THE ANTIBODY DEFICIENCY SYNDROMES

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THESIS

THE ANTIBODY DEFICIENCY SYNDROMES

By

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DEDICATION

To my parents without whom I could not have started;
and to Beth without whom I could not have finished.

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I

Introduction*

When a foreign substance, called an antigen, invades a vertebrate organism certain substances called antibodies are formed in response to the antigen and in one way or another eliminate the potentiality of the antigen doing harm to the organism. This is called the immune response. This process is characterized by (i) its inducibility, being capable of reaction only when activated, (ii) specificity, acting only on those molecules which activate it, and (iii) memory, re- acting much more quickly, to a greater degree and for a lon- ger time the second or more times it is stimulated by any specific antigen; the last phenomenon is termed the anamnes- tic response. In addition to the humoral response, which is mediated by circulating antibodies, there is also a cel- lular, or hypersensitive response which is characterized and mediated by specific kinds of cells whose origin is in

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* In preparing this introductory discussion many texts and reviews were perused by the author. It was decided that the source most relevant and applicable to the main topic was The Gamma Globulins by C. A. Janeway et. al. (36). Unless otherwise indicated all material in this section was drawn from that source. Other good discussions can be found in such texts as Fundamentals of Immunology by W. C. Boyd and Microbiology by B. D. Davis, R. Dulbecco, H. Eisen, H. Gins- berg, and W. Wood.

the lymphoid organs. Hypersensitive immunity includes allergies, atopic (skin) reactions, and delayed-type hypersensitivity.

Antibodies are globular proteins and are contained in the gamma globulin portion of the blood serum when its proteins are separated in an electrophoretic field. The gamma globulins move most slowly toward the anode in a field at pH 8.6 and exhibit a mobility of $10^{-5} \text{ cm}^2 \text{ volt}^{-1} \text{ sec}^{-1}$; they are immediately preceded by the beta globulins, which follow the alpha globulins, which follow the leading fraction, the serum albumen. The alpha, beta, and gamma globulins together are termed the immunoglobulins. These proteins are not, however, found only in the blood; fifty-five per cent of the total body gamma globulin is extravascular (23).

The antibody fraction of the immunoglobulins, abbreviated Ig, is comprised of three major types of molecules designated IgG, IgM, and IgA. These molecules are physically and antigenically distinct. They are comprised of two types of polypeptide chains, light or L-chains which are identical in all three antibodies, and heavy or H-chains which carry the antigenic determinents γ, μ, and α, which characterize the molecules. The antibodies also carry two major genetic markers called allotypes. The Gm allotype, of which some twenty variations have been found, is located on the H-chain of the IgG molecule and so is unique to this class of antibody. The Inv locus appears on the L-chain and is found in all antibodies.

The IgG molecule has a molecular weight of 145,000 to 160,000 and a Y-shape as seen in the electron microscope. This molecule makes up eighty per cent of the serum antibody in adults and is found in the normal adult serum in a concentration of 700-1500 mg%.* The interstitial muscle IgG concentration is 200-250 mg%. It is formed in response to pyrogenic bacterial antigens, viruses and toxins. The IgM molecule is the largest of the antibodies but is only five to ten per cent of the total serum antibody with a normal concentration of 60-170 mg%. It has a molecular weight of 900,000 and is comprised of five gM subunits of molecular weight 180,000 each. Each subunit has two L-chains and two H-chains. This antibody comprises the heterophilic (Forssman) antibodies, Wasserman antibodies, cold agglutinins, isohemagglutinins, and is formed as antibody against the O-antigens of gram-negative bacteria endotoxins. IgA is the hardest to isolate. It has a molecular weight of 160,000 and is ten per cent of the total serum antibody in a concentration of 150-250 mg%. It has few proven specificities but may act as an isohemagglutinin and as anti-Brucellar, anti-diphtherial, and anti-insulin antibody. It is found in the largest concentration in parotid saliva, colostrum, tears, and in lesser amounts in the bile, succus entericus, and prostatic fluid.

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* The notation "mg%" is equivalent to "mg/100 ml."

In the process of the immune response IgM is the first to be present in detectable concentrations followed by IgA and finally IgG. Small doses of antigen elicit only IgM; however, there is then no anamnestic response to a second challenge by the same antigen. The newborn infant starts synthesis of IgM at birth and by the end of his first year has seventy-five per cent normal IgM level. IgA synthesis is usually begun by the third week and is seventy-five per cent normal by the end of the second year. The IgG level is initially high at birth because the infant is protected by maternal IgG which unlike the other antibody molecules can pass the placental barrier. One-half of this antibody is catabolized by the end of the first week, three-fourths by the second month, and so forth. The maturation of the lymph tissue, the organization of follicles and the appearance of plasma cells is complete during the third month of life. At this time the infant starts producing his own IgG.

Antibody is produced by plasma cells in the red pulp of the spleen, the medulla of lymph nodes, and the lamina propria of the bowel. These cells are formed from plasma-blasts which are reticular or other relatively undifferentiated mesenchymal cells in the reticuloendothelial system. In vitro small lymphocytes can be changed into large immuno-globulin producing cells by stimulation with phytohemagglu-tinin, a kidney bean extract. The antibody production occurs in two phases, an afferent phase in which the antigen initiates a response in the cell and an efferent phase in which

the antibodies specific for the antigen are produced. Usually one cell will produce antibody to one antigen and possibly to different specificities of a single antigen; also one cell will synthesize only one type of L- or H-chain. Immunoglobulin synthesis can be inhibited by protein synthesis inhibitors or by purine and pyrimidine analogues which inhibit plasma cell multiplication.

There are two main hypotheses of antibody formation. The template theory argues that the antigen acts as a form on which the gamma globulin is molded into the configuration of an antibody molecule specific for that antigen; the instructional theory states that the antigen in some way affects the plasma cell DNA directly thereby inducing it to produce gamma globulin molecules specific as antibodies for that antigen. Both hypotheses have their strong and weak points, but neither has been proven to be the actual case.

II
The Agammaglobulinemias

In 1952, Colonel O. C. Bruton published the first report of a case in which a child with a history of repeated infections was shown to have no gamma globulin in his blood(5). Bruton termed this disorder agammaglobulinemia. At first it was thought that the absence of both gamma globulin and antibody from the blood were two separate and distinct signs of

the disease (31); it was not shown until later that the gamma globulins were the antibodies. Since Bruton's observations were published several different kinds of agammaglobulin disorders have been distinguished and studied. The major types of this rare disease are transient hypogammaglobulinemia; congenital and acquired agammaglobulinemia; dysgammaglobulinemia; and the even rarer hereditary thymic aplasia, also called alymphocytosis or "Swiss-type" agammaglobulinemia for the location of its first description. Fudenberg also includes a "symptomatic" agammaglobulinemia in which the disorder is not the primary disease but rather a secondary phenomenon caused by the replacement of normal immunologically competent plasma cells by foreign cells in diseases such as myeloma or leukemia (15).

The hallmarks of the disease are an increased susceptibility to bacterial infections as demonstrated by frequently repeated infections over a period of time, an absence of antibody from the blood and tissues, the failure of antibody production in response to antigenic stimuli, and the absence of plasma cells from the tissues (25, 31). However, as assay methods have improved it has been shown that all people with gamma globulin deficiency disorders, even the congenital type, have some small level of immunoglobulin in their body (20, 23, 28).

Transient hypogammaglobulinemia is not actually a disease but rather a physiological state brought about by an abnormally prolonged delay in the onset of immunoglobulin synthesis in the newborn infant after all the maternal IgG has been

catabolized (36, 53, 58). This condition can occur in both
sexes and recovery usually occurs between the ages of nine
and twenty-four months. During this period of deficiency
the infant shows an increased susceptibility to gram-posi-
tive bacterial infections, usually occurring in the skin,
lungs, meninges, and respiratory tract. The IgG reaches
adult level in two to three years (58).

Congenital agammaglobulinemia is a sex-linked disease
and as such occurs only in male children (21, 23). Its onset
is usually at about nine months when all of the remaining
maternal IgG has been catabolized; however, it may start as
late as the second or third year (23). The child is seen to
be subject to repeated infections by pyrogenic organisms such
as Staphylococcus aureus, beta-hemolytic Streptococcus, Mening-
ococcus, Hemophilus influenzae, and usually die of pulmonary
disease if left untreated (53). On the other hand, they show
no increased susceptibility to viral, protozoal, or fungal
diseases, or to infections by gram-negative organisms (23).
They can develop viral diseases expressing typical symptom-
ology and clinical course including recovery and resistance
to reoccurrance indicating a normal capacity to produce inter-
feron in response to viral challenge (22).

There are certain collateral diseases which these child-
ren develop too often for pure chance (28, 46). They include
chronic lymphatic leukemia, an uncontrolled proliferation of
lymphocyte cell-types; collagen diseases, reflecting an

alteration of the connective tissue; and rheumatoid arthri-
tis-like inflammations, many times without a basis in direct
infection of the joints. Occurrence of these with agamma-
globulinemia questions the belief that they are due to ana-
phylactic-type hypersensitivity. But the demonstration that
agammaglobulinemic patients can develop bacterial allergies
even with the inability to form antibodies indicates that
they may have an allergic basis instead.

In congenital agammaglobulinemia the IgG level is found
to be anywhere from less than 10 mg% to as much as 80 mg%
(21, 23, 35, 36, 47, 54) but it is generally around 25 mg%;
the IgM and IgA levels are about one per cent of normal
though no demonstrable isohemagglutinins are present (53).
This is seen to be a total body deficit not just a blood
disorder (21, 23). IgG administered intravenously or intra-
muscularly is catabolized at a normal or slower-than-normal
rate (21, 22, 31, 45, 60) so that the deficit is due to de-
creased synthesis not increased destruction or loss. This
is likewise reflected by the almost total absence of plasma
cells, the antibody producing cells, from the lymph nodes,
spleen, intestine and bone marrow where they are usually
found (21, 23, 46). The lymphocyte count which is a standard
indication of the ability to respond to immune challenge is,
on the other hand, normal at approximately 2000 cells/mm^3 (36).
The serum constituents involved in resistance to infection
such as complement, lysozyme, and properdin are in normal con-
centrations (36, 53). Atopic, allergic and delayed

hypersensitivity reactions, that is, cellular immunity, are
also seen to be normal; however, at the same time antibodies
are just not elicited by any antigenic stimulation including
those by such antigens as diphtheria, pertussis, typhoid,
and tetanus. It is interesting to note that certain animal
viruses and phage particles can cause very low titers indi-
cating that the small amount of antibody present in the
serum is not inert (53). These children cannot reject homo-
grafts (24, 27, 30, 31, 32, 43).

Finally, Tennenbaum observed a sporadic form of congeni-
tal agammaglobulinemia which seemed to represent an autosomal
rather than an x-linked recessive trait (58). The IgG con-
centration was reported as high as 400 mg% and low titers of
IgM, IgA and isohemagglutinins were seen. One-third showed
splenomegaly, and one-sixth lymphadenopathy.

An agammaglobulinemic condition occurring after four
years of age is usually considered an acquired agammaglobu-
linemia. This is an arbitrary cut-off point chosen due to
the overlapping at this early age between this and the con-
genital form of the disease. The acquired disease affects
both sexes equally and may be manifested as late in life as
the fifties (23, 54, 58, 61). These patients exhibit the same
signs and symptoms as do children with the congenital form,
namely, undue susceptibility to infection with pyrogenic
organisms, lack of plasma cells, and decreased antibody con-
centrations. The lack of plasma cells, in this case, is
due to the abiotrophy of the plasma cell containing follicles

instead of a congenital defect in maturation (36, 53). The
IgG level varies greatly with a reported range of 10 mg% to
500 mg% (36), but it is usually between 50 and 100 mg% (23).
A complication of this form but not the congenital type is
a sprue-like syndrome (sore mouth, gastrointestinal mucous
membrane inflammations, loss of weight, weakness, and a per-
nicious anemia-like blood disorder) including malabsorption
difficulties; however, biopsies of the bowel are usually
normal (36). There are frequent instances of noncaseating
granulomas of the lung, spleen, and liver (53). These pa-
tients reject homografts normally (27, 30, 31, 32, 54). One
hypothesis for this disorder is that it may be due to the
failure of a homeostatic mechanism for the immune system (47).

The primary type of acquired agammaglobulinemia, just
described, is not associated with any underlying pathology
but has been genetically linked to family immunoglobulin
disorders and familial predisposition to collagen diseases.
The families of people with acquired agammaglobulinemia show
an unusually high rate of qualitative and quantitative gamma
globulin abnormalities, much more so than do families of
children with the congenital disease (13, 15, 56). Positive
reactions to Coombs' test for Rh antibodies have also been
found in unexpected frequency in first degree relatives (15).
It is most widely hypothesized that this familial disposition
is the reflection of a generalized hereditary disease of the
mesenchymal tissue rather than a defect restricted to the
gamma globulins (13, 15, 27, 62). Therefore, under different

circumstances this genetic trait or group of traits may be expressed as a collagen disease, agammaglobulinemia, bony defects or some other congenital abnormality. One-third of the people with acquired agammaglobulinemia have arthritis, sometimes rheumatoid arthritis, others have collagen diseases and widespread fibrinoid vascular diseases (62).

Secondary acquired agammaglobulinemia is due to diseases nor primarily involving the immune system (58). Patients with this type of disorder have either some blood dyscrasia or diseases characterized by abnormal loses of serum proteins; also seen connected with this syndrome are chronic lymphatic leukemia, multiple myeloma (bone marrow tumors), Waldenstrom's macroglobulinemia (elevated IgM, lymphocytosis of the bone marrow), nephrosis, and protein losing enteropathies.

The dysgammaglobulinemias are disorders in which only specific immunoglobulins are absent while the others are normal or elevated. Janeway et al., classified the dysgammaglobulinemias into three main types: Type I in which IgG and IgA are absent and IgM is elevated; Type II in which IgA and IgM are absent and IgG is normal or slightly depressed; and Type III in which IgA is absent but IgM and IgG are normal (36). This disease affects both sexes and may be congenital or acquired. It is most likely a recessive autosomal trait (58). Plasma cells may be anywhere from absent to present in a normal number. However, a large per cent of sufferers are unable to produce delayed hypersensitivity reactions (58).

Hereditary thymic aplasia, the so-called "Swiss-type" agammaglobulinemia, results from the failure of the embryonic differentiation of the thymus gland (36). This type of agammaglobulinemia is much more serious than the other types because there is no immunologic competency at all in these patients, cellular or humoral. They usually die within their first eighteen months of life despite gamma globulin therapy and/or thymus gland homografts (11, 46). This is mainly an autosomal inheritance and strikes both sexes though it occasionally shows x-linked characteristics in some families (36, 52). Children with this disorder show a sudden precipitous failure to thrive and grow. A distinct "runting" syndrome is evidenced. They show susceptibility to both gram-positive and gram-negative bacteria, delayed hypersensitivity is uniformly absent and vaccination is disastrous causing fatal progressive vaccinia (36). They cannot reject homografts (11, 46). A deficit of lymphocytes in the blood, bone marrow, and lymphoid organs is evident (36). In one case the peripheral lymphocytes were seen to be in a thirty to sixty per cent normal concentration despite the thymic aplasia (42). These cells, however, did not respond to phytohemagglutinin. Rosen reported the successful transferrance of hypersensitivity with maternal bone marrow cells and the concomitant elevation of the peripheral blood lymphocyte count to a normal level (52). Unfortunately, the infant died before its ability to produce antibody could be tested.

III

Delayed Hypersensitivity

The fact that agammaglobulinemic patients could exhi-
bit delayed-type hypersensitivity while apparently remaining
negative as to circulating antibody production proved to be
a great boon to immunologists. Here was a ready-made test
system provided by nature for the determination of whether
delayed hypersensitivity was due to circulating antibody or
a cellular mechanism.

Many investigators have shown that agammaglobulinemic
patients can give positive Schick (3, 6, 31, 47) and Dick
(3, 31) tests even after injection with toxoid, and positive
tuberculin tests (23, 51), though in some cases only after
immunization with BCG (47, 48). In addition, positive skin
reactions to 2,4-dinitroflurobenzene (DNFB) (23, 33, 47, 48);
skin reactions to poison ivy (23, 36, 49), and drug reactions
to penicillin (23, 43, 45) and novobiocin (45) have been re-
ported. Also in the literature are positive monilia reac-
tions (7) and reactions to Ascaris extract (27). Many of
the investigators have been able to transfer the hypersen-
sitivity to normal persons via leukocytes but not via serum
(27, 32, 33, 47). This is the most direct evidence for a
purely cellular basis for hypersensitivity. One investiga-
tor was able to passively transfer hypersensitivity to an
agammaglobulinemic patient from a normal person; this state
endured for one and one-half years (31). In none of these

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cases, however, were any antibody responses elicited, even to bacterial antigens such as diphtheria, pertussis, typhoid, and pneumococcus. No mouse protecting or complement-fixing antibodies to viruses were elicited from these patients though they did show normal symptoms and recovery from viral infections (3, 6, 31, 49). Skin tests to alpha- and beta-hemolytic Streptococcus, pneumococcus, Staphylococcus aureus, Micrococcus tetrogenes, streptokinase or streptodornase proved negative (23). Reactions to vaccinations are erratic (31). Of five patients vaccinated prior to admission, four showed typical reactions while one failed to react to four vaccinations. Two others showed accelerated responses to repeated vaccinations.

Accumulation of evidence of this type led to the conclusion that hypersensitive reactions are mediated by some mechanism other than one involving circulating antibodies. It is believed that it is some sort of cellular response probably mediated by the lymphocytes and macrophages. Exactly how it works, however, is not known, only that it works.

IV

Fate of Homografts

Just as the circumstances of agammaglobulinemia became a proving ground for delayed skin reactions so too it became

the laboratory for the exploration of the graft rejection phenomenon in humans. In this field of investigation the results are nowhere near as clear as in the area of delayed hypersensitivity. Most, if not all, investigators agree that persons with transient (54) and acquired agammaglobulinemia (27, 30, 31, 32, 54) can and do reject skin homografts; persons with congenital agammaglobulinemia usually accept them with more alacrity (24, 27, 30, 31, 32, 43) though on occasion they can reject them normally (51, 54). Investigators tried to utilize lymph node and thymus transplants as therapy, hoping the grafts would take and provide a population of cells with the ability to provide the recipient with some protection or with some factor which would help him become immunologically competent. The few experiments along these lines were somewhat uniform in their results but erratic in their conclusions.

Using lymph node transplants Good got no gamma globulin production in congenital agammaglobulinemia but did restore a definite but minimal immune response to subjects with the acquired form (30). Martin got full function in eight transplants into patients with the congenital disease (41). The nodes functioned normally for 100-110 days and then partially for 50-60 days after that. There was still never any detectable rise in gamma globulin concentration, but the patients did develop a specific delayed cutaneous hypersensitivity to donor leukocytes though they produced no circulating antibody to them. This was also noted by Gitlin (24). Martin's

subjects remained free of major infection for the life of
the transplant but suffered severe repeated infections once
again after their rejection. Working with congenital agamma-
globulinemia Gitlin found that after implantation of unstim-
ulated lymph nodes, stimulation caused low titers of antibody
to appear for pertussis (23). These nodes were further seen
to hypertrophy during periods of upper respiratory infection.
In patients with the acquired form, implantation of previously
stimulated lymph nodes gave an antibody titer for about two
months (22, 23).

Experiments with thymus implants have shown that the
graft can survive but has little or no effect on the recip-
ient (24, 34, 52). Gitlin et. al. found at autopsy that the
implant was compressed, the small thymocytes were gone though
the large thymocytes (reticular cells) remained, only remnants
of Hassall's corpuscles were visible, plus there had never
been any host tissue reaction (24). A lymph node draining
the area of the implant showed no histological change, it
was still devoid of lymphocytes. In addition, the number of
lymphocytes in the peripheral blood was unaffected by the
implant. In Harboe's experiment a fetal thymus was implanted
in the rectus abdominus of a patient with agammaglobulinemia
and severe lymphocytopenia (34). Prior to the transplant
no plasma cells were seen in the bone marrow, afterwards
small numbers amounting to one to two per cent of the leuko-
cyte population appeared. Cell migration to the graft was
negligible (in neonatally thymectomized mice, lymph cells

repopulate a thymus graft after the donor cells are gone). No delayed-type hypersensitivity was ever restored though an increased concentration of donor type gamma globulin appeared in the host's circulation. This did not affect the wasting disease or the clinical course of the agamma-globulinemia.

These studies were meant to help decide whether homograft rejection is mediated by circulating antibodies or a cellular-type immune mechanism. Stetson concluded that delayed homograft rejection in patients with agammaglob-ulinemia supported the participation of circulating antibodies in this process (57). However, most other investigators showed that the graft rejection process was not associated with detectable antibody formation but rather was probably a delayed hypersensitivity type reaction (10, 42, 51).

This prompts one to ask why children with congenital agammaglobulinemia who can express delayed hypersensitivity cannot readily reject homografts. It may be that the minimal amount of antibody present in acquired agammaglobulin-emia is enough and/or necessary to mediate graft rejection possibly acting as a cofactor with the cellular immune process.

V

Pathology

The singularly distinguishable defect in the agammaglob-
ulinemias is the absence of plasma cells and plasma cell pre-
cursors from the lymphoid tissue, even after stimulation with
virulent antigens (10, 19, 23, 31, 51, 63). The lymphoid
tissues themselves are disorganized or atrophied, showing
little or no follicular development (23, 46, 53). In the
congenital form there is a striking absence of adenoid tissue
in lateral view x-ray photographs of the nasopharynx (23, 36,
39, 53). This is, in fact, a diagnostic test for this form
of the disease. There is usually a hyperplasia of reticular
cells but the lymphocytes will be lowered in number (19, 53).
The tonsils and appendix show hypoplasia and disorganization
(36, 53, 58). There are more small lymphocytes seen in the
lamina propria and spleen than in the lymph nodes, but no
germinal or toxic centers are evident (19). The thymus is
usually of normal size and may even have a fairly well de-
veloped lobular structure (15, 19, 40, 58) but the Hassall's
corpuscles are absent or gone and so are the small thymo-
cytes (62).

Treatment of normal persons with cortisone can produce
the symptoms of agammaglobulinemia, but pituitary-adrenal
cortical function has been shown to be normal in agammaglob-
ulinemia (26, 31, 33) as has liver function (30, 51).

Hematological disorders are the rule (8, 15, 21).

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There are defects in the maturation of neutrophils, eosino-
phils, and lymphocytes expressed as neutropenia and aleuko-
cytosis. Whether infections are the primary etiology and
hematological disorders are secondary to the toxic effects
of the infection, or whether the disturbances in the peri-
pheral blood represent an inherent cellular defect peculiar
to agammaglobulinemia is not clear (22). Also evident is
the absence of beta$_{2A}$ and beta$_{2M}$ globulins (8, 15, 21) and
the presence of the abnormal globulins beta$_{2E}$, beta$_{2K}$, and
gamma$_{1A}$ (4).

The pathology is somewhat more striking in the "Swiss-
type" (alymphoplastic) agammaglobulinemia. The thymus is
extremely small, weighing from a few milligrams to around
three grams, and sometimes even unrecognizable from sur-
rounding connective tissue. No Hassall's corpuscles are
visible, and the lobules, poorly defined if present at all,
are separated by large amounts of connective tissue (11, 18,
36). Some autopsies have shown that the gland did not des-
cend to its normal intrathoracic position but remained in
an embryonic location in the neck, thereby being a truly
vestigial organ (46). Lymphocytes as well as plasma cells
are completely absent from the lymph nodes, spleen, tonsils,
and lamina propria (19, 46). Gitlin found that despite the
thymic aplasia, there were significant numbers of small
lymphocytes in the peripheral blood, perhaps originating
from the appendix (19).

The complement system has been found to be subtly

affected in all types of agammaglobulinemia. This immun-
ologically important system consists of eleven proteins,
designated C'1 through C'9, C'1 having three components.
It exists naturally in the blood and can combine with an
antigen-antibody complex causing lysis of the antigen if
the antigen is an intact cell. Though as a whole its level
is always found to be normal or slightly elevated (1, 52, 58)
this has been shown to be an artifact (22, 37). Jonsen
and Käss in 1957 showed that though the total complement
level was normal the C'1 fraction was depressed. This
was seen to have been balanced by a concomitant elevation
of the C'4 concentration. Gewurz in 1968 showed that it
was specifically the C'1q fraction of the C'1 that was
diminished. C'1q is a gamma globulin and it directly
mediates the binding of the other proteins to sites on the
antibody molecule. It was found to be markedly more dimi-
nished in the "Swiss-type" (27% normal) than in any other
form of agammaglobulinemia (75% normal). At the same time,
C'1q titers were normal or elevated in other diseases asso-
ciated with repeated infections and malignancy (17). There-
fore, this deficiency was related to the type of agammaglob-
ulinemia not the extent of the immunological deficiency,
and seemed to be a part of the inborn defect. The child
does retain the ability to exert complement dependent
bacterial and immune adherence functions (unfortunately,
the complement-fixing antibodies are not produced).

Chromosome studies done by Fudenberg and Ahuya in both

congenital and acquired agammaglobulinemic cases showing no underlying disease such as lymphoma or leukemia, were negative as to gross aberrations of the chromosomes (12).

VI

The Immune Systems

Immunological experiments involving the chicken led to the first unequivocal demonstration of an animal with two distinct and independent immune systems (9, 17). One is rendered competent by the thymus gland and is represented by the small lymphocytes and the white pulp type of development in tissues. It is responsible for the development of immunologic competence reflected in the ability to initiate a response to an antigen. The other system is directed by the Bursa of Fabricius, an organ located near the cloaca, and is represented morphologically by the large lymphocytes and functionally by the ability to produce antibodies. This separation is also seen in rabbits, where the thymus has been shown to be necessary for the development of an immune response but at the same time plays no part in the enhancement or inhibition of antibody production (1, 38, 39). It is thought that the gut lymphoid tissue (Peyer's patches and the appendix) is the mammalian equivalent of the Bursa of chickens. Studies showed that manipulation of these two

systems in the chicken could produce agammaglobulinemia syndromes identical to those seen in humans. This was the first time that agammaglobulinemia could be tied directly to the workings of the immune response in an experimental model.

Thymectomy and irradiation of chickens caused them to lack a substantial population of small lymphocytes, to lose the ability to develop allergic reactions and exhibit graft-versus-host reactions, and to be unable to reject homografts. They were also unable to form antibodies to certain antigens even though there were normal amounts of IgG and IgM in the blood (9). Bursectomy and irradiation did not influence the normal development of a system of small lymphocytes in the lymphoid tissue, the ability to reject homografts, or the showing of normal graft-versus-host reactions. It did, however, impair their ability to synthesize clearly definable immunoglobulins, completely destroyed their ability to form circulating antibodies even to strong antigens, and prevented the formation of germinal follicles and plasma cells (9, 45). These symptoms and manifestations are almost identical with those seen in congenital agammaglobulinemia in humans (46). In addition, chickens which were irradiated, bursectomized and thymectomized were agammaglobulinemic, leukopenic, and lacked both the humoral and cellular immune responses (9). This is identical with the "Swiss-type" of agammaglobulinemia seen in man.

The discovery of two independent immune systems which

allow the production of conditions in fowl identical to those manifested in human agammaglobulinemia has allowed investigators to more clearly approach an explanation for the pathology of the disease in man. It is this separation of functions that would explain why agammaglobulinemic persons can display cellular immunity while being devoid of humoral antibody, why the lymphocyte count may be normal while there is a virtual absence of plasma cells, and why patients with certain agammaglobulinemias can reject homografts while others cannot. We are probably looking at various degrees of impairment of one or both of the systems rather than a defect in a single integrated response mechanism.

Evidence for this is seen in that the thymus in man too appears to have no clear effect on the germinal centers or plasma cells (the immunoglobulin production center of man) (9, 22). The tonsils and appendix are found to be disorganized in congenital agammaglobulinemia and these organs have been indicated by many as being the possible human counterparts of the Bursa in chickens (2, 9, 32). Recently, however, this has been seriously questioned and Peyer's patches have been most strongly implicated along with the appendix and other gut lymphoid tissue (Personal Communication with R. Hong of R. A. Good's group at the University of Minnesota).

VII

Hypotheses for the Defect

There are two main hypotheses for the defect which causes the agammaglobulinemic condition in persons with the typical forms of this disease. One group feels the fault lies in the genetics of cell transformation (22, 50, 59) while the other cites the genetics of antibody polypeptide chain synthesis (14, 15, 18). Both agree that the result is the failure of the transformation of pre-plasma cells to plasma cells; it is the process causing this that they disagree on. (However, one cannot get around the virtual congenital absence of plasma cell precursors that underlies the "Swiss" form of agammaglobulinemia.)

One argument is that since some gamma globulin, no matter how slight, is produced in agammaglobulinemia it is unlikely that the disorder can be attributed to the absence of gamma globulin alleles (22). Furthermore, the mode of inheritance of agammaglobulinemia, according to Rosen, is different from that of the gamma globulin allotype making it unlikely that these immunoglobulin disorders are directly due to a genetically determined inability to synthesize all or part of the antibody molecule (50). It is more likely due to a genetic variation involving plasma cells either as (i) an absence or suppression of genes necessary for the synthesis of a substance essential to plasma cell formation, or (ii) a genetic variation resulting in a substance inimical

to plasma cell formation. (The latter seems questionable since Tormey et. al. demonstrated that serum from agamma-globulinemic patients did not inhibit plasma cell production from normal precursors induced in vitro with phytohemagglut-inin (69).) Rosen goes on to state that since in the absence of plasma cells, gene complexes for gamma globulin synthesis lack the means of expression, the formation of plasma cells could be dependent on activation of gamma globulin genes and consequently these cells could not develop in the absence of these genes. This would seem to be almost exactly what Fudenberg is saying except that instead of the gamma globulin genes being absent, Fudenberg sees them as being present but defective (14, 15); this would amount to the same thing if the transcription was inhibited or in some way defective.

In experiments with phytohemagglutinin and streptolysin-S Fudenberg showed that lymphocytes from agammaglobulinemic patients showed the same mitotic potential as did normal lymphocytes but no gamma globulin synthesis; he therefore concluded that the problem was not in the genetics of cell transformation but rather in its inducement. He feels that it is the initial production of antibody that initiates the transformation of plasmablasts to plasma cells rather then vice versa as Nossal postulated (Sci. Am., Dec. 1964). The primary defect is therefore the aberrant or lack of produc-tion of the L- or H-chains resulting in defective antibodies, and the lack of differentiation of lymphocytes to plasma cells is the secondary morphological result of this genetic defect.

This conforms with Rosen's hypothesis that the defect is the absence or suppression of genes necessary for the synthesis of a substance required for plasma cell formation. In this case, that substance is antibody itself.

The defect in antibody synthesis could possibly be (i) a mutation at regulator gene loci controlling quantitative aspects of immunoglobulin chain synthesis; (ii) the loss or duplication of genetic material due to unequal homologous crossing-over during mitosis or meiosis of chromosomes bearing the structural genes for the H- and L-chains (55); or (iii) a mutation at a structural gene (14). The structural gene codes for a messenger RNA (mRNA) whose sequence is read on the ribosomes and translated by transfer RNA into an amino acid sequence thus creating a protein, in this case, part of an antibody molecule. Cline et. al. showed quantitative abnormalities in net RNA labeling in lymphocytes from agammaglobulinemic persons. However, since the synthesis of ribosomal and transfer RNA was grossly normal, it seemed apparent that the defect was associated with either the afferent phase of the cell's response or with the transcription of the DNA (8). In this case a mutation in a structural gene could possibly result in (i) the formation of appropriate mRNA but in insufficient quantities; (ii) the formation of altered mRNA incapable of coding for normal immunoglobulin; or (iii) the formation of faulty mRNA capable of binding to and "blocking" ribosomes responsible for the synthesis of

immunoglobulin polypeptide chains (15). Any one of these defects would cause aberrant production and, therefore, aberrant plasmablast transformation.

As one can see, there are intrinsic contradictions in each of these theories. When the antibody producing mechanism is available in a normal cell, stimulation with phytohemagglutinin will initiate antibody formation prior to mitosis (15). So, if the genome for antibody production is unimpaired but those for the cells that utilize them are, why is it that precursor cell lines can be induced by nonspecific stimulants into transforming into unproductive antibody producing cells? On the other hand, if it is the antibody coding genes that are defective but not the transformation ones, why is some small level of antibody found in all patients with agammaglobulinemia? The answer to the latter question might be found in abnormalities at the Gm or Inv loci. The Gm markers are found only on IgG molecules but the Inv allotype is found in all antibody classes. Aberrations at all Gm and the Inv locus would result in true agammaglobulinemia, but abnormalities of only the Inv would result in antibody molecules completely lacking or having nonfunctional antibody combining sites. Patients so affected would have measurable but physiologically inert immunoglobulins (18). This could explain why there might be low levels of perhaps "natural" antibodies present in the blood but none produced by an immune response since the inducer molecules, the antibodies themselves, are defective and unable to cause

a response to a challenge. This is assuming, of course, that the change of a single amino acid in the allotypic marker sequence would be enough to completely inhibit the effectiveness of the molecule. It is obvious, though, that if the condition were due solely to a defect in the antibody coding genome, then the disease would have to appear as an autosomal trait. In the case of the sex-linked varieties there may then be a represser molecule being coded for on the x-chromosome. This cannot be said for the transformation genome, however, since it is not known how this is inherited.

VIII

Summary and Conclusions

The immune response of man protects him from invasion by foreign and therefore potentially damaging organic materials. This response can take two forms, a humoral one mediated by proteins called antibodies, and a hypersensitive one mediated by cells from the lymphoid organs. The antibodies are gamma globulins and are synthesized by the plasma cells in three major types, IgG, IgM, and IgA.

Recently, a condition has been discovered in man in which the blood and tissues are devoid of the antibodies. This has been termed agammaglobulinemia. The disorder can take several forms including a nongenetic physiological

state occurring shortly after birth, and a genetically determined defect which may be congenital or acquired. The acquired form is so called because it occurs later in life and was identified and named before it was known to have a genetic basis. A third type of agammaglobulinemia, hereditary thymic aplasia, is a result of embryonic defects in the differentiation of the thymus gland.

The agammaglobulinemic disorders are uniformly characterized by the absence of plasma cells from and the general disorganization of the lymphoid tissues. Since it is this absence of plasma cells that is the singular gross defect responsible for the lack of gamma globulin, the agammaglobulinemia must be thought of as a secondary condition brought about by the actual disease which this author believes could more accurately be termed some sort of aplasmacytosis.

In the clinical course of the disease patients suffer repeated virulent infections without the ability to produce antibodies against the invading organisms. They can, on the other hand, demonstrate allergic (cellular) reactions to them. Children with hereditary thymic aplasia cannot exhibit humoral or cellular immunity and, in addition, cannot reject homografts. Patients with the congenital form cannot reject homografts either, but those with the acquired type can. People with the acquired form also develop collagen diseases too frequently for pure chance thereby suggesting the possibility of some reciprocal or common causal relationship.

The paradox of patients with typical agammaglobulinemia being able to exhibit cellular but not humoral immunity has been partially explained by the discovery of the existance of two independent immune systems. One system, dependent on the thymus, is responsible for the cellular immunity, the other dependent on the gut lymphoid tissue is responsible for Ig competency. Experiments with these systems in chickens has led to the creation of syndromes in fowl identical to those seen in human agammaglobulinemias. Destruction of only the Ig system resulted in typical agammaglobulinemia with intact cellular immunity, while destruction of both systems caused a syndrome identical with hereditary thymic aplasia.

The circumstances of agammaglobulinemia and the syndromes produced by it have been used as a model system for the elucidation of the basis for hypersensitivity and homograft rejection. It has been shown that hypersensitivity is the result of cellular immunity since it can be transferred from agammaglobulinemic patients to normal persons via leukocytes. The basis of homograft rejection, however, is still not clear since children with congenital agammaglobulinemia cannot reject them while people with the acquired form can.

Even though this insight has been gained into the nature of the normal immune response, the nature of the disease itself is essentially as much a mystery now as it was in 1952. The more that speculation is made in this area,

the more questions there are raised. For instance, if a person with 100 mg% gamma globulin can reject homografts with the same alacrity as a person with 1200 mg% who is to say what a "minimal" amount of gamma globulin is? A "normal" amount may be 700-1500 mg% but is all this gamma globulin really necessary or is it a supersaturation for the purpose of being a totally unassailable defense? There are persons with congenital agammaglobulinemia who lead perfectly normal lives even without gamma globulin therapy. The only sign of their deficiency is an abnormal electrophoretic pattern.

Hypotheses for the cause of the agammaglobulinemic condition are based on explaining the fundamental defect, the absence of plasma cells. There are two main hypotheses, both are genetic in nature. One contends that the defect lies in the genetics of plasma cell precursor differentiation thereby eliminating the possibility of antibody synthesis. The other states that plasmablast differentiation is actually antibody induced and therefore the defect is in the genome coding for antibody production thereby depriving the system of its inducer molecule. Both these hypotheses have their drawbacks and neither has been conclusively proven. The problem with making genetic hypotheses at this time is that not enough is known about the antibody producing and trans-formation genomes themselves. With the possibility of re-presser and inducer mechanisms, histone concentration var-iables, and interacting autosomal and sex-linked genes, the variety of theories that could be compounded is staggering.

Experiments in bone marrow replacement and general lymphoid tissue transplantation has pointed to a possible direction for finding a cure for the disorder. Currently, the routine therapy is gamma globulin replacement. Interestingly enough, though, the cure might be found before the disease is discovered. This might have to wait until DNA reading and genetic surgery are realities.

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APPENDIX

APPENDIX

The DiGeorge Syndrome

Another syndrome which lends evidence for the presence
of two independent immune systems in man was first described
by DiGeorge in 1965.[1]   It is caused by a congenital failure
in the development of the thymus gland from the third pharyn-
geal pouch. (The parathyroid glands also fail to develop
causing hypothyroidism, but this plays no known part in the
syndrome.) The symptomology resulting from this anomaly,
which should not be confused with Swiss-type agammaglobulin-
emia, is a mirror image of that manifested in congenital agam-
maglobulinemia, thereby demonstrating unequivocably the exist-
ance and independence of the two systems. The DiGeorge syn-
drome is characterized by the failure of the thymus and thymus
dependent lymphocyte system to develop. The presence of nor-
mal immunoglobulins and normal antibody formation is paralleled
by an absence of cellular immunity including impaired delayed
hypersensitivity, homograft rejection, and in vitro lymphocyte
response to phytahemagglutinin. In congenital agammaglobulinemia

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the latter is normal and the former is grossly impaired. The children described by Kretscher showéd negative hypersensitive reactions to monilia, streptodornase, streptokinase, diphtheria toxoid, DNFB, and PPD while exhibiting prompt and extremely high secondary humoral responses to diphtheria and tetanus toxoids.[2] However, patients with this syndrome die of repeated infections with bacteria, viruses, and fungi even with normal immunoglobulin concentrations. (This would imply the import of the cellular defense in combating disease.) They have normal cortical germinal centers in the lymph nodes and spleen with at least normal numbers of plasma cells present there and in the medullar regions. The follicular development of the Peyer's Patches is normal. On the other hand, there is a moderate to marked deficit of lymphocytes in the deep cortical (thymus dependent) areas of the lymph nodes and the venules and periarteriolar sheaths of the spleen.[3] The circulating blood lymphocyte count is normal or nearly so but these cells show no response to PHA. The polymorphonuclear-leukocyte function is normal as are the erythroid and myeloid precursors in the bone marrow. This indicates no accompanying disorders as is regularly seen in agammaglobulinemia.

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Cleveland has reported total immunologic restoration of a
patient with the DiGeorge Syndrome by thymus transplantation
therapy.[4]

This syndrome in humans is equivalent to that which can
be induced in chickens by total body irradiation and removal
of the thymic masses while leaving the Bursa of Fabricius
intact.

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