MEDICAL GRAND ROUNDS

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# The Immunoglobulin Deficiency States

## THE IMMUNOGLOBULINS

1) Terminology

2) General Features

3) Molecular Structure

4) Relation of Subunit Structure to Antibody Function

5) Genetic Control of Synthesis

## THE DEFICIENCY STATES

1) Classification

2) Clinical Features

3) Proposed Genetic Defect

4) Diagnosis

5) Case Report

THE IMMUNOGLOBULINS

1) Terminology: In an effort to standardize the nomenclature of the immunoglobulin classes the following terminology was proposed in 1964 by the immunology section of the World Health Organization:

TABLE I

| Proposed terminology | IgG or γG | IgA or γA | IgM or γM | IgD or γD | IgE or γE |
|---|---|---|---|---|---|
| Previous terminology | γ<br>γ2<br>γSS<br>7Sγ<br>6.6Sγ | γ1A<br>$B_2A$ | γ1M<br>$B_2M$<br>19Sγ<br>γ macro glob iota | --- | --- |

2) General Features of the Immunoglobulins

TABLE II

| | IgG | IgA | IgM | IgD | IgE |
|---|---|---|---|---|---|
| Physicochemical | | | | | |
| Molecular weight | 150,000 | 150,000+ | 900,000 | 150,000? | 150,000? |
| Ultracentrifugation | 6.6S | 6.6 (9, 11,135) | 18S(24, 325) | 7S | 7.8S |
| Electrophoretic mobility | γ | Slow β | Between γ and β | Between γ and β | Between γ and β |
| Immunological Characteristics | | | | | |
| First detectable ab | 0 | 0 | + | -- | -- |
| Major part of secondary response | + | 0 | 0 | -- | -- |
| Bind complement | + | ? | + | -- | -- |
| Active placental transport | + | 0 | 0 | 0 | -- |
| Sensitize guinea pig skin | + | 0 | 0 | 0 | -- |
| React with rheumatoid factor | + | 0 | 0 | -- | -- |
| Reagin activity | ± | +? | ± | -- | ++ |
| Normal Serum Level (mg/ml. ± 1SD) | 12.4 (±2.2) | 3.9 (±0.9) | 1.2 (±0.35) | 0.03 (0-0.3) | ? |
| Serum half-life (days) | 23 | 6 | 5 | -- | -- |

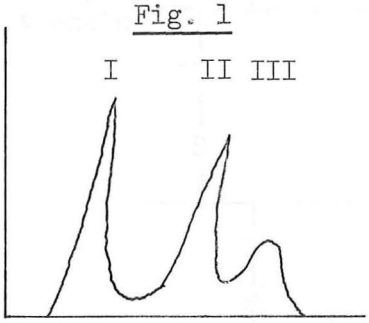
-Adapted from Fahey

## 3) Molecular Structure

The present concept of the structural design of the antibody molecule is based on methodologic approaches designed to split peptide bonds within polypeptide chains and/or to reduce disulfide bonds binding one polypeptide chain to another.

a) Products of papain digestion of gamma globulin and separation of fractions (Porter pieces) on carboxymethylcellulose column.

Fig. 1



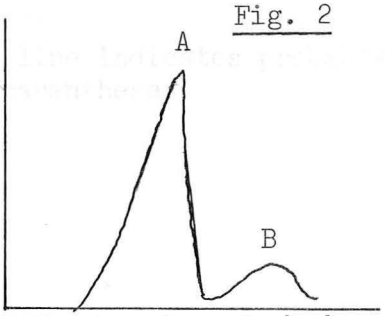

Eluates from CMC

Table III

| Fraction | Molecular Weight | Antibody Activity |
|---|---|---|
| I | 50T | + |
| II | 50T | + |
| III | 70T | 0 |

b) Products of reduction of sulfide bonds and separation of fractions on Sephadex.

Fig. 2




Eluates from Sephadex

Table IV

| Fraction | Molecular Weight |
|---|---|
| A | 110T (2 H chains) |
| B | 40T (2 L chains) |

The relationship between the fragments obtained by splitting peptide linkages within polypeptide chains and the fragments produced by reduction of disulfide bonds between polypeptide chains was established by use of the Ouchterlony technique of double diffusion in agar. Fraction A (H chains) reacted antigenically to antisera against Porter fractions I and III while Fraction B (L chains) reacted only against antisera against Fraction I. This evidence suggested that the portions of the molecule having antibody activity (Porter pieces I and II) contained both L and H chains while the non-antibody fragment (Porter piece III) contained only H chains. On the basis of that interpretation a hypothetical structure for γg was proposed by Porter:

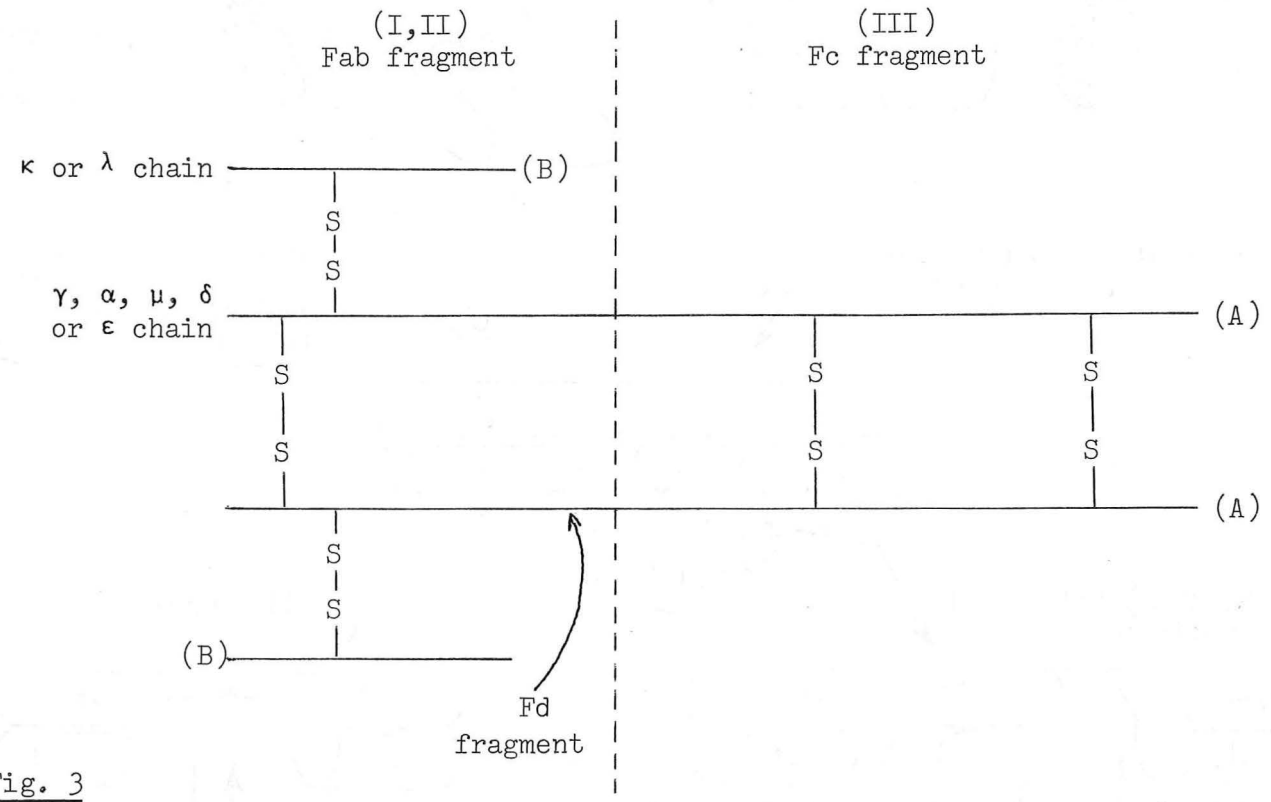



Fig. 3

Dotted line indicates probable site of papain cleavage. Porter's terminology is in parentheses.

By low x-ray scattering experiments it has been determined that a γG molecule is a cylinder of elliptical cross section with dimensions of 240 A x 57 x 19 . Utilizing these dimensions Edelman has devised a hypothetical model which incorporates all the present evidence gained through disruption of the molecule by various means.

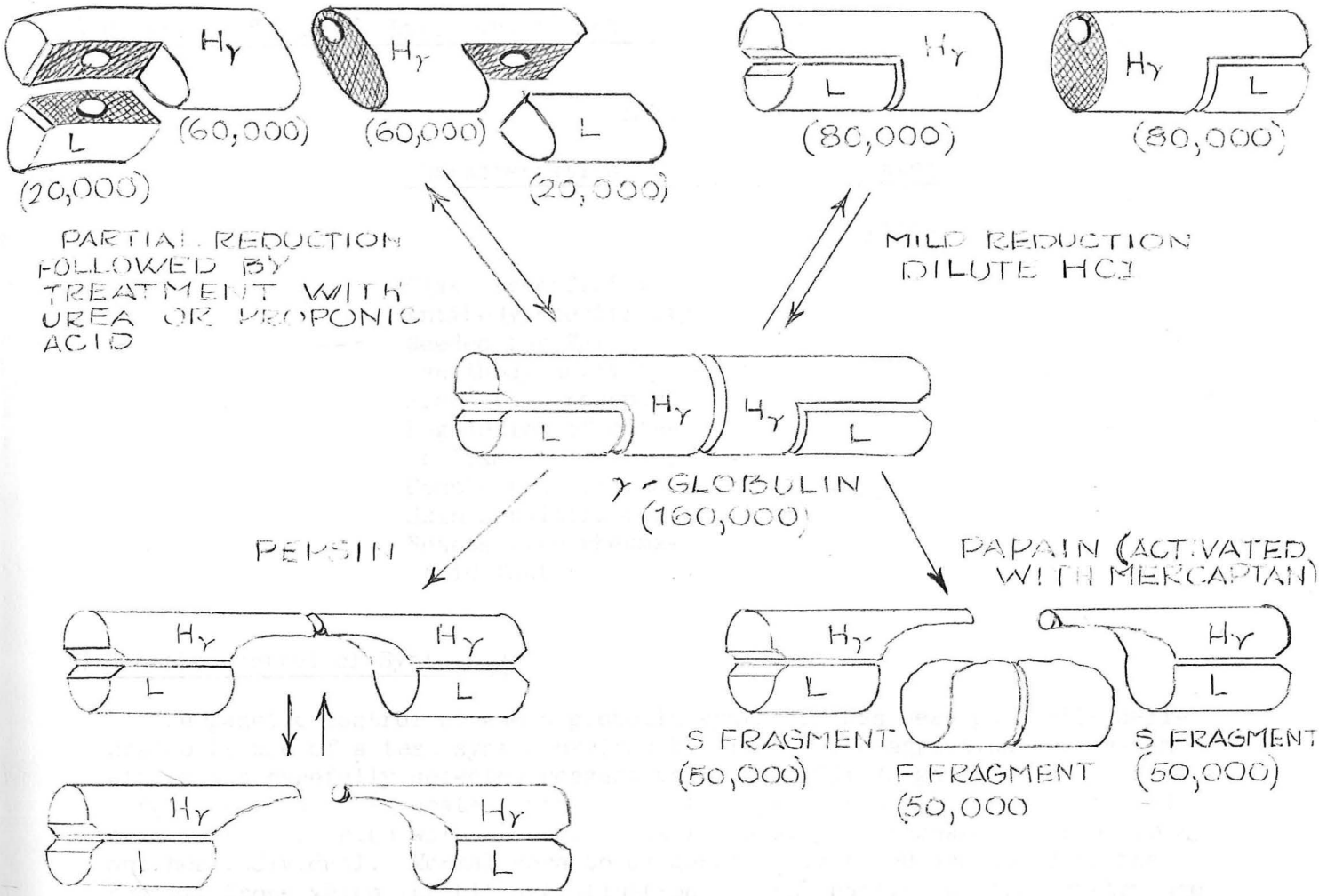



Fig. 4

Schematic diagram illustrating the ways in which the 7S antibody molecule may be degraded. Numbers in parentheses are approximate molecular weights. H —heavy chain; L—light chain. Hatched areas indicate regions of non-covalent interchain bonding. Disulfide bonds or half-cystines are indicated in these regions.

L chains are known to be of two types (κ and λ) which are antigenically indistinguishable from the two types of Bence-Jones proteins described by Korngold and Lipari. Both κ and λ L chains are found in all classes of immunoglobulins and their presence accounts for the common antigenic reactions between classes. H chains differ widely between immunoglobulin classes and there is probably marked heterogeneity in a given class (4 antigenically distinct types presently recognized in γG H chains).

4) Relation of Subunit Structure to Antibody Function

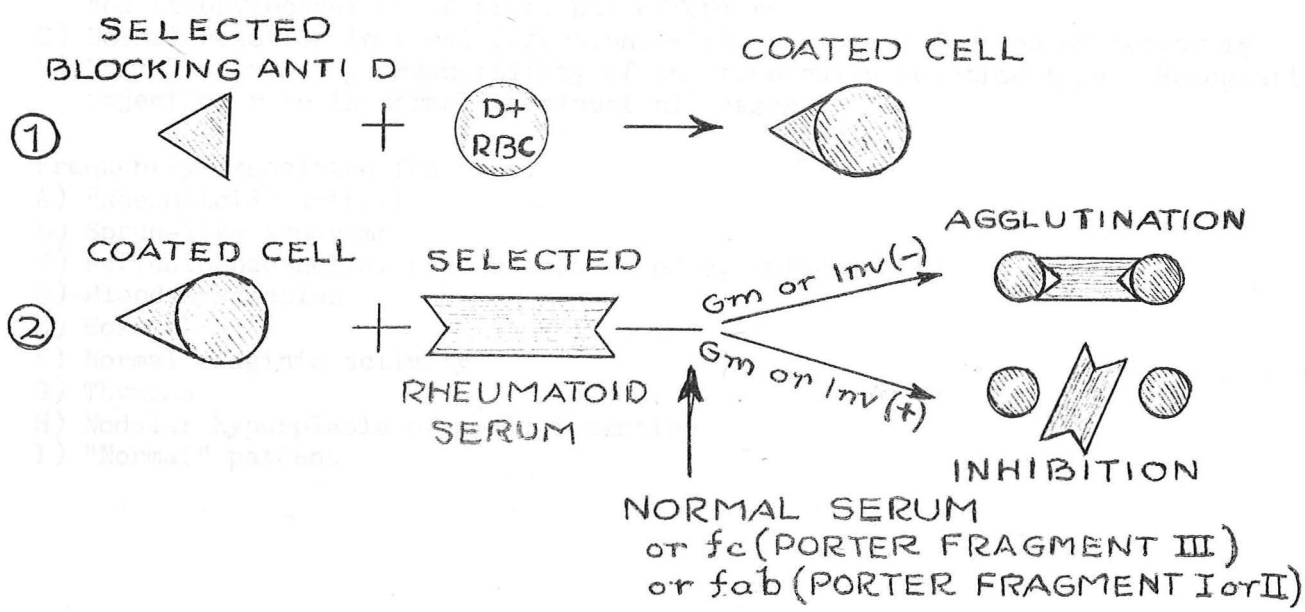
TABLE V

Characteristics of Polypeptide Chains

| | Heavy | Light |
|---|---|---|
| Class specificity | + | 0 |
| Antibody specificity | + | 0 |
| Needed for full antibody activity | + | + |
| Placental transport | + | 0 |
| Regulation of catabolism | + | 0 |
| Complement binding | + | 0 |
| Skin sensitization | + | 0 |
| Reacts with rheumatoid factor | + | 0 |

5) Genetic Control of Synthesis

The genetic control of gamma globulin synthesis has been partially delineated by use of a test system devised by Grubb. The agglutinating system utilizes a carefully selected reagent pair (Fig. 5): 7S gamma globulin from a single individual is coated onto an inert (Type O) red cell and the coated cell is then reacted with an agglutinator (usually a rheumatoid serum) from another individual. Normal sera to be genetically typed are added to the system; those which inhibit agglutination in that particular test system are said to be positive for the factor in question, those which permit agglutination are negative



By changing the anti D and/or the rheumatoid agglutinator the system can be changed to check for multiple inhibiting factors present in normal gamma globulin. Thus far the inhibitory factors found have fallen into two categories, Gm (abbreviation for gamma globulin) and Inv (In = inhibitor, v = patient's initial). Nine subtypes are known thus far for the Gm system (Gm a, b, e, f, x, etc.) and two for the Inv system (Inv(a or 1) and Inv(b) ). The elaboration of these inhibitory factors is under the control of two sets of non-linked genes (termed Gm and Inv) and family studies have shown that the major alleles at each locus express themselves as codominants.

By testing the Porter fragments in Grubb's system it has been shown that Fc (piece 3) of γG demonstrates only Gm activity and fab (piece 1) demonstrates only Inv activity. This evidence suggests that the two types of polypeptide chains in human γG are under independent genetic control with Gm genes regulating H chain production and Inv genes reulating L chain production.

## THE IMMUNODEFICIENCY STATES

### 1) Classification

A) Symptomatic (secondary) - associated with myeloma and lymphatic leukemia
B) Physiologic - infants between 3 and 6 months of age - transient
C) Idiopathic (primary)
   1. Swiss type (alymphocytosis): rare, quickly lethal
   2. Congenital: onset 8 months-2 years. Sex linked
   3. Acquired: onset any time; typically 15-30 years

### 2) Clinical Features

Features common to idiopathic forms:
A) Diminution in one or more of the immunoglobulins
B) Predisposition to certain bacterial infections with pneumococci, streptococci and staphylococci being principal offenders
C) Normal reaction to viral infections with possible exception of hepatitis
D) Normal delayed hypersensitivity of the tuberculin reaction type. Homograft rejection rate is normal in almost all cases

Frequently associated features:
A) "Rheumatoid" arthritis
B) Sprue-like syndrome
C) Reticuloendothelial hyperplasia - nodes, splenomegaly
D) Blood dyscrasias
E) Eczema
F) Normal reaginic activity
G) Thymoma
H) Nodular hyperplasia of small intestine
I) "Normal" patient

3) Proposed Genetic Defect

Studies of thefamilies of patients with immunoglobulin deficiency have revealed a high incidence of symptomatic collagen disease (lupus erythematosus, rheumatoid arthritis, polyarteritis) and an even higher incidence of asymptomatic serum abnormalities (increased globulin, b.f.p. serology, LE factor, rheumatoid factor). The familial occurrence of these "immunological" abnormalities has led to the hypothesis that both congenital and acquired hypogammaglobulinemia are genetically determined.

TABLE V

Observed Globulin Patterns and Their Proposed Genetic Defects

| | γG | γA | γM | Infection Rate | Response to Antigenic Stimuli | Involved Gene(s) (postulated) |
|---|---|---|---|---|---|---|
| 1 | ↓ | ↓ | ↓ | ↑ | 0 | Inv or all Gm |
| 2 | N | ↓ | N | N | + | Gm α |
| 3 | ↓ | ↓ | N↑ | ↑ | + | Gm γ, α |
| 4 | ↓ | N | N | ↑ | + | Gm γ |
| 5 | N | ↓ | ↓ | ↑ | 0 | Gm γ, μ |

Pattern 1 is expected in congenital and Swiss types and is rarely seen in acquired form. Pattern 2 is seen in otherwise normal people and is of interest from the genetic standpoint only. Patterns 3 and 4 account for most of the acquired forms with 5 being rare. It is noteworthy that patients with normal γM and decreased γg are susceptible to infection although they form macroglobulin antibody; γg antibody seems to be required for protection.

Supporting the existence of the proposed genetic defects is evidence gained through a sophisticated case study by Barth. The patient had decreased levels of γG and γA with elevated levels of γM and γD. Rate of synthesis of γ and α heavy chains was markedly reduced while that of μ and δ heavy chains was increased. L chain synthesis was normal.

The manner in which the defect is expressed at a cellular level has not been delineated but intriguing studies are in progress. Some pertinent comparisons between the normal and agammaglobulinemic lymphocyte are shown in Table VI:

TABLE VI

| | | Morphologic Change to "Plasma" Cell | Globulin Production | Blocked by Actino D** |
|---|---|---|---|---|
| Normal sensitized lymphocyte | + antigen | + | + | + |
| | + PHA* | + | + | + |
| Agamma lymphocyte | + antigen | 0 | 0 | - |
| | + PHA | + | 0 | + |

* Phytohemagglutin - non-specific mitogenic agent
** Specifically blocks formation of mRNA

Since the agammaglobulinemic lymphocyte is capable of undergoing "normal" morphologic changes with PHA stimulation it has been proposed that the defect is manifest by failure to recognize antigen--a form of tolerance. Alternate views would hold, however, that the mRNA formed during mitosis is quantitatively or qualitatively inadequate for coding for globulin synthesis.

4) Diagnosis

History:

1. Suspected in any case having repeated bacterial infections
2. History of familial disease would strengthen suspicion but frequently is lacking

Physical Examination:

Multiple anomalies frequently exist but physical exam may be normal except for those associated with the acute infection

Diagnostic Tests:

1. Screening:
   a) Electrophoretic pattern: May appear normal in cases with deficiency of 1 or 2 globulins
   b) Isoagglutin titer: May be positive in severe deficiency state
   c) Febrile agglutinins (typhoid H, O, etc.): As routinely done these do not distinguish between γM and γG. γG antibody seems to be required for protection
2. Definitive:
   a) Quantitation of individual globulins by immunoelectrophoresis or Ouchterlony technique (double diffusion in agar)

b) Demonstration of ability to produce γgG antibody
   1) Schick test negative or conversion of positive to negative after immunization
   2) Determining 2-mercaptoethanol sensitivity of antibodies formed to standard antigens (typhoid, etc.). γG antibodies are 2ME-resistant.

CASE REPORT: [redacted]

The patient is a 24-year-old [redacted] male who was first seen in the [redacted] system in [redacted] 1963 when he presented with acute pneumococcal pneumonia. Response to therapy was favorable and he remained well until [redacted] of 1964, when he presented with pneumococcal meningitis. Additional history obtained at that time revealed that between the ages of 15 and 20 years he had been hospitalized approximately 10 times with respiratory infections. Immunological evaluation during that admission revealed diminished γG, absent γA and slightly increased γM globulins. Although there was a documented history of previous immunization with diphtheria toxoid, he was Schick positive on initial test and remained so after repeated challenge. Upon stimulation with typhoid vaccine, very high titers of γM antibodies developed without detectable γG antibodies. A similar pattern was seen in tetanus antitoxin and diphtheria antitoxin antibodies. Tuberculin and fungal skin tests were negative. The diagnosis of acquired idiopathic hypogammaglobulinemia seemed secure.

His meningitis responded completely, albeit slowly, to therapy and he was discharged without gamma globulin prophylaxis. During the ensuing six months he had five additional hospitalizations for either pneumonia, sinusitis or otitis. In [redacted] 1964 gamma globulin therapy (20 ml. every 4-6 weeks) was instituted and for one year he was free from infection. In [redacted] of 1965 he was readmitted with pneumococcal bronchopneumonia which responded promptly to therapy. He was readmitted some 4 weeks later with recurrence of pneumococcal pneumonia and bacteremia. Response to therapy was again favorable. Despite additional gamma globulin therapy, his level was estimated at approximately one-half normal on the last admission.

Throughout his period of observation the patient has had a normal physical exam except for those features related to his acute illness. Bone marrow examination revealed plasma cells to be normal in number and morphology. There is no history of familial disease other than diabetes mellitus in a paternal grandfather.

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