or in an acid medium. Antigen-antibody complexes may often be dissociated in a 6 M urea solution or in an acid medium. KUNKEL *et al.* [10] and PEETOOM *et al.* [17] separated IgG-IgG and IgG-IgM complexes respectively into the initial constituents using these methods. The physiological IgM is not dissociated under these conditions.

In the present study, the macroglobulin isolated

Fig. 2. Immunoelectrophoresis of patient's serum (bottom well) and normal serum (top well). Pattern developed with equine antihuman serum (a), equine anti-IgG antiserum (b), equine anti-IgM antiserum (c) and unabsorbed sheep anti-IgA antiserum (d).

Fig. 3. Ultracentrifuge pattern of the whole serum (a, b, c) and of the isolated macroglobulin (d).

a, b, and c. Speed 59,780 rpm; photographs taken 25, 41, and 73 minutes after full speed.

d. Speed 47,660 rpm; photograph after 20 minutes. A peak $S_{20,W}^{\circ} = 4.44$; M_1 peak $S_{20,W}^{\circ} = 17.4$; M_2 peak $S_{20,W}^{\circ} = 26$.

Fig. 4. Immunoelectrophoresis of the isolated macroglobulin (P. macrogl) and of the total serum of the patient (PS). Patterns developed with equine anti-human serum (a) and equine anti-IgM antiserum (b). The second lower well in A had been filled in with normal IgG after the electrophoretic run. There is a pattern of identity between IgG and one of the precipitation lines. Note the precipitate near the well filled with IgG caused by a reaction between the macroglobulin of the patient and normal serum IgG.

Fig. 5. Turbidity curve after addition of increasing quantities of fresh human serum to 1 mg of macroglobulin in saline solution. The precipitate is dissolved in excess of normal serum.

from the patient's serum, which contained both IgM and IgG determinants, was not dissociated by 6 M urea (fig. 8a). Nor did lowering the pH with glycine hydrochloride, pH 3.3, result in dissociation. When sufficient IgG was added to the macroglobulin *in vitro* to produce a gel, however, this gel dissolved again in 6 M urea as well as in glycine hydrochloride, pH 3.3. On Sephadex G 200 gel filtration and ultracentrifugation, IgG was found to have been separated again (fig. 8b).

Dissociation into monomers. When normal IgM was dissociated by the method of DEUTSCH and MORTON [3], monomers were formed with a 7 S sedimentation constant. Dissociation of the isolated macroglobulin, however, produced two fractions, 85 % having an S_{20} of 6.7 and 15 % having an S_{20} of 11 (fig. 9). Filtration on G 200 also gave two fractions (fig. 10). Immunoelectrophoresis of the shaded areas showed that the 11 S fraction contained both IgG and IgM determinants and the 6.7 S fraction, only IgM determinants.

It can be concluded that a fraction containing both IgG and IgM determinants must be present in the isolated, nondissociated macroglobulin, which must be the 26 S fraction.

Dissociation into H and L chains. When the macroglobulin was dissociated by the method of ROWE and FAHEY [19], a curve identical to that following dissociation of normal immunoglobulins was obtained after gel filtration. After converting the transmission curve into an extinction curve, the ratio between the amounts of H and L chain proteins was calculated. The findings were as follows:

Fig. 6. Turbidity curve after addition of increasing quantities of IgG (Cohn fraction II) to 0.2 mg of macroglobulin in saline solution (final volume 0.4 ml). There is no dissolution of the precipitate in excess of IgG.

Normal IgG	H chain protein 81 %	L chain protein 19 %
Isolated euglobulin	H chain protein 83 %	L chain protein 17 %

ROWE and FAHEY [19] recorded 77 and 23 %, respectively, in their studies. In the present study, the L chain fraction showed relatively low levels, probably because the H and L chain proteins were not completely separated. The H chain fraction still contained some L chain protein. The specific anti-IgM and anti-IgG antibodies were completely absorbed from anti-IgM and anti-IgG antiserum with the H chain protein; the isolated H chains, therefore, did not contain fewer determinants than did the H chains of normal IgM and IgG. An antiserum to the macroglobulin of the patient was prepared in the rabbit; this also produced precipitation with normal IgM. Efforts were made to remove the anti-IgM determinants from this antiserum by absorption with normal serum in order to determine whether this antiserum was also directed against determinants that were specific for the macroglobulin of the patient. The serum, however, could no longer be tested with this absorbed antiserum, since precipitations constantly occurred between the macroglobulin and the IgG then present in the antiserum. The macroglobulin was found to contain both κ and λ determinants.

Fig. 7. Ouchterlony plate demonstrates precipitation between the isolated macroglobulin (central well) and normal human serum (NHS), human IgG (Cohn fraction II) and rabbit serum. There is no precipitation with human IgA and horse or sheep serum.

Fig. 8. Ultracentrifuge pattern of: *a*. Four mg of macroglobulin in 0.7 ml 6 M urea solution; *b*. Four mg of macroglobulin and 3.2 mg of IgG; the gel produced having been dissolved by addition of 250 mg of urea (final volume 0.7 ml in 6 M urea solution) $S_{20} P_1 = 3.6$, $S_{20} P_2 = 9.36$. Speed 47,660 rpm, photographs taken 16, 32, and 48 minutes after full speed. The isolated macroglobulin is not dissociated in 6 M urea (*a*); IgG added *in vitro*, however, is dissociated under this condition. (The sedimentation coefficient of macroglobulin and IgG decline in 6 M urea to 9.36 S and 3.6 S, respectively.)

Fig. 9. Ultracentrifuge pattern after dissociation by method of DEUTSCH and MORTON [3] of the isolated macroglobulin (top) as compared with that of untreated macroglobulin (bottom). Speed 59,780 rpm; photographs 3, 19, and 35 minutes after full speed. After dissociation, there are two fractions with S_{20} of 6.7 S and 11 S, respectively.

Fig. 10. Gel filtration over Sephadex G 200 (equilibrated with saline-phosphate buffer 0.1 M pH 7.0. Height of column 39 cm, surface area 5.7 cm², elution rate 12.5 ml/h, fractions of 3 ml) after dissociation by DEUTSCH and MORTON's method of

a. Isolated macroglobulin of a patient with Waldenström's disease;

b. Isolated macroglobulin of the patient.

The patient's macroglobulin dissociates in two fractions; the shaded areas were investigated by immunoelectrophoresis (see text).

Discussion

A large amount of macroglobulin, which may be isolated as euglobulin, was present in the serum of this child with an antibody deficiency syndrome. Ultracentrifugation showed that 85 % of the protein had a sedimentation constant of 17.4 S and that 15 % had a sedimentation constant of 26 S. Immunochemical studies showed that the macroglobulin contained both IgM and IgG determinants. One fraction of the macroglobulin contained only IgM determinants; another undoubtedly contained IgG and possibly IgM determinants. All IgG in serum was present in the macroglobulin; free IgG no longer occurred in the serum after removal of the euglobulin. Dissociation of the macroglobulin into monomers produced a 7 S fraction composed solely of IgM determinants and an 11 S fraction including both IgG and IgM determinants. Because the latter fraction had a sedimentation constant of 11 S and could not be further dissociated by mercapto-ethanol, it must have been built up of IgG molecules and IgM monomers. It is believed that this union was not based on S-S bonds.

In the present study, the findings that the macroglobulin contained IgM and IgG determinants not dissociated by mercapto-ethanol, that the macroglobulin showed anti-IgG antibody activity (fig. 5), and that there was no free IgG in the serum led us to believe that these conditions were caused by antibody activity of the macroglobulin against the IgG of the patient. If this conclusion is correct, the 26 S macroglobulin fraction should be regarded as a complex consisting of IgM and IgG immunoglobulin molecules and would imply antibody activity against one of the patient's own proteins, which is an auto-immune disease.

Sera showing high rheumatoid factor titers were frequently found to contain a fraction having a sedimentation constant of 22 S. This fraction is considered to be a complex of rheumatoid factors and native IgG [6, 11]. It is unusual that the serum of the patient contained a 26 S but not a 22 S fraction. When normal serum was added to the euglobulin *in vitro*, however, a 21.7 S fraction could be identified. It may be that 22 S fractions were also formed *in vivo*, but these fractions were less readily soluble and were more rapidly phagocytized by the reticulo-endothelial system. The presence of a fraction with a very high sedimentation constant, 26 S, in the serum would appear to suggest that, in this case, a relatively large number of IgG molecules were linked to one macroglobulin molecule. KUNKEL *et al.* [10] and PEETOM *et al.* [17] reported that immunoglobulin complexes are readily separable into component parts. The complex isolated from the serum of this patient could not be dissociated into IgG and

IgM in 6 M urea or in an acid medium, whereas this could be done with complexes resulting from addition of IgG to the euglobulin *in vitro*. IgM and IgG, therefore, are likely to be bound more firmly together in this complex occurring *in vivo* than in rheumatoid IgM-IgG complexes.

The anti-IgG antibodies constitute a heterogeneous group and may show a wide variety of properties. These have been reviewed by HARBOE *et al.* [6] and NÄRVIC [16]. The macroglobulin isolated from the serum of the child in the present study showed the characteristics of all groups of anti-IgG antibodies differentiated by these authors. It was heterospecifically directed against rabbit IgG and isospecifically against the IgG of normal human serum. It had the properties of a precipitin and reacted very intensely not only with aggregated IgG but also with native IgG. It also showed the anti-antibody activity described by MILGROM *et al.* [14] and as stated previously, this macroglobulin was also believed to be directed against the IgG of the patient.

Since the serum of the patient was shown to precipitate with native IgG, there must have been a considerable antibody excess with respect to native IgG. As a result, the IgG produced by the body promptly combined with the antibody excess, and insoluble precipitates absorbed by the reticulo-endothelial system were most likely formed in the process. Insoluble products are known to have powerful antigenic properties [7], and it is possible that these complexes alone stimulated antibody production. At least part of the IgM-IgG complex must have been soluble, since it was found to be present in the serum.

The patient showed recurrent infections although she was still capable of producing particular specific antibodies, including diphtheria antitoxin (table I). When the symptoms of antibody deficiency syndrome appeared, however, it may have been possible that the antibodies did not penetrate into the tissues sufficiently to exert a protective effect. There are two alternatives in this case. Either the IgG antibodies produced were immediately bound to the IgM then rapidly broken down so that a sufficiently high titer would not be attained, or the large IgM-IgG complex produced was no longer capable of leaving the blood stream to a sufficient degree, resulting in antibody deficiency of the tissues. It is unknown to what extent the IgM antibodies combining with IgG are the result, rather than the cause, of infection. The concentration of γ -globulins, however, was found to be very high (3.5 g/100 ml) when the patient developed pneumococcal meningitis for the first time, and changes in the immunoglobulins must have been present even then.

Studies using labelled IgG were not undertaken to determine whether the catabolic rate was excessive or

Table I. Studies on the ability to produce antibodies

Diphtheria antitoxin:	before booster injection		
	0.006 A.U./ml		
	after booster injection		
	2.00 A.U./ml		
Isohemagglutinins	anti-A: 1:8		
	anti-B: 1:4		
Antistreptolysin titer	1954: 640 U	1961: 50 U	
L-agglutination	1954: 0		
Rose-Waaler test	1954: 1:128	1962: 1:4076	
Latex fixation test		1962: 1:5120	
Paul Bunnell test		1962: 1:1280	
	after absorption with guinea pig cells	1962: 1:80	
	after absorption with		
	bovine erythrocytes	1962: 1:640	
L.E.-cell phenomenon		1962: negative	
Cold agglutinins: with 0 erythrocytes		1962: 1:5	
	with erythrocytes of the patient,		
	1:2 dil.	1962: negative	
	albumin, 1:2 dilution	1962: negative	

whether the rate of synthesis was below normal. Auto-
logous IgG could not be isolated. *In vitro* studies with homologous IgG had previously shown that this IgG was precipitated by the serum of the patient. Homologous IgG undoubtedly disappears more rapidly from the circulation on intravenous injection. Treatment with intramuscular injections of γ -globulin failed to produce any effect and free IgG could not be identified in the serum during this treatment. As the IgG of the patient occurred only in the form of an IgG-IgM complex, it could be expected that the IgG would be broken down simultaneously with IgM and would also be broken down more rapidly, since the catabolic rate of IgM is much higher than that of normal 7 S IgG.

It was undetermined whether the large numbers of plasma cells observed on histological investigation also included IgG-producing plasma cells. The majority of these cells contained PAS-positive material that is consistent with the large amount of IgM found in the serum; however, occasional PAS-negative cells were found also. Fluorescent antibody studies with the antisera available at the time were not attempted, since immunochemical studies had resulted in various kinds of precipitations. The fluorescent antibody technique is particularly sensitive to such precipitations and correct conclusions could not have been drawn. Reduced IgG synthesis, therefore, cannot be definitely ruled out as a cause of IgG deficiency, but there is evidence that strongly suggests increased catabolism of the IgG produced.

Rheumatoid symptoms, hematological disorders, or impairment of kidney function are frequently out-

standing features of auto-immune disease. These manifestations, however, were absent in the present study. Large numbers of plasma cells were present in bone marrow, lung, spleen, and lymph nodes at necropsy. Changes characteristic of auto-immune disease, however, were not detected in the various internal organs, including the kidney, nor was there any family history of auto-immune disease.

There has been only a limited number of studies of antibody deficiency syndrome caused by auto-immunization. BARANDUN *et al.* [1], GOOD *et al.* [5], and STOOP [22] do not refer to this cause in their reports on the antibody deficiency syndrome.

PEETOOM *et al.* [17] reported on a woman who showed recurrent infections, symptoms of impaired kidney function, and hemolytic anemia, in which a cryoglobulin, found to be an IgM-IgG complex, occurred in the serum. A fair amount of free IgG (0.6 g/100 ml), however, was present in the serum of their patient. The isolated cryoglobulin also displayed anti-IgG activity and the authors concluded that auto-immune disease was present.

The following speculation is based on the results of the present study. An unknown triggering event that occurred at an early age triggered auto-immunization against the IgG of the patient and resulted in the appearance of an IgM-IgG complex in the serum. This showed antibody activity against human and rabbit IgG. Antibodies produced when infection occurs are bound by this macroglobulin and result in excessive susceptibility to bacterial infection, giving rise to symptoms of an antibody deficiency syndrome.

The cause of this auto-immunization is obscure. It is either the result of bacterial infection or of congenital impairment of the mechanism of recognition. When this pathogenesis is taken into account, in searching for the causes of the antibody deficiency syndrome, this auto-immunization phenomenon may possibly be verified by others.

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