LOW RESISTANCE TO INFECTION: RELATIONSHIP TO ABNORMALITIES IN GAMMA GLOBULIN*

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I WOULD like to take a moment to review briefly what is meant by the term "γ-globulin." As we all know, the γ-globulins are a group of proteins present in normal human plasma with which are associated the antibody properties of blood. With the role γ-globulin plays and may play in modern medicine, it is somewhat disillusioning to note that the term γ-globulin was applied to this group of plasma proteins simply because it was the slowest of three main groups of globulins migrating in an electrical field and what could be more logical than simply designating it by "γ", the third letter of the Greek alphabet? Through the ingenuity and perseverance of Dr. E. J. Cohn and his collaborators, it was found possible to chemically isolate the γ-globulins from pooled normal human plasma and subsequent investigation has revealed that almost all the antibodies of human blood are in this γ-globulin fraction. It is at once apparent, therefore, that low resistance to infection would be one of the most probable consequences of a deficiency or absence of this group of proteins in an individual.

This evening, I should like to discuss several clinical conditions in which a marked deficiency or even absence of γ-globulin does indeed occur in association with severe recurrent bacterial infections. Since such a deficiency may result either from failure in formation of γ-globulin or from excessive loss of γ-globulin from the circulation, these conditions may be divided into a primary group and a secondary group. In the primary group, the marked deficiency or absence of γ-globulin is due to a failure in the *synthesis* or formation of γ-globulin, whereas

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in the secondary group, the deficiency is due to excessive catabolism of γ-globulin or to direct loss of γ-globulin from the circulation. The primary group may be tentatively subdivided into at least three clinical forms of hypogammaglobulinemia: 1) congenital agammaglobulinemia, 2) adult agammaglobulinemia, and 3) transient or physiological hypogammaglobulinemia. The secondary group is even less clearly defined but an example of this group would be the nephrotic syndrome in children.

With Dr. Charles A. Janeway, Dr. Leonard Apt, Dr. John Craig and with the help of our colleagues at other institutions, it has been our privilege to observe and study fifteen children with congenital agammaglobulinemia. Of these fifteen patients, all have been males; in three instances there has been a history of other male members of the immediate family having died of presumably the same condition, and, in three families, maternal uncles or maternal male cousins were similarly afflicted. In one case, three male siblings succumbed to bacterial infection, and the only female escaped unscathed—and this in the last ten years during the age of antibiotics. These findings plus the fact that this condition is first manifested in infancy or very early childhood have suggested to us that it is probably congenital and that the defect is presumably hereditary, being recessive and sex linked, the inheritance pattern resembling that for hemophilia. As a word of caution, may I remind you that, with this type of inheritance pattern, it is at the moment theoretically possible, although unlikely, that a female may have this condition.

Clinically, these children when untreated are characterized by an unusual frequency of severe bacterial infection.[1-3] Pneumonia, septicemia and even meningitis are of relatively common occurrence in this group of patients. The individual picture, however, is by no means constant. One patient may be afflicted with repeated attacks of pneumonia; another may suffer several attacks of meningitis alternating with episodes of pneumonia or septicemia; while still another patient may have persistent sinusitis and otitis media eventually culminating in meningitis. Thus, the pattern of infections encountered varies considerably from patient to patient. While congenital agammaglobulinemia would be an obvious possible diagnosis in the child with recurring severe infections, it might not be so apparent in a patient with a milder course. Our awareness of this condition is increasing as our experience grows; as an ex-

ample, a random sampling in a small bronchiectasis clinic revealed two children with agammaglobulinemia. Since available prophylactic therapy has proven quite effective, early recognition of this condition is essential *before* irreversible structural damage to organs occurs, *before* the child develops irreversible bronchiectasis as a consequence of bronchopneumonia, or cerebral palsy and mental retardation as a result of meningitis.

In view of the severity and frequency of the infections endured, it is doubtful that many of these children would have survived before the days of chemotherapy. Although these children are extremely susceptible, and several have succumbed, to multiple recurring bacterial infections, their response to some of the viral infections of childhood has been relatively normal. In accord with this finding is the fact that although these children failed to produce detectable antibodies in response to artificial stimulation with a variety of bacterial antigens, vaccination with vaccinia virus resulted initially in normal primary takes followed by an immune response to vaccination two to three weeks later. Antibodies against vaccinia virus were either absent, however, or present in very low titer even after three or four vaccinations in the same individual in different sites at different times. And interestingly enough, vaccination six months after two preceding vaccinations in two individuals resulted in an accelerated type of reaction followed by immune reactions. Thus, human immunity against vaccinia virus may depend upon a change in host cells as well as upon circulating antibodies.[4] In addition, for some viruses very little antibody may be required for immunity; the classic example is the use of very small doses of γ-globulin derived from *normal,* not convalescent, plasma for passive protection against measles.

In studying the antibody responses of these children, it was also found that these patients lacked isohemagglutinins in their sera, irrespective of their blood groups. In fact, in an early stage of our investigation the presence or absence of isohemagglutinins was used as a simple laboratory screening test for this condition in patients of blood groups O, A or B. Obviously, it could not be used for patients of type AB.

Although all of these patients failed to show γ-globulin upon electrophoretic analysis of their plasmas, more sensitive immunochemical analyses show that very small amounts of γ-globulin, less than 30 mg. per cent, may be present in some of these patients; the level of most of the

patients, however, has ranged from 4 to 18 mg. per cent. The normal concentration of γ-globulin in plasma is about 10 to 15 per cent of the plasma proteins or about 600 to 1200 mg. per cent. The quantitative immunochemical procedure proved far more reliable and accurate than electrophoresis for the diagnosis of this condition. A simple procedure was developed using horse antiserum against human γ-globulin incorporated in agar and placed in a long thin tube. The serum of the patient is simply placed over the antiserum-agar in the tube and the tube allowed to remain at room temperature for eighteen to twenty-four hours; sterile conditions are not observed. The presence of a band of precipitate in the agar indicates the presence of γ-globulin in the patient's serum and the distance the precipitation band has migrated away from the interface between the agar and patient's serum indicates the concentration of γ-globulin.[5]

We have been able to demonstrate that the marked deficit or absence of γ-globulin in these patients is in fact due to a failure in the formation or synthesis of γ-globulin and cannot be attributed to an increased rate of destruction of γ-globulin. Gamma globulin administered to these patients, whether intravenously or intramuscularly, is metabolized at a normal or even slower than normal rate and hence the deficiency could arise only as a result of failure of synthesis.[2]

The failure of synthesis of γ-globulin has also been demonstrated on a cellular level as well.[6] The histopathology of this condition is characterized by a marked deficiency or absence of those cells presumed to be the source of antibody, the plasma cells. In the normal child, antigenic stimulation of a lymph node results in the appearance of plasma cells containing antibody specific for the stimulating antigens. Such cells are not found in the stimulated lymph nodes from children with agammaglobulinemia. In fact, while gamma globulin was readily demonstrated in the blood vessels, lymph nodes and connective tissues of normal children,[7] it was not detectable in the tissues of children with this disease. More conventional examination of the tissues of these patients revealed a marked diminution of lymphoid elements with complete absence of plasma cells from sites where they would ordinarily be found, such as in the lymph node, spleen, and intestinal wall.

The antibiotics, although useful in controlling an immediate infection in these children, have been only partially successful in prophylaxis. On the other hand, γ-globulin administered intramuscularly, 0.1 to 0.15

grams or 0.6 to 1.0 cc. per kilogram of body weight once a month, has given these children considerable protection. Conversely, in the control of an infection, the antibiotics have been more useful than gamma globulin alone.

This then constitutes the syndrome we have chosen to call congenital agammaglobulinemia.

There is another form of agammaglobulinemia which is manifested in adults.[3] Adult agammaglobulinemia is similar in many respects to that seen in children. It differs from the disease in children in that: 1) The concentration of plasma γ-globulin has tended to be a bit higher in those patients studied, with a range from zero to 100 mg. per cent. 2) Either males or females may be affected. 3) The disease did not become manifest until adulthood, the age range being seventeen to seventy-one years of age; in one case of agammaglobulinemia occurring in a female, however, recurring infections began at seven years of age. Adult agammaglobulinemia may be an acquired disease, but it is, of course, possible that this form also is inherited and does not become manifest until adulthood.

There is one form of hypogammaglobulinemia that occurs in infants as a variant of a normal physiologic process. The γ-globulin possessed by the newborn infant has apparently been obtained from the maternal circulation; adequate synthesis of γ-globulin by the infant, however, ordinarily does not occur until the infant is between four to twelve weeks of age. Thus, the γ-globulin level in the infant slowly declines as the γ-globulin of maternal origin is metabolized and the level reaches its lowest point between four and twelve weeks of age.[8] Then the amount synthesized by the infant exceeds the amount destroyed and the level of γ-globulin slowly rises. In several patients, the low level reached has been in the hypogammaglobulinemia range; the lowest level we have observed, however, was 75 mg. per cent. Because the hypogammaglobulinemia is transient and lasts but for a short period as a rule, the patient usually encounters no difficulty. Rarely the hypogammaglobulinemic state has persisted several months with associated recurrent severe infection. The existence of such a state makes a definite diagnosis of congenital agammaglobulinemia very difficult in a patient under six months of age unless the patient is followed very carefully.

In classifying hypogammaglobulinemia, or deficiency in circulating γ-globulins, we described a secondary group and mentioned nephrosis

as an example. In nephrosis, there is persistent severe loss of γ-globulin from the circulation through the renal glomerulus, resulting in serum γ-globulin levels averaging about 200 mg. per cent. In the edema and ascitic fluids of these patients, the concentration of γ-globulin is exceedingly low, the averages being 2 and 10 mg. per cent, respectively. Comparable body fluids in the normal child would contain about 200 to 300 mg. per cent. Thus the ascitic fluid from nephrotic patients could serve and has served as a culture medium. However, factors other than diminished γ-globulins in the nephrotic syndrome may be related to the low resistance to infection exhibited by these patients and the γ-globulin picture may not be the whole story.

It must be remembered that the term γ-globulin is not synonymous with antibody since it is the individual specific groups of antibodies that as a whole comprise part of the γ-globulin fraction. It is probable that proteins other than antibodies, whose functions are at the moment obscure, constitute some fraction of γ-globulin. And to further compound the complexity, antibodies have been found in other protein fractions such as α and β globulins, although even when in these fractions they appear to be immunochemically related to the γ-globulins. Hence, it may be entirely possible to have low resistance to infections or low resistance to a group of organisms through: 1) an error in the metabolism of a specific group of antibodies; 2) deficient or even defective formation of antibodies in general either with a) normal synthesis of other γ-globulins or with b) abnormal synthesis of γ-globulin. Thus, it might well be possible to have a condition of low resistance to infections with normal or even elevated concentrations of γ-globulin in the circulation. Cases which may fall into such a group have been observed.[9] These clinical states, however, must await further investigations.

Although this evening we have discussed γ-globulin in relation to low resistance to infection, when confronted with the patient subject to recurring infections it is imperative to remember that there are many factors in natural resistance other than antibodies: to mention a few—lysozyme, the phagocytic system and complement.

And finally, while such studies in modern medicine have become more and more complex, paradoxically they have served to simplify the diagnosis and treatment of our patients.

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