HOST-PARASITE RELATIONSHIPS IN PATIENTS WITH DYSPROTEINEMIAS[1]

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One means by which information on the essential relationships between host and parasite may be obtained is through study of patients having limitations in their capacity to defend themselves against infection. During recent years, considerable technical progress has been made in protein chemistry, making available methods for defining and studying the various disturbances in protein metabolism which may bear on *specific* defense mechanisms (1–4). Further, experimental studies have been carried out which appear to define to some extent the relationships of several forms of *specific* defense mechanisms to one another in man and animals (5–7). In a sense, it may be possible to gain useful information concerning the operation of nonspecific factors in resistance to infection, the subject of this symposium, by studying the characteristics, limitations, and behavior of patients having a distinct disturbance in *specific* mechanisms of defense. Thus far, our own studies have been concerned primarily with deficiencies in patients having various forms of congenital or acquired agammaglobulinemia (8–23) or moderate hypogammaglobulinemia; with immunological deficiencies which characterize the newly born (24); with disturbances of protein metabolism in patients with multiple myeloma (25), disturbances in capacity for resistance and in immunological reaction in patients with Hodgkin's disease (26), and abnormalities of defense mechanism and capacity to resist infection in a large group of children with hyperglobulinemia (27, 28). It is the purpose of this report to review these and related studies.

In table 1 are listed the general categories of clinical disease in which profound alterations and potential disturbances of host-parasite relations exist. All of these have been studied to some extent in human material in various clinics and laboratories throughout the world, with the possible exception of the last three. Whether immunological paralysis (29, 30), immunological tolerance (31–34), or antigen overloading (35, 36) actually exist in man is not yet known, but the possibility deserves consideration.

AGAMMAGLOBULINEMIA-HYPOGAMMAGLOBULINEMIA

Since Bruton (37), using free electrophoresis, first discovered the lack of γ-globulin in the serum of an 8-year-old boy, ample opportunity to study this deficiency has been presented. Approximately 150 cases of agammaglobulinemia have been discovered and studied from all parts of the western world (38–93). Thus, although representatives having agammaglobulinemia in one form or another are still uncommon in clinical practice, the diseases certainly are not rare. As an example, during the past 6 years we have discovered and studied 27 such cases in our own laboratory. Eighteen of these have been male children with a congenital disease; 9 have been adults with a disease of later onset which presumably has been acquired. All evidence obtained from study of our series of patients, and from patients studied in Boston (94, 95) and New York (59), indicates that one congenital form of agammaglobulinemia is an inborn error of metabolism transmitted as a sexlinked recessive trait. Thus, this form of the disease occurs in males, and clinical expression of the disease begins at an early age, usually during the second half of the first year of life. We have observed the occurrence of multiple cases among brothers in four families and evidence of the disease among cousins. Similar observations have been made by Gitlin *et al.* (95) and Porter (59). In patients with the acquired form of agammaglobulinemia, the disease may occur in either sex and at any age. Whether this form of the disease is truly an acquired disease, or begins later in life as the de-

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TABLE 1

Disturbances of protein metabolism associated with deficiency of immune mechanism

1. Agammaglobulinemia
   a. Congenital—sex-linked recessive
   b. Congenital—non-sex-linked recessive
   c. Acquired
   d. Transient—of infancy
2. Hypogammaglobulinemia associated with generalized hypoproteinemia
   a. Nephrosis
   b. Starvation and malnutrition
   c. Severe burns
   d. Idiopathic hypoproteinemia
   e. Exudative enteropathy
3. Hypergammaglobulinemia with abnormal globulin
   a. Multiple myeloma
   b. Macroglobulinemia
   c. Cryoglobulinemia
   d. Combinations of above
4. Dysgammaglobulinemia
   a. Vaccinia gangrenosum—Kempe
   b. Janeway's cases with hypergammaglobulinemia
   c. Barandun's cases with normal levels of gamma globulin
5. Immunological unresponsiveness—animals to date
   a. Immunological tolerance
   b. Immunological paralysis—Felton
   c. Protein overloading—intact animal—Watson, Dixon; irradiated animal—Dixon; 6-MP treated animal—Schwartz

layed expression of a congenital biological inadequacy, has not been established. However, thus far no evidence of multiple cases occurring in the same family has been presented.

In addition to these two primary forms of agammaglobulinemia, British workers (86, 96) have observed the occurrence of this disease in young girls; and D. G. Traggis and R. L. Lawson (*personal communication*), Van Gelder (97), as well as P. Sturgeon (*personal communication*), have studied similar cases in female children in this country. Notable differences between the cases described in young girls and those observed in the male children justify comment. Whereas in the disease linked to the male sex the lymphoid tissue is hypoplastic, enlargement of the spleen, lymph nodes, and liver, sometimes with hemolytic anemia, have characterized the disease occurring in female children.

In the strictest sense, the term, agammaglobulinemia, is a misnomer. Immunochemical studies (98) and immunoelectrophoretic studies (99–101) have regularly revealed the presence of minute amounts of γ-globulin in the sera of patients with either the acquired or congenital form of agammaglobulinemia. In those with the acquired form of the disease, slightly more γ-globulin is found than is the case in those suffering from the congenital anomaly. This observation makes it most important that all cases, particularly those from which conclusions regarding immunological mechanisms are to be drawn, be carefully studied and precisely defined. The conclusion to be derived from the presence of capacity for defense against virus infection, for example, in a patient with 100 mg of γ-globulin per 100 ml of serum may be quite different from that to be derived from a patient having a circulating γ-globulin concentration of only 1 or 2 mg per 100 ml.

Furthermore, since study of these patients as one of nature's own experiments (102) promises to suggest new points of view and to raise numerous questions of potentially critical significance to immunobiology, it is important that as complete a definition of the disease as possible be provided. Although much remains to be learned, at least a first approximation in this direction has been made (17, 95), and studies are continuing. The abnormality is apparently due to failure of γ-globulin and antibody synthesis (17, 73, 79, 95, 98) and can be presumed, at least in some cases, to be due to a genetic defect, probably operating through a deficiency in enzyme synthesis essential to antibody and γ-globulin production. Studies of the γ-globulin survival time, following the parenteral injection of γ-globulin in these patients, reveal a biological half-life of 25 to 40 days (17, 94, 98), somewhat longer than the best estimates for the biological half-life of γ-globulin in normal individuals (47, 98, 102, 103). The morphological basis for the immunological defect appears to reside in the failure of differentiation of the multipotent reticulum to plasma cells in response to antigenic stimulation (8, 9, 12, 15, 42). Extensive hematological studies, indicating that production of lymphocytes, neutrophiles, eosinophiles, and even red blood cells, as well as plasma cells, may be deficient in certain of these patients (15, 17), have been interpreted as evidence that the basic disturbance involves a disturbed functional capacity of the undifferentiated hemato-

TABLE 2

Characteristics of patients with agammaglobulinemia

1. Lack of or extreme deficiency of γ-globulin in blood and tissues.
2. Lack of or extreme deficiency of antibodies in blood or tissues.
3. Failure or gross deficiency of γ-globulin synthesis.
4. Normal or decreased rate of utilization of γ-globulin.
5. Failure of formation of circulating antibodies in amounts demonstrable even by the most sensitive serological techniques.
6. Poorly organized lymphoid tissue and lack of plasma cells in the reticular tissues.
7. Failure of plasma cell formation in bone marrow and lymphatic tissue even upon the most intensive antigenic stimulation.
8. Frequent association with other hematopoietic disturbances.
9. Associated deficiency of certain β_2-globulins.

poietic reticulum cells which may be the progenitors of each of these several cellular lines. This defect is regularly reflected in these patients by failure of differentiation to plasma cells following antigenic stimulation, an abnormality which precludes antibody and γ-globulin synthesis. Ramos and Loeb's case (74), in which agranulocytosis, thymic tumor, thrombopenia, aplastic anemia, and agammaglobulinemia were associated in a single person, might be interpreted as support for this view. Table 2 lists the characteristics of this syndrome, as defined to date.

With this extraordinary experiment of nature making available to the biologist an opportunity to study a model in which γ-globulin synthesis and antibody production are either absent or very markedly impaired, it has been of primary importance to establish the clinical nature of the disease presented by these patients. This has been most uniform. In the absence of treatment with prophylactic antibiotics, or without regular injections of γ-globulin, life for patients with agammaglobulinemia represents a continuous succession of severe, life-threatening bacterial infections. For example, these patients have innumerable episodes of lobar and bronchial pneumonia, septicemia, otitis media, sinusitis, pyoderma, meningitis, and urinary tract infections. The organisms usually to be implicated include pneumococci, meningococci, streptococci, hemophili, and staphylococci. An occasional instance of pseudomonas or proteus infection has also been observed. In other words, these patients are extremely prone to manifest clinically infections caused by the pyogenic pathogens. On the other hand, individually and as a group, they do not seem to be more troubled by virus diseases than is the population at large. Although several instances among agammaglobulinemic patients of recurrent virus infections (37, 41) have been observed, for the most part these patients have demonstrated a capacity to handle virus diseases without undue difficulty and even to resist recurrences of them. For example, among the patients with congenital agammaglobulinemia studied at the University of Minnesota, we have observed the occurrence of measles, mumps, chickenpox, poliomyelitis, Asian influenza, and numerous unidentified virus respiratory infections. These infections have apparently expressed themselves clinically in a manner not noticeably different from that observed in immunologically normal persons, and the patients have recovered from the infections following their usual duration, even though γ-globulin levels were extremely low and antibody production could not be demonstrated. Most striking is the apparent ability of these patients to resist recurrence of the virus infections mentioned. Indeed, several of our patients with the most complete immunological defect, reflected in the lowest levels of γ-globulin observed, have been intimately re-exposed to measles and chickenpox on numerous occasions over periods of several years following characteristic initial attacks of these diseases, without manifesting clinical recurrences (104). One of the agammaglobulinemic children, after having had characteristic chickenpox at 8 years of age, suffered from a typical herpes zoster infection following exposure to chickenpox at 12 years of age.

Although the few cases of vaccinia gangrenosa occurring in children with agammaglobulinemia (105, 106) make it unwise to recommend regular vaccination of agammaglobulinemic children with vaccinia virus, our observations, as well as those of Gitlin *et al.* (95), indicate that vaccination in these patients is usually a benign procedure. Fourteen of our patients have been vaccinated, demonstrating a characteristic primary reaction which reached a maximal lesion on the 7th or 8th day and finally resulted in sloughing of the scab on the 16th to 18th day. Revaccination in 9 resulted in accelerated reaction, and a third vaccination in

5 resulted in an accelerated or immediate reaction. Gitlin *et al.* (95) have presented evidence indicating that the accelerated reaction to vaccinia may be due to a delayed allergy to the vaccinia virus, which may be transferred to nonimmune recipients with peripheral blood leucocytes. It thus seems clear that these patients, who have a very marked inability to form circulating antibody, handle many virus infections very well and even resist recurrence upon re-exposure. This is particularly striking when the capacity of these patients to handle these virus infections is compared to their apparent inability to cope with infections due to the pyogenic bacterial pathogens.

Certain experiences already suggest that it is unwise to conclude from these observations that agammaglobulinemic patients handle all virus infections well and bacterial infections poorly. For example, three of the agammaglobulinemic children have developed clinical hepatitis, presumably due to hepatitis virus B; all of these have died (95, 107). One of our patients, a 58-year-old man, developed hepatitis during the course of a long series of clinical studies often involving needle punctures. He had never been given γ-globulin. The episode of hepatitis took a violent course, and he died with a clinical and pathologic diagnosis of subacute yellow atrophy of the liver. One of the children studied by the Boston group developed chronic hepatitis during a period when the only injections he was receiving were γ-globulin. He also died following a long, progressive illness. Another of our cases developed hepatitis during a prolonged period when the only injections being given were γ-globulin. Indeed, prior to the development of jaundice, no injections save γ-globulin had been given to this child during the previous 10 months. The patient's hepatitis progressed to typical, fatal, postnecrotic cirrhosis over a period of approximately 1 year. It is of interest that Janeway's case, as well as the latter one of our series, had been receiving very large doses of γ-globulin every 3 to 4 weeks for a prolonged period prior to developing hepatitis. Following development of hepatitis, massive doses of γ-globulin were given to each of the three patients, without effect on the clinical course or the outcome of this virus disease.

Furthermore, an additional child, recently studied in our laboratory, developed fatal encephalomyelitis following a respiratory illness. Although no agent for either the respiratory infection or the encephalomyelitis was identified, the clinical and pathological features suggest that this illness was due to virus infection.

These cases are cited to make it clear that although these agammaglobulinemic patients may handle certain virus infections very well and even resist recurrences of some of the virus diseases in spite of their immunological deficit, this is not always the case. Indeed, the observations to date indicate that patients with agammaglobulinemia are almost certainly inordinately vulnerable to infection with the virus responsible for homologous serum hepatitis.

Studies in our laboratory and elsewhere indicate that agammaglobulinemic patients fail to respond to the parenteral injection of virus antigens, just as they fail to respond to similar injections of bacterial antigens and other vaccines. For example, we have made repeated attempts to demonstrate an antibody response to poliomyelitis virus, Western equine encephalitis, mumps, and rickettsial antigens, without success in any instance. Thus, the capacity for resistance to virus infection which exists in agammaglobulinemic patients must depend either on minute amounts of antibody subliminal to present techniques for detection, or be dependent on specific and nonspecific factors of resistance independent of the capacity to produce circulating antibody.

DELAYED ALLERGY AND TUBERCULOSIS IN AGAMMAGLOBULINEMIC PATIENTS

Initially, observations made in our laboratory suggested that agammaglobulinemic patients were deficient in their capacity to develop delayed allergic reactions just as they were deficient in their capacity to produce circulating antibody. These data consisted of a comparison of the frequency of positive reactions to pneumococcal and streptococcal products among agammaglobulinemic patients and normal children and adults (15, 20). Whereas immunologically normal children and adults showed a high frequency of positive reactions to streptococcal and pneumococcal products, none of 15 agammaglobulinemic patients, studied in this way, showed positive skin test reactions. The conclusion was drawn that a deficiency in capacity to develop delayed allergy certainly existed among these patients. One of the agammaglobulinemic youngsters in our series became positive to the Mantoux test following a clinical episode compatible with primary tuberculosis (20); another demonstrated angry skin lesions, associated with positive cultures for *Can-*

dida albicans, in the diaper area, which responded to treatment with Mycostatin and were followed by the persistence of strongly positive delayed skin reactivity to commercial candida antigens (108). In the meantime, Zinneman (51, 78) described an adult agammaglobulinemic patient with clinical tuberculosis and a positive Mantoux reaction; and Kulneff *et al.* (72), as well as Porter (59), showed that agammaglobulinemic children could be immunized with BCG, would handle the immunization procedure normally, and would develop positive delayed skin reactivity to tuberculoprotein. Porter (59, 109) showed further that his agammaglobulinemic patient was able to develop skin sensitivity to 2,4-dinitrofluorobenzene following application of the drug to the skin, and that this sensitivity could be transferred to immunologically normal recipients by cells but not by serum. In an intensive study of delayed allergy in agammaglobulinemic patients (15, 17, 20, 108, 110), we observed the regular development of delayed allergy to diphtheria toxoid and horse serum, when these antigens were injected intradermally in agammaglobulinemic patients as specific immunological precipitates prepared respectively with horse antitoxin or rabbit antihorse antibody in the zone of antibody excess. These patients were also regularly sensitized to simple chemical compounds, such as 2,4-dinitrofluorobenzene, applied in vesicant dose to the skin. The sensitivity produced in agammaglobulinemic patients by both of these means could be transferred to nonsensitized normal individuals by subcutaneous injection of the agammaglobulinemic patient's leucocytes, but could not be transferred by even very large doses of his serum. Further, it was shown that the previously nonsensitized agammaglobulinemic patient developed a long lasting high degree of delayed type sensitivity to tuberculin or streptococcal products following subcutaneous injection of cells, but not following injections of serum from highly sensitive, immunologically normal individuals.

The occurrence of clinical histoplasmosis, resulting in characteristic, widespread pulmonary calcification and positive skin reactions to histoplasmin, has been recorded (64), and Parkes (111) has emphasized that agammaglobulinemic patients do not have tuberculosis with unusual frequency, nor do they show an unusual course of tuberculosis once the disease has been established. From the data thus far available, one must conclude that the immunological machinery in the agammaglobulinemic patient is capable of normal, or nearly normal, capacity to develop delayed allergy and that the agammaglobulinemic patient has a much better capacity to handle such infections as tuberculosis, histoplasmosis, and superficial fungus infections, than he has to resist and handle infections with the extracellular, pyogenic, bacterial pathogens.

In this regard, one must consider the observations which have been presented with respect to the microorganism, *Pneumocystis carinii*. This microorganism produces a characteristic picture of acute pneumonia, with rapid respiratory rate and cyanosis, in infants 6 weeks to 3 months of age. Premature and debilitated infants have been particularly susceptible to these infections, and devastating epidemics have occurred in foundling homes and hospital nurseries (112–114). Infections with this microorganism have occurred in large number with high mortality rate throughout Europe, but have been described only more recently in Britain (115) and the United States (116).

The morphological characteristics of this disease, featured by interstitial plasma cell pneumonia, with organized proteinaceous exudate in the alveoli, are quite typical. In 1956 Hutchison (117) described a strange form of pneumonia occurring in an agammaglobulinemic patient. On further investigation he found that the child's older sibling had also died of the same disease. Baar recognized the process to be that of pneumocystis pneumonia, in spite of the absence of plasma cells in the exudate (118). Bird and Thomson (119) reported a similar observation from Scotland. It is of interest, if the logical assumption is made that both older siblings, like their brothers, were victims of both agammaglobulinemia and *Pneumocystis carinii* pneumonia, that these two rare diseases in Scotland have occurred together on at least four separate occasions. It seems probable that agammaglobulinemic patients have a high degree of susceptibility to infection with this parasite. The first case of *Pneumocystis carinii* pneumonia occurring in the State of Minnesota was recently observed by L. J. Krovetz, B. A. Burke, and R. A. Good (*unpublished data*) in a patient with proved agammaglobulinemia. It is worthy of comment that in our case, as in those reported from Scotland, *Penumocystis carinii* pneumonia, so-called plasma cell pneumonia, occurred without any plasma cells in the interstitial inflammatory exudate.

COLLAGEN DISEASES IN AGAMMAGLOBULINEMIC PATIENTS

As patients with agammaglobulinemia have been studied throughout the world, it has become increasingly evident that they experience certain of the so-called collagen diseases with inordinate frequency (21, 43, 44, 120, 121). For example, approximately 30 per cent of the agammaglobulinemic patients studied in our laboratory and by Gitlin and Janeway, have suffered from classical rheumatoid arthritis, tenosynovitis, and probable rheumatoid arthritis. In addition, Van Gelder (97) studied a patient in whom agammaglobulinemia occurred together with scleroderma; A. Hansen (*personal communication*) and Gitlin *et al.* (95) have each studied patients in whom dermatomyositis and agammaglobulinemia were associated; and Good *et al.* (21) have studied a child, dying of a diffuse fibrinoid vascular disease, who presumably also had agammaglobulinemia. These findings must be interpreted as strong evidence against the essential participation of circulating antibody, rheumatoid factor, and γ-globulin in the pathogenesis of these particular "collagen" diseases. They should, further, serve to direct attention of investigators to the possible operation of other, perhaps nonspecific, host adjustments to infection which may result in tissue damage in both agammaglobulinemic and immunologically normal individuals. Because of these observations, it becomes more important than ever to define as completely as possible the limitations and capacities of the patients with agammaglobulinemia.

REACTIONS TO GRAM-NEGATIVE BACTERIAL ENDOTOXINS

Intradermal injection of bacterial endotoxins produces, in immunologically normal persons, local reaction featured by erythema, induration, edema, and tenderness. This reaction, remindful in its gross and microscopic characteristics of the reactions due to delayed allergy (122), appears within 4 hr and reaches a maximum approximately 18 hr following intradermal injection of typhoid vaccine, Piromen, or lipopolysaccharide from *Escherichia coli*. Intradermal injection of these same compounds produces reactions in the agammaglobulinemic patient identical to those observed in normal individuals (15, 17). Similarly, intravenous injections of endotoxins (15, 17) produce systemic reactions in the agammaglobulinemic patient which cannot be differentiated from those observed in immunologically normal individuals. Repeated intravenous injections of typhoid vaccine in immunologically normal persons result in a progressive diminution of response to the endotoxic effect. With each injection, the symptomatic reaction, chills, and fever become less pronounced until no apparent effect is produced by the injection. As refractoriness develops, however, antibodies against a variety of antigens appear in the serum, and it is difficult to dissociate refractoriness from the immune response. However, the agammaglobulinemic patient provides a clear dissociation of refractoriness to endotoxin from formation of antibody. Whereas no antibodies are produced to the repeated intravenous injections of endotoxin in these patients, refractoriness develops promptly, just as in immunologically normal individuals (15, 17). Figures 1 to 3 illustrate the effect of endotoxins on C-reactive protein production in normal and agmamaglobulinemic patients. In both groups injections of typhoid vaccine result in the appearance of this acute-phase protein in the serum. Following the development of refractoriness, this same dose of endotoxin may be injected without calling forth a C-reactive protein response in either group. When the dose of typhoid vaccine is again increased, the refractory state is overcome, and C-reactive protein appears again in the serum, and symptoms of the endotoxin effect are observed again. It may be concluded from these studies that local and systemic reactions to gram-negative endotoxin, as

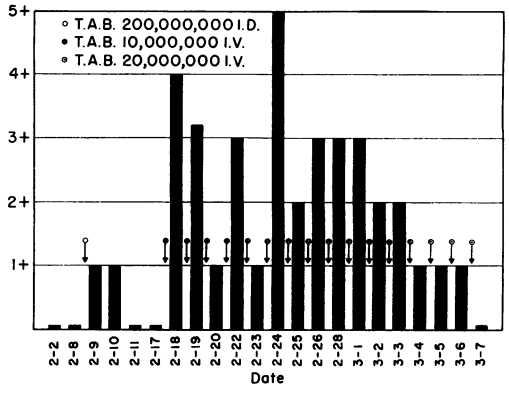

Figure 1. C-reactive protein responses to typhoid-paratyphoid vaccine in a normal child. Note the sharp C-reactive protein response to initial injection of vaccine, followed by progressively decreasing response to repeated injections of the same dose.

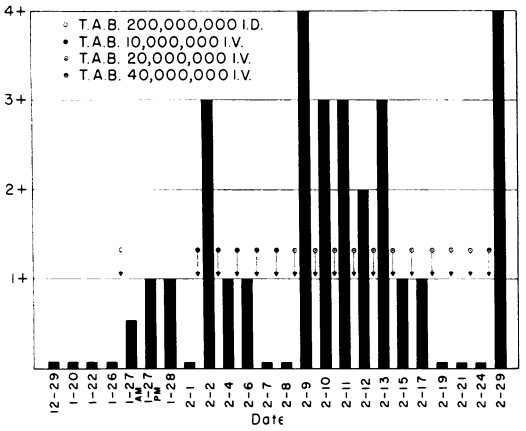

Figure 2. C-reactive protein responses to typhoid-paratyphoid vaccine in a patient with congenital agammaglobulinemia. Note the good C-reactive protein responses to injections of typhoid vaccine, with decrease and disappearance of response upon development of refractoriness. This patient produced no demonstrable antibodies to the injections of vaccine, but capacity to develop refractoriness is reflected in the C-reactive protein response.

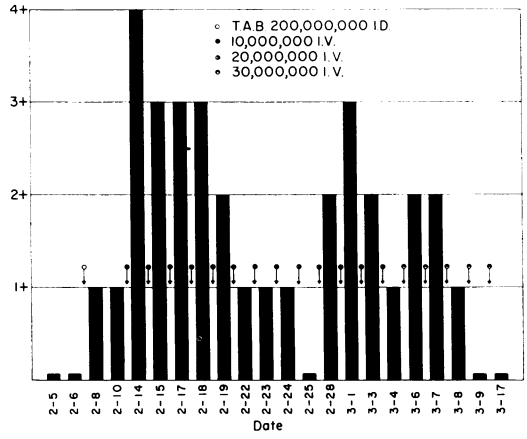

Figure 3. C-reactive protein responses following repeated injections of typhoid-paratyphoid vaccine in a patient with acquired agammaglobulinemia. Note again the development of refractoriness to repeated injections of the vaccine, as in figures 1 and 2.

well as the capacity to develop refractoriness, may be dissociated from the classical immune response and formation of circulating antibody (15, 17) by studying these reactions in the agammaglobulinemic patient. It also seems likely, from these observations, that the formation of C-reactive protein is not directly linked with the actual formation and liberation of circulating antibodies.

ACUTE-PHASE REACTIONS

Both during the course of natural infections and following a variety of experimental, stressful stimulations, changes occur in the blood which have been referred to collectively as acute phase reactions (123–125). These include increase in erythrocyte sedimentation rate, increase in concentration of fibrinogen (126), increase in concentration of mucoproteins and protein-bound carbohydrates (127–129), appearance in serum of C-reactive protein (123, 130, 131), increase in concentration of hyaluronidase inhibitor (132), decrease in concentration of iron-binding protein (133), increase in concentration of heparin-precipitable protein (134), and increase in complement concentration (135). Each of these acute-phase reactions has been studied in agammaglobulinemic patients and compared to the reactions occurring in normal individuals. With respect to these so-called acute-phase reactions, the agammaglobulinemic patients have behaved entirely as normal individuals (15, 17, 104). Furthermore, Barandun and Isliker (136) in their own cases, and L. Pillemer and R. A. Good (*unpublished data*) studying our material, have found total properdin concentrations to be normal in most agammaglobulinemic patients. One of our cases, a child with congenital agammaglobulinemia, had what Pillemer concluded was a low value for free properdin. Complement concentrations in the agammaglobulinemic patients, measured by the technique of Wedgwood and Janeway (137), were within the normal range or were slightly higher than the levels observed among normal individuals (17). Finally, nonspecific bactericidins, effective in destroying certain strains of β-hemolytic streptococci and *Bacillus subtilis*, were found to be present in normal concentrations in the healthy agammaglobulinemic patient and to increase in concentration during acute disease in these patients, as in normal individuals (104, 138).

IMMUNOELECTROPHORETIC STUDIES IN PATIENTS WITH AGAMMAGLOBULINEMIA

Gitlin *et al.* (95) showed that not only is the term "agammaglobulinemia" incorrect technically, since patients so described regularly possess

small amounts of γ-globulin in the serum (17, 94, 98), but that it is also incomplete. Their immunoelectrophoretic studies established that these patients were deficient in two additional protein components. Gitlin *et al.* (99), Scheidegger (100), and Grabar *et al.* (101) all recognized the same protein deficiencies in agammaglobulinemia and identified the missing proteins as β_{2A} and β_{2M}, according to Scheidegger's (139) nomenclature. Recent immunoelectrophoretic analysis of sera of well-defined and well-characterized agammaglobulinemic patients in our laboratory established conclusively that most of these patients lack β_{2A} and β_{2M}, and possess minute amounts of the classical γ_2 (S 7) globulin in the serum. Rather surprising, however, was the finding in these patients of several additional proteins, not seen in the sera of normal individuals, traveling electrophoretically in the γ area (140). These proteins, tentatively designated as β_{2K}, β_{2E}, γ_{1A}, are not ordinarily detectable in the sera of healthy normal individuals but appear to be present in variable amounts and with variable frequency in the sera of patients with a variety of acute and chronic diseases. We interpret these observations to indicate that patients with electrophoretic agammaglobulinemia, of either the acquired or congenital form, may suffer from dysgammaglobulinemia of considerable complexity. Studies of this relationship are being continued.

In the course of these studies, we have found a patient with no demonstrable γ_2-globulin, who originally possessed apparently normal amounts of β_{2M} in her serum. She was unable to form demonstrable amounts of antibody to a variety of antigens, but possessed a normal (1:320) titer of isoagglutinins against the heterologous blood group A antigen. The lymphoid tissues of this patient were disorganized and lacked plasma cells, but the bone marrow contained plasma cells in normal numbers. During the period of study, lasting more than a year, isoagglutinins in the serum declined to low levels, and plasma cells decreased markedly in number. Barandun *et al.* (141) identified a familial disease in which the patients possessed perfectly normal amounts of γ-globulin, but were unable to form antibodies against a variety of antigens. They considered these patients to reflect the existence of "Antikörpermangelsyndrom" without agammaglobulinemia. Contrary to the situation in agammaglobulinemic patients, they found plasma cells to be present in normal numbers in reticulo-endothelial tissues, as well as in inflammatory lesions.

γ-GLOBULIN METABOLISM AND ANTIBODY DEFICIENCY IN THE NEWLY BORN

It has been recognized for a long time that newborn mammals, including humans, have a deficiency in immunological responsiveness during the early part of the neonatal period (142–145). Humans are born with a serum γ-globulin concentration slightly higher than that of their mothers (98, 146, 147). Following birth, the serum γ-globulin concentration goes through a period of logarithmic decline lasting for a period of 2 weeks to several months (24, 146–149), so that it often declines to levels considerably below those normally present in the serum of older children and adults. When γ-globulin concentration begins to rise, rapid accumulation in the serum takes place (24, 149) and normal adult levels are regularly reached during the second year of life. The half-life decline of γ-globulin during this period, assuming little or no production by the child, is very similar to the γ-globulin half-life decay rate observed in agammaglobulinemic children given parenteral injections of pooled γ-globulin (98). It is presumed that most, if not all, of the γ-globulin present in the serum of newly born infants is obtained by passive transfer of the protein from the mother (98). During this period of immunological inadequacy which characterizes the newly born baby, plasma cells are absent from the tissues and do not appear in them, even in response to antigenic injections, until several weeks have elapsed (24, 95). A similar deficiency of plasma cells, and failure of plasma cell response to antigenic injection, may be observed during the first several weeks of life in the newborn rabbit (24).

Hitzig (150) and Scheidegger and Martin du Pan (151) have observed that newborn babies lack the two proteins also absent from the serum in agammaglobulinemic patients: β_{2M} and β_{2A}. Newborns are also lacking in isoagglutinins, which are not transferred across the placental barrier. Our study of 5 infants, born of immunologically normal mothers who had previously given birth to agammaglobulinemic offspring, is of interest (24, 98, 152). Two of these infants turned out to be agammaglobulinemic and three to be immunologically normal. It is of interest that it was impossible to tell these infants apart from studies of their morphological characteristics and their γ-

globulin curves in the neonatal period. All 5 began life with normal γ-globulin concentration; all 5 showed logarithmic decline in γ-globulin concentration during the first weeks of life; all 5 lacked plasma cells in their bone marrow and lymph nodes. Three of the babies showed a break in the decay curve at times varying from 3 weeks to 4 months of age, and then rapid accumulation of γ-globulin in the blood and tissues. Two showed continued logarithmic decline in γ-globulin concentration until agammaglobulinemic levels were reached toward the end of the first year. The latter continued to reflect the immunological and γ-globulin deficiency characteristic of agammaglobulinemia. Converse were the results of study of 2 infants born of an agammaglobulinemic mother (24, 98, 152). In this instance, the children were born with agammaglobulinemia and remained agammaglobulinemic until between 3 and 4 weeks of age in one, and 6 and 7 weeks of age in the other. During the neonatal period, these children could not be distinguished by morphological, immunological, or biochemical procedures from patients with true, persistent agammaglobulinemia.

The conclusion drawn from these observations is that the neonatal period in man and some animals is a period of immunological inadequacy, similar in many respects to the abnormality which persists in agammaglobulinemic patients. Although the newborn must obtain considerable protection by passive transfer of γ-globulin and antibody from the mother, it is possible that this immunological defect may account for some of the susceptibility to infection which characterizes the neonatal period in both man (153–155) and animals (142). Other studies suggest, however, that additional deficiencies in defense mechanism may contribute to the jeopardy of the prematurely born and newly born human (156–158).

Recently, Giedion and Scheidegger (159) and Hitzig and Giedion (160) have reported older children, suffering from increased susceptibility to infection, who do not lack γ-globulin in the serum, but are instead lacking in the β_{2M} and β_{2A} components. Studies of immunological response in these patients reveal a lack of isoagglutinins; decreased capacity to form antibodies against such antigens as salmonella H antigens, and diphtheria and tetanus toxoids; and virtually complete immunological unresponsiveness to such antigens as salmonella O antigens. It is of interest that one such patient showed prolonged survival of a skin homograft, as have two children with congenital agammaglobulinemia.

MULTIPLE MYELOMA

Multiple myeloma is a malignant disease of the plasma cell system, often characterized by excessive production of abnormal blood proteins immunologically related to γ-globulins (25, 161–164). In addition, some of these patients divert a tremendous amount of energy for protein synthesis to the production of Bence-Jones protein (165). The best evidence indicates that these proteins are produced in the abnormal plasma cells which characterize these disease states. Whether the disturbance in protein synthesis represents a greatly enhanced production of proteins, produced in small amounts by normal persons, or represents production of large amounts of proteins foreign to normal persons, is the subject of controversy. When abnormal protein synthesis exists and is sufficiently great, a gross deficiency of normal γ-globulin synthesis may occur, so that patients with multiple myeloma often have true γ-globulin levels much lower than normal (63, 166, 167). As a reflection of this deficiency, patients with multiple myeloma may manifest extreme susceptibility to infection (168–170), and the responsible microorganisms are usually the pyogenic pathogens. Studies of immunological responsiveness in these patients (170–173) indicate a definite disability which, however, is usually not so profound as that observed in agammaglobulinemic individuals. The status of other host responses in patients with multiple myeloma has not been systematically investigated, but demands further study.

MACROGLOBULINEMIA AND CRYOGLOBULINEMIA

Profound disturbances in protein metabolism also exist in patients with cryoglobulinemia (165, 174–176) and macroglobulinemia (177–180). The majority of these patients, however, do not show gross defects in classical γ-globulin, and, although demonstrating hemorrhagic phenomena, Raynaud's phenomenon, and even necrotizing vascular disease, have not generally been noted to suffer from increased susceptibility to infection. Although systematic studies of immunological responses and other host reactions in these patients have not been carried out, the observation that some of them appear clinically to suffer from fre-

quent infections (181–182) should encourage comprehensive investigations in this direction.

DYSGAMMAGLOBULINEMIA

Several diseases of man, some of which have been described only recently, are associated with increased rather than decreased concentrations of γ-globulin. Janeway *et al.* (183) described a group of such patients whose illness was featured by marked hypergammaglobulinemia associated with hematological abnormalities, and by markedly increased susceptibility to infection. In contradistinction to the agammaglobulinemic patients, most of the infections in these children were due to staphylococci and pseudomonads. Although no specific immunological analyses were presented, these investigators postulated the existence of a dysgammaglobulinemia in which the immunological deficiency was thought to be due to formation of γ-globulin inadequate as antibody. Kempe *et al.* (184) have presented evidence that certain patients who develop malignant, necrotizing, progressive vaccinia may have normal γ-globulin levels and normal antibodies to antigens other than vaccinia, but fail in their immune response to the latter virus antigen. It is possible that in these patients the initial virus infection, for some unexplained reason, gets a head start on the host's defense, and enough antigen is produced by the infection to produce a state comparable to immunological paralysis (29) or protein overloading (35). That a few of these patients have had agammaglobulinemia suggests that the postulated development of paralysis, perhaps capable of abrogating aspects of the immune response additional to formation of circulating antibody, may occur more easily in these patients than in normal individuals. Kempe's (*personal communication*) apparent success in arresting the progress of one such case by injecting peripheral blood leucocytes from a highly immunized individual, and the previous failure of massive amounts of antibody to alter the course of the disease, suggest that either an acquired or congenital disturbance in capacity to develop or express delayed allergy may be basic to the disease process in these patients. Such patients as those described by Landing and Shirkey (185), Aldrich *et al.* (186), Krivit and Good (28) Bridges *et al.* (27), Chediak (187), and Higashi (188), in whom the basic problem regularly leading to fatal termination at an early age is decreased capacity to resist infection, justify intensive efforts to define the basic defects in host resistance responsible for the anomaly. Studies already carried out in these patients indicate that general immunological reactions, such as capacity to form agglutinating, complement fixing, virus neutralizing, and antitoxic antibodies, and to develop delayed allergy, are all intact in these patients ((27, 28) and R. A. Good, *unpublished data*). It seems likely that, as in agammaglobulinemic patients, information pertinent to understanding nonspecific host factors in resistance to infection in normal individuals may be obtained from study of these unusual patients.

HODGKIN'S DISEASE

It has long been recognized that patients with Hodgkin's disease are particularly prone to develop infections with organisms which might be classified as intracellular pathogens. Such infections as tuberculosis (189), brucellosis (190), and cryptococcosis (191) and other fungus diseases (192, 193) occur with inordinate frequency in these patients. Schier *et al.* (194, 195) have discovered that, as a group, these patients have a lower frequency of positive delayed skin reaction to these antigens than is present in normal healthy or other diseased patients. Studies in our laboratories showed that 60 per cent of patients with Hodgkin's disease were anergic to all of a battery of antigens which detected the existence of delayed allergy in all but 3 of 300 normal controls (26, 196). Furthermore, attempts to produce delayed allergy in patients with Hodgkin's disease, using injections of specific immunological precipitates according to the method of Uhr, Salvin and Pappenheimer, failed to produce delayed allergy in these patients (196). Additional studies in our laboratories, as well as by Epstein (197), have demonstrated that these patients are more difficult to sensitize to simple chemical compounds, such as 2,4-dinitrofluorobenzene, than are members of the normal population. Further, we (26, 196, 198) have observed that patients with Hodgkin's disease will often permit the prolonged survival of skin homografts. That none of these abnormalities can be attributed to a defect in production of γ-globulin or circulating antibody is indicated (a) by the fact that γ-globulin levels in patients with Hodgkin's disease are generally as high as normal and often considerably higher, and (b) by the observation that these patients produce plasma cells and circulating agglutinins, complement fixing antibodies, and antitoxic antibodies, just as do normal individuals.

An apparent defect in production of poliomyelitis neutralizing antibody, following injection of Salk vaccine in these patients, may have been fortuitous and due to inadequacy of the lot of vaccine used. Vigorous efforts to define the existing defect in patients with Hodgkin's disease are indicated and are in progress.

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DISCUSSION

Although patients with agammaglobulinemia are immunologically grossly inadequate, they do not seem to have an unusual susceptibility to progressive tuberculosis. On the other hand, as indicated in the paper, tuberculosis may be a rapidly progressing disease in patients with Hodgkin's disease. This phenomenon suggests that serum antibody may not be involved in host resistance to progression of tuberculous infection. The inability of patients with Hodgkin's disease to develop delayed allergy, however, indicates that this may be a primitive immunological mechanism independent of, though perhaps related to, antibody synthesis, and possibly associated with resistance to some infections (Good, Minneapolis).

The infections to which patients with agammaglobulinemia seem to be peculiarly susceptible are, for the most part, characterized by extracellular parasitism.

It has been observed that recurrence of measles may not take place in the child with agammaglobulinemia even after repeated intentional exposure. Although this fact suggests that acquired resistance in this virus infection may not be attributable to serum antibody, it is important to remember that these patients may be able to produce some antibody but not in presently measurable amounts. One must not too quickly associate such resistance to cellular immunity or cellular susceptibility (Good, Minneapolis).

In considering patients with agammaglobulinemia, the increased susceptibility to infection must not be equated with failure to produce antibody. Although absence of serum antibody probably has an influence upon the progress of infection, once established, or after a second challenge, presumably it plays no role in conditioning host susceptibility to the initiation of the first infection. It is in the latter circumstance that factors of nonspecific host resistance play a dominant role, and there is little information as yet on the status of these factors in agammaglobulinemia (Cluff, Baltimore).

No observations have been made to determine whether the inability to demonstrate delayed allergy precedes the development of Hodgkin's disease. However, observations of the reactivity durlng the course of the disease, including remissions and exacerbations, have not shown clearly definable variations in delayed allergic response (Good, Minneapolis, and Bennett, Baltimore).