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# The Structure and Function of Immunoglobulins in Man

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**Abstract**
The cells of the blood, and their supporting fluid are among the most extensively studied biological systems. It is with the fluid portion of the blood that this article is concerned and with a small group of proteins in particular, the immunoglobulins. These show a peculiar and unique behaviour in the presence of other substances called antigens. This behaviour may take the form of combination forming an insoluble precipitate (precipitin reaction), or rendering it more easily phagocytosed by the microphages or macrophages (opsonisation). Other reactions between antibody globulin and antigen are complement fixation in which the four components of complement take part, immune adherence between antigen and adsorbed antibody, and sensitivity reactions such as passive cutaneous anaphylaxis and the Prausnitz-Kustner reaction. However, the central feature of immune reactions is that antibody by definition can only be identified by its reaction with antigen. Identifiable antibody forms only a small part of the total globulin fraction of serum. The remaining globulin may be physically indistinguishable from antibody, but lacks its demonstrably specific activity; this has resulted in the term "Immunoglobulin" being substituted for "antibody" in this article whenever this sense is intended. The greatest barrier to the understanding of the nature of immunoglobulins is the classification used to describe them.



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# THE STRUCTURE AND FUNCTION OF IMMUNOGLOBULINS IN MAN

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## INTRODUCTION TO PART I — STRUCTURE

The cells of the blood, and their supporting fluid are among the most extensively studied biological systems. It is with the fluid portion of the blood that this article is concerned and with a small group of proteins in particular, the immunoglobulins. These show a peculiar and unique behaviour in the presence of other substances called antigens. This behaviour may take the form of combination forming an insoluble precipitate (precipitin reaction), or rendering it more easily phagocytosed by the microphages or macrophages (opsonisation). Other reactions between antibody globulin and antigen are complement fixation in which the four components of complement take part, immune adherence between antigen and adsorbed antibody, and sensitivity reactions such as passive cutaneous anaphylaxis and the Prausnitz-Kustner reaction. However, the central feature of immune reactions is that antibody by definition can only be identified by its reaction with antigen. Identifiable antibody forms only a small part of the total globulin fraction of serum. The remaining globulin may be physically indistinguishable from antibody, but lacks its demonstrably specific activity; this has resulted in the term "Immunoglobulin" being substituted for "antibody" in this article whenever this sense is intended. The greatest barrier to the understanding of the nature of immunoglobulins is the classification used to describe them. This classification has been imposed by the technical procedures necessary for the isolation and identification of these proteins. Thus an understanding of these methods is a necessary requirement and is dealt with in the first part of this article. The classification and the physical, molecular and chemical structure of immunoglobulins are also discussed.

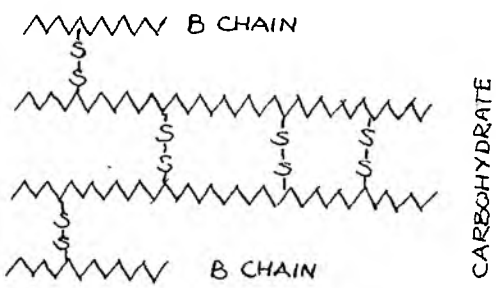
## METHODS OF STUDY

Globulins may be separated from the other serum proteins by selective precipitation with saturated ammonium chloride solution or with ethanol at low temperatures; methods which yield a relatively crude protein fraction of low solubility. If immune serum is treated in this manner, most of the antibody activity is found to remain in the reconstituted precipitate. The globulins themselves are a heterogenous group of proteins differing widely in terms of molecular size and chemical composition. Crude "salting down" yields little information as to the physical properties of any antibody, other than its behaviour as a globulin.

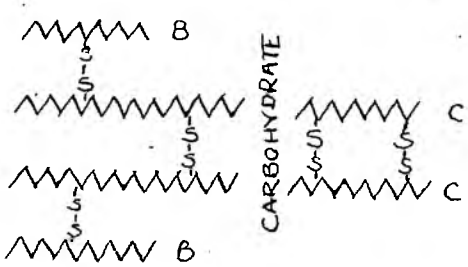
Globulins may be separated into three main classes by a process known as electrophoresis. This principle employs the movement of proteins in an electric field at constant pH; the rate of migration towards the cathode being proportional to the excess ionic charge each molecule carries, and to its size and behaviour in the suspending medium. By this method, three broad classes of globulin emerge, called alpha, beta and gamma, the latter being the slowest moving at a pH of 8.6 in agar gel. It is among the gamma globulins that antibody activity is found. Further electrophoresis under different conditions of pH and potential difference will separate the slow moving gamma globulins into two further groups termed gamma 1 and gamma 2. The former migrate in a band close to the beta globulins, and have therefore, in some classifications, been termed $beta_2$ globulins.

Again electrophoretic separation tells comparatively little about the fine physical struc-

ture, the size, or the shape of the immunoglobulin molecule. These characteristics may be studied by ultracentrifugation. In the ultracentrifuge, the heavier molecules separate first, and lighter fractions later. The behaviour of these molecules is measured in Svedburg units, a measurement derived from a modification of Stoke's Law. The heavier molecules are termed 19S in terms of sedimentation characteristics and the lighter ones 7S. Antigen combines with one or other of these fractions of gamma globulin, more usually with the 7S fraction which is also the greatest in bulk. By these methods, a complete separation of gamma globulin is possible into reproducible fractions. The different behaviour of these fractions must be determined by more sophisticated immunological and physical techniques which are beyond the scope of this article; the scheme below is sufficient for its purpose.




4 CHAIN STRUCTURE




6 CHAIN STRUCTURE

AFTER S. COHEN & R.R. PORTER 1964

The gamma$_2$ Globulins are a homogenous group of proteins upon ultracentrifugation, while the gamma$_1$ globulin may be separated into components with both 7S and 19S characteristics. In this group also small fractions with intermediate sedimentation rates emerge, although to the lighter end of the scale.

#### CLASSIFICATION

Employing the methods described, three types of immunoglobulin may be distinguished. They are classified as follows:—

(1) The gamma$_1$ globulins with sedimentation characteristics of 19S, and belonging to the group with fast motility upon electrophoresis ($\beta_2$ globulins). They are also called "macroglobulins". Equivalent terms for this group are $\alpha_1$M; $\beta_2$M; or IgM.

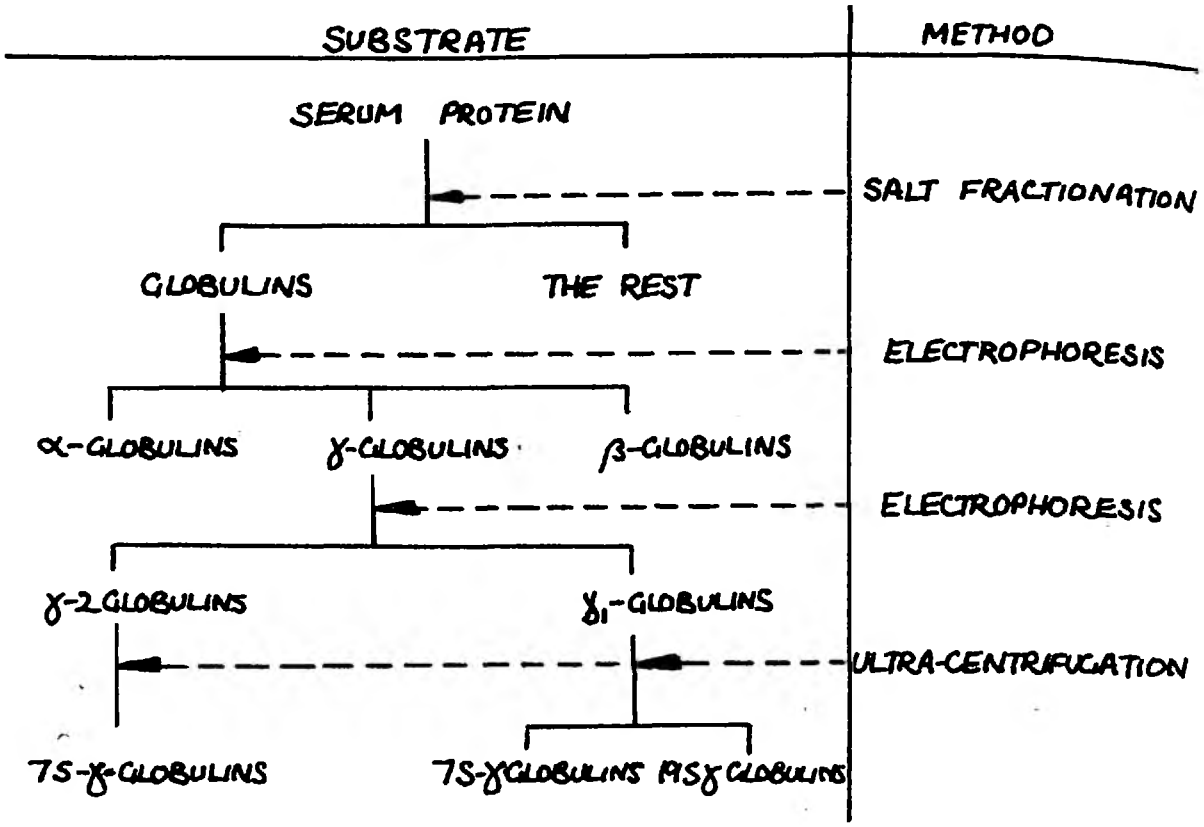
(2) The remainder of the fast gamma group with sedimentation characteristics of 7S. These are also called $\alpha_1$A; $\beta_2$A; or IgA.

(3) The gamma$_2$ globulins which all sediment at 7S. These are termed also $\alpha_2$A; or IgG.

Gamma globulins may also be identified by the cells producing them; and by their immunological reactivity, although they cannot be usefully classified by these means. For example, reaginic antibodies or "reagins" are classified as those antibodies spontaneously produced in susceptible individuals which produce skin sensitisation. This kind of classification is one which make use solely of the immunological reactivity of the antibodies studied. Other classes of antibody might be called "Opsonins" or "Precipitins" but fundamentally such appellation is misleading since precipitating antibodies may be opsonising under certain conditions. Even more significantly, the class of opsonising antibody is indistinguishable from the class of precipitating antibody by the physical characteristics displayed on electrophoresis or ultracentrifugation. Fortunately, the reaginic antibodies, which are the most difficult to study immunologically, in general show the physical characteristics of the IgA group of immunoglobulins. To date it appears that the most satisfactory way of classifying immunoglobulins is by their physical rather than immunological behaviour. Each class of immunoglobulin classified by such means has several important members, both naturally occurring and pathological.

#### PHYSICAL STRUCTURES

The structure of immunoglobulins has lately




become the subject of close scrutiny, firstly by reason of investigating the synthesis of highly specific proteins by the cell, such as enzymes and hormones, and secondly because antibodies are thought to provide a unique example of an "adaptive" alteration in the synthetic mechanisms of the cell. Students of the structure of immunoglobulins hope to discover the answers to both these questions in the scrutiny of the physical, molecular, and chemical structure of these proteins.

Of the immunoglobulin content of human serum IgG (gamma$_2$ A) globulin forms 80-90%, Igm (gamma$_1$ M) 5-8%, and IgA somewhat less than 2% of the total.

The molecular weights of IgG and IgA are somewhat similar, being in the order of 150,000 to 190,000. The macroglobulin, on the other hand, has a molecular weight of 1,000,000 and in some diseases abnormal macroglobulins with twice this molecular weight have been reported.

These molecules also differ in their shape. The molecule of IgG is found to be elliptical, with a ratio of long:short axis of 8-9:1, and a maximum dimension of some 70Å. The molecule of IgM is almost spherical in shape with a diameter of at least 3000A. Since different observers have recorded similar dimensions and molecular weights under varying experimental conditions we may assume their true dimensions to lie within this range.

#### MOLECULAR STRUCTURE

The reactive site of an antibody molecule is relatively small, since reactive fragments of low molecular weight can be discovered after fragmentation of the molecule. Such treatment also reveals that each antibody molecule can be split into four or six primary fragments by the hydrolysis of disulphide bonds. These fragments are called A, B or C chains, and are made up of amino acids linked in polymeric form. Further study has shown the B chain fragments of any human immunoglobulin to be similar to the B chain fragments of any other, while the A chains are distinct in each of the three classes. It is also clear that the specificity of antibody is due more to the sequence of amino acids in each B chain, than to the tertiary structure. Despite this, NO clear concept relating structure to biological activity has been suggested. For interest, the two theoretical structure diagrams of immunoglobulin molecules are given.

### CHEMICAL STRUCTURES

All three major classes of immunoglobulin contain carbohydrate, and this is true of all species studied, including man. The macroglobulins contain five times as much carbohydrate as the IgA and IgG globulins, amounting to 12%-15% of the total dry weight of the protein. Although clearly an important part of the molecule, antibody fragments free of carbohydrate may still react with antigen. The carbohydrate is retained almost entirely on the A chain after enzymic splitting. The small portion associated with the B chain may also be a functionally important part of the molecule. The carbohydrate is always composed of a combination of the following sugar groups known as hexose, fucose, hexosamine or sialic acid.

It might be expected that different antibodies produced in the same animal would show differences in amino-acid composition; but the results obtained from such studies have been disappointing. This might indicate that the antibody combining site is a small part of the molecule. Obviously the secret of antibody specificity resides in the sequence of amino acids rather than in the preponderance of one or other reactive group. Yet differences detectable by amino acid analysis do exist between one antibody and another, although they are slight compared with the more obvious differences between immunoglobulins and other classes of protein. The characteristic features of immunoglobulin are their content of hydroxy and dicarboxylic amino acids, especially proline.

Although differences between individual immunoglobulins are difficult to detect, similarities are more easily demonstrated. Antisera prepared to the human immunoglobulins IgA, IgG and IgM all cross react. This indicates some basic structural similarity between different types of globulin; indeed except for the antibody combining sites, the B chain fragment of any immunoglobulin is similar to that of any other on immunological testing, while the A chains appear to be distinct in each of the three classes.

### INTRODUCTION TO PART II — FUNCTION

An antibody response is found in primitive vertebrates such as the lamprey (Petromyzon) and in all later evolutionary phyla. As shown by comparative embryological studies, the ontogenic development of anatomical structures, such as the pharyngeal pouches is paralleled in the ontogenic development of lymphoid tissue and synthesis of antibodies. In primitive vertebrates, all the antibody formed is macroglobulin of the 19S type, while in mammals the bulk of it is 7S globulin. The production of antibodies in the neonate parallels the phylogenic development of the antibody response. Initially unresponsive, the foetus first acquires the ability to reject homologous tissue. Then it acquires, in late intra-uterine life, the ability to produce 19S macroglobulin in response to appropriate stimulation. Not until some months after birth does the capacity to produce IgA or IgG develop. This chage in the production of IgG in preference to IgM in the mammalian phyla, is recapped in the transition from primary to secondary response at any stage of life. In the primary response, macroglobulin is produced, to be superseded by IgG as the secondary response develops. Thus, in early neonatal and late intra-uterine life, the mammal appears to repeat those evolutionary changes from Lamprey to mammal in respect of antibody synthesis. It would appear obvious that the synthesis of immunoglobulin is necessary for the life of both vertebrates of primitive type, and mammals. It has been assumed that the rôle of the immunoglobulins is the protection against infection. But in the amphibia, for example, the secretion of antibodies is slow, and their protective effects negligible. Such reasoning leads to reflection upon the actual nature of the antibody reaction — is the secretion of antibody an end, or is it merely the serological reflection of some fundamental change occurring within the cell? The second half of this article will attempt to answer this question by examining the rôle of immunoglobulin as a defence mechanism, as a metabolic intermediary, as part of an integrated system of immunity and metabolism, and finally as a theoretical postulate.

### AS A DEFENCE SYSTEM

Following the injection of antigen into an animal, specific antibodies begin to appear among the immuno-globulins of the serum. If a primary response occurs, the specific antibodies are of the macroglobulin type, and occur in low titre. These are soon replaced by the appearance of IgG, and any subsequent challenge by antigen evokes the same IgG response. A few antigens evoke a biphasic response, in which IgM and IgG both persist together; an example of this is the tubercle bacillus. The antibodies secreted combat the infection which stimulates their production in

several ways. Firstly they tend to render the organisms more liable to phagocytosis and ultimate destruction within the macrophages of liver, spleen and lymph nodes. Secondly, antibodies immobilise bacteria by a process known as immune adherence, whereby the organisms are bound to cells which have adsorbed the specific antibody, and thirdly, the antibodies in conjunction with complement may bring about lysis of the bacteria. However, by themselves the immunoglobulins are relatively ineffective inhibitors of bacterial multiplication. In most cases the lethal agent is the cell which phagocytoses the bacterium. Yet the presence of antibodies to a certain organism may exert a protective effect, and the extent to which they do this depends upon:—

(a) the type of antibody present, and its concentration
(b) the virulence of the organism and its type
(c) the time interval between the primary challenge which evoked the antibodies and the secondary challenge.

In the initial primary response, the antibody formed is macroglobulin, and it is present in low concentration. Its protective effects are not as great as those of the 7S gamma globulin which supersedes it. Organisms of high virulence, such as the meningococcus, and salmonella typhi although very susceptible to the effects of antibody may overwhelm the host before sufficient antibody can be produced. In the secondary response, the antibody is 7S gamma globulin, present in high titre, and rapidly produced. As a consequence even virulent organisms are quickly eliminated. It is this type of antibody which confers immunity of the classical descriptions and which must be accorded a central rôle in defence.

Certain types of organism are susceptible to attacks by antibody. Among the bacteria, the pneumococcus, meningococcus, and salmonellae must be mentioned. Viruses are among the most susceptible of all organisms, and the presence of specific antibody inhibits the viraemic phase of most infections with virus. Paradoxically, the life-long immunity conferred upon an individual by an attack of mumps or measles, is not due to humoral antibody, which becomes undetectable in a relatively short time, but to an alteration in susceptible cells which renders them immune to virus attack.

In infections with protozoa, or metazoan parasites such as cestodes or nematodes, the antibody formed appears to modify the course of the infection but slightly, often because of the situation of these parasites.

The duration of the primary, or macroglobulin response is from 5 days to three weeks. The secondary response to a single dose of antigen may produce blood levels which remain detectable from months to years, depending on the type of antigen. The duration of this secondary response is related to the persistence of antigen; pneumococcal polysaccharide may persist in mice for up to 200 days after a single injection. Furthermore, small, almost undetectable, amounts of antigen may persist for very long periods within the cells, and adsorbed onto reticulin fibres within the spleen and lymph nodes. A detectable secondary response will occur within 2 days of the injection of antigen if the primary challenge has occurred within 2 to 3 weeks prior to the secondary challenge. As a general rule, the longer the interval between two injections of antigen the more sluggish is the secondary response. In foetal, neonatal and germfree animals, no secondary response appears to occur; the antibody formed being always macroglobulin unless adjuvants or very high doses of antigen are used.

#### METABOLIC AND REGULATORY FUNCTIONS

It was not until very recently that some proof of a direct intervention of immunoglobulin in the regulatory mechanisms of the body was discovered. In thyrotoxic patients, the substance, Long Acting Thyroid Stimulating hormone (L.A.T.S.) was shown to be a specific 7S immunoglobulin, which fixed to microsomal fractions of thyroid cells. The bulk of the immunoglobulins, as stated earlier, have no demonstrable antimicrobial activity. Indeed, since the antibiotics were introduced, many patients with very low immunoglobulin levels have been recorded; they suffer from the condition of hypogammaglobulinaemia. Despite this relative lack of immunoglobulins many of these patients survive for ten or twenty years. On closer analysis, NO case has been found in which immunoglobulins are entirely absent, and it may be concluded that a complete absence of the immunoglobulins is incompatible with life. Thus the immunoglobulins may be depressed without hazard providing infections are controlled, yet their complete absence has never been recorded. By analogy with the discovery of L.A.T.S. the small fraction of immunoglobulin necessary for life may serve to regulate the external or internal secretions of glandular tissues. Indirect

evidence of such activity may be inferred from studies of the "auto-immune" diseases of thyroid, pancreas, salivary gland, stomach and adrenal, where hypofunction is frequently associated with specific immunoglobulins directed towards microsomal fractions of these tissues. It could be postulated that immunoglobulins are to some extent merely another aspect of the fine feedback mechanisms controlling the functions of glandular tissues.

An essential part of the integrity of function of the body is the ability to repair and replace dead or damaged tissues with either new cells or scar tissue. After trauma resulting in massive cell death, changes can be detected in both the immunoglobulins, and the alpha II fractions of serum proteins. An increase in both these fractions occurs in response to tissue injury; that of the immunoglobulins may result in the facilitation of removal of dead tissue by opsonisation, and the alpha 2 globulins are increased whenever rapid tissue growth occurs. In haemolytic anaemias, the presence of antibodies to red cells shortens their survival time; in the post-irradiation regeneration of bone marrow the alpha 2 globulins are increased. Therefore, a balance of these two factors might be expected to result in controlled regeneration of damaged tissue.

### THE ROLE OF IMMUNOGLOBULIN IN AN INTEGRATED SYSTEM

As far as is known, immunoglobulins are secreted only by the lymphoreticular system, which for present purposes may be regarded as a trio composed of the macrophage, the lymphocyte, and the plasma cell. The immunoglobulins in the serum mirror the changes of cellular pattern in the lymphoreticular system in subtle and fascinating manner. Thus an increase in macroglobulin means hyperplasia in the large lymphocyte element of the R.E.S.; increase in IgG means hyperplasia of the plasma cell. Neither cell type is capable of producing specific immunoglobulin in the absence of the macrophage, which removes bacteria and damaged tissue wherever they occur. The most recent considerations of antibody formation suggest that the macrophage passes on a substance, possibly R.N.A., to the large lymphocyte prior to the secretion of macroglobulin antibody. In the secondary response, the macrophage may not be the initiating cell. The rôles accorded to the different types of immunoglobulin can be reconciled with their cellular origins, and the immunoglobulin can be reconciled with their cellular origins, and the immunological status of the organism. In the foetus, the only antibody present appears to be of maternal origin. This crosses the placenta in selective manner; only 7S gamma globulin will pass, macroglobulins are excluded as are 7S antibodies of reaginic type. Yet when the neonate forms immunoglobulin it forms macroglobulin, the first antibodies to appear being the blood group substances. Thus the macroglobulins might be termed "identity proteins", and the 7S immunoglobulins "immunity proteins". In the primary response macroglobulin is secreted, following which the "identity" of the animal becomes more or less permanently changed, since any further challenge with the same antigen evokes a secondary response. This indicates some cellular change of a permanent nature by at least some cells. Animals in a germ-free environment will synthesise only macroglobulins, even when a fresh antigenic challenge is supplied, again suggesting an "identity" type of change in the organism, rather than an "immunity" one. The most frequent example of "identity" changes in an organism excluding primary infection, is probably tumour growth. The association of lymphoreticular hypoplasia with advanced tumour growth, cachexia, and immunological disturbance is evidence, admittedly diffuse, of some reaction to tumour growth which can scarcely be termed "immunological" in that sense. Moreover, "immunity" to transplantable tumours is only partial and no secondary response occurs.

In response to tissue injury, macroglobulins only are formed in non-pathological states, yet pathological states can be induced by causing the synthesis of 7S immunoglobulin with adjuvants. Here, the non-pathological "identity" change has been superseded by a pathological "immunity" one. The antibodies work with the macrophages to remove or neutralise all extraneous material with antigenic properties, whether this is "foreign" in the form of bacteria or viruses, or arises from the tissues of the organism itself. Their structure and their immunodynamic characteristics fit them for their respective rôles; the prompt synthesis and high combining power of the 7S immunoglobulins in combating bacterial invasion may be cited. The widespread distribution of the lymphoreticular tissues which produce the immunoglobulins also determines that local disturbances, however small, will be met with the appropriate response. The rôle of macroglobulin in this integrated system remains

enigmatic; some macroglobulins, called Milgrom factors, inactivate 7S gamma globulins, and also complement, and could thus act as a control upon the reactivity of the 7S antibodies.

#### THEORETICAL CONSIDERATIONS

In considering the functions of immunoglobulins, the realisation of the state of the tissues producing them is essential. The serum can never be considered in isolation; it is merely a reflection of the widespread changes in underlying cell systems. The functions of immunoglobulins as a system of defence, of metabolic significance, and as an integration system co-ordinating those functions termed "identity" with those termed "immunity", have been considered. Theoretically, the function of immunoglobulin may extend even beyond these considerations. Start with the assumption of Le Chatelier's principle that in a closed stable system any disturbance is met with a change in the physical state which tends to negate the initial disturbance and restore equilibrium. This results in the establishment of an oscillating system analogous to the damped simple harmonic motion familiar in physics. Many well defined examples of servomechanisms occur in biological systems, both at the cellular and organisational levels. The disturbances the whole organism is subject to may be regarded immunologically as affecting the integrity of the body, and the functions of the immunoglobulino-lymphoreticular system act to restore the equilibrium state.

The mechanisms employed, or theoretically able to be employed to these ends are, (a) Stimulating increase in function of some cells, (b) Removal of malfunctioning cells, (c) Inactivation of biologically active materials, such as hormones or enzymes, (d) Neutralisation of toxic materials, (e) A change in the balance between types of tissues; for example, the excess red cell mass occurring in people adapted to high altitudes, (f) Adaptive cellular changes. The immunoglobulins are the effector agents of the lymphoreticular tissues. They can, under certain conditions, increase the functions of cells; for example, the discovery of L.A.T.S. Their rôle in the removal of malfunctioning cells, and inactivation of biologically active materials may be regarded as probable, and neutralisation of toxic materials is achieved by the antibody — Kupffer cell — liver parenchymal cell relationship.

The last two considerations are problematical; but suffice it to say that a relationship can be established between the mass of lymphoid tissue and body mass. People with lymphopenia and hypogammaglobulinaemia, however induced, are always wasted: experimental examples of this are runting syndrome, and long term corticosteroid administration.

In the field of adaptive changes it is obvious that specialised cells, such as liver, kidney and brain, can only adapt within the context of genetically predetermined functional capacity. The lymphoreticular system can adapt in a more subtle way by altering permanently the types of immunoglobulins secreted, and their specificity. The white cells of a sensitised individual are permanently changed from their pre-sensitised state, thus ensuring that any subsequent challenge is met with a modified repsonse. This has been teleologically interpreted as "recognition" of self or not-self, but fundamentally it is merely the reactive state of the organism at the time of challenge before or after adaptive changes have taken place. An amputee fitted with a prosthesis regards it a "self" when walking with it, because he has adapted his form of locomotion to using it. Similarly, it is "not-self" when he removes it before bed because he has not adapted to sleeping with it. The ability to adapt not merely the cells of the R.E.S. but the cells of the whole of the body to the external environment occurs at and after birth. During this short period, the infant is without macroglobulin, as it is throughout the period of intrauterine life. This process, called "adaption" in this article, means the establishment of an initial state of equilibrium. Any antigen introduced during the initial neonatal period of refractivity becomes accepted and treated as self. It is incorporated into the immunological "body image". Subsequent challenge with the same antigen shows the animal to be tolerant to it: no antibodies are formed. To prevent pathological bacteria being incorporated into the "body image", the neonate is protected by transferred maternal 7S immunoglobulin. It is interesting to postulate that the symbiotic bacteria of the mouth and bowel are immunologically treated as "self" and it is because of this they owe their favoured position as symbiants. Germ-free animals remain in a state of foetal organisation in regard to intestinal tract and lymphoreticular system if deprived of these bacteria. They may indeed be the agents which provoke the synthesis of 7S immunoglobulins which marks the maturation of the lymphoreticular system. This

postulated theoretical proposition of the immuno-globulin-lymphoreticular tissue system shows how even the structure of immunoglobulins may be of importance in attempting to unravel the complexity of this most complex structure. The central point is the selective passage of 7S immunoglobulin across the placenta, while macroglobulin is adsorbed and fixed to the placental villi. If macroglobulins are indeed "identity" proteins, their presence in the placental villi might prevent the rejection of the placenta by the mother. Whatever the actual functions of the immunoglobulins prove eventually to be, it is certain that they have some part to play in the organisation and regulation of the growth of the tissues of the body.

#### PART III — SUMMARY

The methods used to classify immunoglobulin in respect of its physical and chemical structure are described. The rôle of immunoglobulin as a defence mechanism together with an analysis of its probable metabolic functions is discussed. The theoretical possibilities of the immunoglobulin and lymphoreticular system as both an integration system and an adaptive one are examined.

#### APOLOGY

In this article two parts may be distinguished, that which may be accounted fact forms the first part. The second is an admixture of fact and ideas, and on reflection it is by no means easy to distinguish one from the other. As an apology, allow this warning to be offered; this article is not a textbook, the ideas put forward may well be wrong. It was written as both an exercise and an amusement and should be read in the same spirit.

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## IS THAT SO?

"The warp of magnetic-fluid reaching between the person impregnated with such fluid, and the air-loom magnets to which it is prepared, which being a multiplicity of fine wires of fluid, forms the sympathy, streams of attraction, repulsion etc. as putting the different poles of the common magnet to objects operates; and by which sympathetic warp the assailed object is affected at pleasure: as by opening a vitrolic gaz valve he becomes agitated with the corrosion through all his frame, and so on in all their various modes of attacking the human body and mind, whether to actuate or render inactive . . ."

from "Illustrations of Madness"—with a description of the tortures experienced by bomb-bursting, lobster-cracking and lengthening the brain in the air loom. by John Haslam, 1810.