The Immunological System of the Child*

Part II: Immunological Deficiency States

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In the first lecture, the development of the organs, cells, and proteins responsible for the immune response was discussed. Resistance to invasive infection depends upon non-specific factors as well as upon specific immune responses to the infecting organism. Poor resistance may be the result of deficiencies in either non-specific or specific mechanisms, but the main concern of this lecture will be with deficiencies of specific immunological mechanisms, which have only been recognized as disease entities during the past 12 years. However, in order to put these new disease entities in perspective, we must first examine the various ways in which the body's defences against bacterial infection may be impaired.

From the clinical point of view, the physician seeing a child with the complaint of recurrent infections should first get a clear picture of whether these have been repetitive infections of the same anatomical area or a whole variety of severe infections with different anatomical sites. The former type of history strongly suggests a local cause, the latter a deficiency in the over-all capacity of the individual to resist infection. But, first of all, the physician must evaluate the mother's anxiety in order to determine whether, as so often happens in paediatrics, her expectations of good health for her child leave no place for the hundred or so infections, most of them mild and involving the respiratory tract, which usually develop in the first decade of life and constitute the major manifestations of immunological maturation of the child.

Impairment of Non-specific Defences Against Bacterial Infection

Failure of surface protection. This is a frequent predisposing cause to local infection by bacteria. In the case of the *skin* this may be due to trauma from burns or penetrating wounds, to loss of

integrity from a congenital defect such as epidermolysis bullosa, or to an acquired disease like eczema or exfoliative dermatitis. In the *eye*, lack of tears or loss of the corneal reflex can lead to corneal ulceration and infection. Achlorhydria may diminish the resistance of the *gastro-intestinal tract* to enteric infection. In the *respiratory tract*, failure of the cough reflex, due to anaesthesia or to coma, and loss of ciliary action, such as occurs in certain viral infections, thermal and chemical injuries, or bronchiectasis, may pave the way for invasion of the lung. Obstruction of the air passages with viscid secretions, as in cystic fibrosis, recurrent asthma, or bronchitis, or local obstruction by a foreign body, frequently leads to pneumonia. Finally, the oedema produced by the viruses of influenza or the common cold, by the allergic response, or in the nephrotic syndrome, alters the respiratory tract so that pyogenic bacteria, when present, multiply rapidly and produce invasive infection.

Failure of the clearing mechanism. This is another important predisposing cause to infection. Deficiency in production of the principal wandering phagocytic cell—the polymorphonuclear leucocyte—usually is followed by infection, very frequently due to staphylococci. This occurs very early in a rare condition incompatible with life—*congenital aleukia* (de Vaal and Seynhaeve, 1959; Gitlin, Vawter, and Craig, 1964)—but is a constant threat in patients with neutropenia, which may be congenital, cyclic, or acquired as a result of bone-marrow failure in leukaemia, reticulo-endotheliosis (Letterer-Siwe's disease), aplastic anaemia from radiation or chemical injury. Failure of the fixed tissue phagocytes of the reticulo-endothelial system may result in severe overwhelming septic infections. Although there has been great dispute about whether there is such an entity as a *post-splenectomy syndrome* (King and Shumacker, 1952; Gofstein and Gellis, 1956; Horan and Colebatch, 1962), there is no question but that following splenectomy,

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especially in infancy or early childhood, the child, who also has a serious underlying disease of the blood-forming organs for which the splenectomy was done, is unusually vulnerable to overwhelming bacteraemia, and perhaps to viraemia as well.

Failure of the inflammatory reaction. This may play an important part in allowing infection to spread unchecked. This is seen when there is impairment of the blood supply to a part, or when under the influence of anaesthetics, narcotics, or coma the local reflexes involved in vascular responses are deficient. Finally, the anti-inflammatory and antipyretic effect of the corticosteroids, when given in massive doses, can produce the strange paradox of a septic patient feeling and looking comparatively well while his bacteraemia proceeds unchecked.

Deficiencies of the Immunological System

Deficiencies in the normal immunological responses of the host lead to frequent recurrent severe bacterial infections. Understanding of this field is developing rapidly, as clinical observations and fundamental immunological investigation keep adding to our knowledge. But before presenting what has been learned since α - γ -globulinaemia was first reported by Bruton (1952), a miscellaneous group of diseases, characterized by unusual susceptibility to infection, for which no adequate explanation has yet been found, must be mentioned for the sake of completeness and to show that there is still much to be learned.

Diseases of Uncertain Pathogenesis Associated with Unusual Susceptibility to Infection

The Wiskott-Aldrich syndrome. This is a familial disease, characterized by recurrent otitis media, thrombocytopenic purpura, and eczema, in which recurrent superficial infections and bleeding usually lead to death in early childhood (Aldrich, Steinberg, and Campbell, 1954; Wiskott, 1937; Krivit and Good, 1959). Laboratory studies have not revealed any single consistent immunological abnormality, though a raised level of γ_A -immunoglobulin and a decreased or absent titre of iso-haemagglutinins are found in many, but not in all cases.

Ataxia telangiectasia. This is a hereditary disease in which multiple telangiectases are associated with progressive ataxia developing in childhood or in early adult life (Young, Austen, and Moser, 1964; Peterson, Kelly, and Good, 1964; Fireman, Boesman, and Gitlin, 1964). In many patients, recurrent infections, particularly pneumonia, become a problem and may lead to death. In

approximately 70% of the patients who have been studied, there is an absence of γ_A -immunoglobulins, a phenomenon that has been observed in some healthy children without any evidence of increased susceptibility to infection. There does appear to be a defect in the ability to develop delayed hypersensitivity in some ataxia telangiectasia patients, despite a normal number of circulating lymphocytes.

There is a poorly defined syndrome of serious granulomatous disease occurring rarely in children, which sometimes is familial. It is characterized by recurrent or persistent superficial infection often due to staphylococci and frequently exhibiting relative neutropenia and an increase in monocytes, lymphadenopathy, hepatosplenomegaly, and hyper- γ -globulinaemia (Carson, Chadwick, Brubaker, Cleland, and Landing, 1965). This has been described under different names by different workers. A few cases have been seen in nearly every paediatric clinic. Whether they represent a heterogeneous group of cases with different aetiologies or a few distinct clinical entities remains to be discovered.*

Metabolism of the Immunoglobulins

Since hypo- γ -globulinaemia is the characteristic laboratory finding in most instances of the antibody deficiency syndrome, a brief discussion of the metabolism of the immunoglobulins is necessary in order to clarify the mechanisms that may be responsible for this finding. The work of Gitlin has given us the clearest understanding of the normal and pathological metabolism of individual plasma proteins and particularly of the γ -globulins. The blood level of any plasma protein is *usually* a reflection of the size of the body pool of that protein. The size of the body pool in turn depends upon the relation between the rate at which that protein is being synthesized and the rate at which it is being removed from the body pool by loss from the body or by katabolic breakdown. Thus hypo- γ -globulinaemia might result from a decrease in the rate of synthesis, from an increase in the rate of loss of katabolism, from both, or from a greatly increased rate of loss and katabolism, even with some increase in the rate of synthesis. Ordinarily approximately half of the body pool of γ -globulin is present in the circulating plasma and the remainder in the extravascular portion of the extracellular fluids, but in concentrations varying considerably in different areas, with the greatest concentration in thoracic duct lymph. Synthesis of γ -globulin occurs where-

* P. G. Quie, J. G. White, B. Holmes, and R. A. Good (Annual Meeting of American Society for Clinical Investigation, Abstract to be published in *J. clin. Invest.* (1966), have demonstrated an inability of the polymorphonuclear leucocytes to kill engulfed bacteria in three cases of this syndrome.

GAMMA GLOBULIN METABOLISM-70kg.MAN

FIG. 1.—Diagrammatic scheme of γ metabolism in a normal adult of 70 kg. (*Advances in Pediatrics*, Vol. IX, edited by S. Z. Levine. Copyright © 1957, Year Book Medical Publishers, Inc. Used by permission of Year Book Medical Publishers)

ever there are plasma and plasmacytoid cells. Under normal conditions γ -globulin is probably lost into the gastro-intestinal tract and urine in relatively minute amounts, and most of the disappearance of γ -globulin is accounted for by katabolism, though where this occurs is unknown. In the steady state, approximately half the circulating γ -globulin leaves the blood stream daily, presumably through the walls of the peripheral capillaries, while the same amount returns to the blood stream by way of the lymphatics (Gitlin and Janeway, 1960) (Fig. 1).

Hypo- γ -globulinaemia in the antibody deficiency syndrome is usually an isolated deficiency of γ -globulins and is due to a failure of synthesis, as shown by a normal or prolonged half-life of injected tracer doses of labelled γ -globulins, by the failure to form antibodies in response to antigenic stimulation, and by the absence of plasma cells in the lymphoid tissues (Gitlin, Janeway, Apt, and Craig, 1959). Hypo- γ -globulinaemia due to increased loss and katabolism occurs in exudative skin lesions, exudative gastro-intestinal lesions ('exudative enteropathy'), and in the nephrotic syndrome, and is associated with deficiencies of other lower molecular weight plasma proteins as well (Gitlin, Janeway, and Farr, 1956). Only in the nephrotic syndrome, where the hypo- γ -globulinaemia is very severe and the concentration of γ -globulin extremely low in the extracellular oedema fluid, does this latter type of hypo- γ -globulinaemia predispose to recurrent invasive infections.

Antibody Deficiency Syndrome

The antibody deficiency syndrome (Barandun, Cottier, Hassig, and Riva, 1959), the name given by the Swiss workers, which is a better term than hypo- γ -globulinaemia or a- γ -globulinaemia, because it

stresses the fundamental defect in all the patients, exists in a number of different forms as shown in Table I. No classification is entirely satisfactory, but this outline will provide a sequence for presentation.

Thymic alymphoplasia. This clinical entity, undoubtedly first described by Glanzmann and Riniker (1950) as *lymphocytophthisis*, then by Donohue (1953) as *alymphocytosis*, and finally recognized as a distinct variety of a- γ -globulinaemia by Swiss and French workers (Hitzig and Willi, 1961; Tobler and Cottier, 1958; Freycon, Jeune, Larbre, and Germain, 1961), seems to be a familial disease and the most serious form of immunological deficiency. It is characterized by the early onset of intractable infection, failure to thrive, and death from infection before the age of 2. Its diagnostic feature is a striking paucity of lymphocytes both in the blood and tissues (Table II).

Although the families reported by Freycon and by Hitzig and Willi include children of both sexes, in all of the families we have observed the affected children have been boys, suggesting a sex-linked inheritance,

TABLE I
Antibody Deficiency Syndromes

A. Thymic alymphoplasia
B. Congenital a- γ -globulinaemia
C. Acquired a- γ -globulinaemia
1. Primary (idiopathic)
2. Secondary to
(a) radiation injury
(b) chemical suppression
(c) replacement of lymphoid tissue (lymphomas)
D. Dys- γ -globulinaemia
1. Transient
(a) neonatal dys- γ -globulinaemia
(b) transient hypo- γ -globulinaemia of infancy
(c) transient dys- γ -globulinaemia
2. Congenital dys- γ -globulinaemia
3. Acquired dys- γ -globulinaemia

so possibly more than one mechanism of inheritance may give rise to this syndrome (Rosen, Gotoff, Craig, Ritchie, and Janeway, 1966).

The characteristic clinical manifestations are depressingly uniform—onset of cough with pulmonary infiltration, thrush, and failure to thrive, with poor appetite, poor growth, abdominal distension, and loose stools at a few months of age. These symptoms persist and progress, despite temporary remissions of the more acute pulmonary or monilial infections with appropriate chemotherapy, and almost invariably during the second year if not before, the miserably scrawny child succumbs. Injections of γ -globulin exert little if any protective effect.

The pathological picture is striking. The thymus is often difficult to find and consists of a small epithelial structure, without Hassal's corpuscles or any sign of the thymocytes which make up such a large portion of the normal infant thymus. Lymph nodes are small and almost unrecognizable, with complete absence of follicular architecture, few if any lymphocytes and no plasma cells (Rosen, Gitlin, and Janeway, 1962). In the bowel the lymphoid follicles and the lymphoid cells, which normally crowd the *lamina propria*, are absent.

Immunologically, these infants are totally incompetent. They not only have the antibody deficiency syndrome with α - γ -globulinaemia, which becomes apparent with the disappearance after 6 or 7 months of the γ_6 -immunoglobulins derived from the mother, but they also lack the capacity to develop delayed hypersensitivity; which probably accounts for the persistent moniliasis and also for the fact that, as a review of the published reports suggests, the deaths from progressive vaccinia, which have been described in α - γ -globulinaemia patients, have occurred principally in infants with this disease (Rosen and Janeway, 1964).

Experiments in animals suggest that 'runt disease' bears many resemblances to thymic alymphoplasia in man. It is of interest that runt disease can be prevented with syngenic lymphocytes if they are given before runting occurs (Yunis, Hilgard, Martinez, and Good, 1965). Efforts to treat thymic alymphoplasia have been directed towards the homotransplantation of two tissues—thymus and lymphoid cells. These children, lacking the capacity either to develop delayed hypersensitivity or to form antibodies, should be the perfect homograft recipients and do not exhibit the rejection reaction. The optimal time to help them should be the first month or two of life before runting and infections begin. This means that the disease must be recognized in the sib of an affected child before it

TABLE II
Summary of Thymic Alymphoplasia

1. Familial—both sexes
2. Onset—early (2-6 months)
3. Intractable course: Pulmonary infection, thrush, diarrhoea, failure to thrive
4. Death under 2 years
5. Pathology: Thymus—aplasia Lymph nodes—absent lymphocytes and plasma cells Circulating lymphocytes < 1,000/c.mm.
6. Immunology: Delayed hypersensitivity 0 Homograft rejection 0 Antibody formation 0

becomes symptomatic. Nobody has yet succeeded in maintaining one of these children for long with transplanted tissue, but hopeful results have been achieved by two groups of investigators (Rosen *et al.*, 1966; Rosen *et al.*, 1962; Hitzig, Kay, and Cottier, 1965).

Congenital α - γ -globulinaemia. Children with this, the commonest form of the antibody deficiency syndrome, appear normal for from 9 months to 2 or 3 years of age, depending upon the degree to which they are exposed to infection in their home and environment (Table III). The infections which they develop are no different, except for their severity, frequency, and tendency to recurrence, from those experienced by normal children, and they respond satisfactorily to antimicrobial therapy. Thus it may be some time before the physician's suspicions are aroused by the frequency with which the infections occur. There are certain signals which an alert physician may detect—the small size and smooth surface of the tonsils, the absence of an adenoid shadow in a lateral radiograph of the nasopharynx, and the comparatively small size of the cervical lymph nodes in a child with recurrent respiratory infections. A very high or very low white blood count with an acute infection, recurrence of infection with the same strain of organism such as

TABLE III
Summary of Congenital α - γ -globulinaemia

1. Sex-linked recessive—boys
2. Onset—6 months-3 years
3. Course: Recurrent severe bacterial infections Respond to antimicrobial therapy Prophylactic γ -globulin effective
4. Complications: Tissue damage from infection (Bronchiectasis, deafness), arthritis frequent
5. Pathology: Thymus normal Lymph nodes—poor follicles, no plasma cells Circulating lymphocytes normal
6. Immunology: Delayed hypersensitivity ++ Homograft rejection + Antibody formation ±

FIG. 2.—Immunoelectrophoretic analysis of normal (lower pattern) and α - γ -globulinaemic (upper pattern) serum. The serum proteins have been separated in a lateral direction by electrophoresis in a gel and then detected by precipitation with an antiserum against normal human serum which diffuses into the gel from the central trough. The three bands of precipitation due to the immunoglobulins (labelled γ_M , γ_A , and γ_G) in normal serum are absent from the α - γ -globulinaemic serum.

H. influenzae type B, or the development of hydrarthrosis in a child with a history of frequent infections, are also warnings to look into the situation more closely. The vast majority of these children are boys, and the evidence for a sex-linked recessive form of inheritance is overwhelming from study of a large number of families. The fact that occasional girls develop symptoms of α - γ -globulinaemia in infancy or early childhood suggests that there are other mechanisms of inheritance, or that the antibody deficiency syndrome may be acquired very early in life (see below).

Early recognition of the disease is important, because the institution of adequate replacement therapy with γ -globulin before anatomical damage has been done to the brain, bronchi, middle ear, or joints by infection usually means that the child can enjoy a relatively normal life. Certain complications do occur, however, which may be serious. The arthritis, which tends to be indolent and relatively painless with effusion into large joints, and which has been observed in about one-third of the patients, usually disappears with γ -globulin therapy. On the other hand, a dermatomyositis-like syndrome with skin rash, brawny oedema, muscular weakness, and contractures has developed in several of our treated patients who have ultimately succumbed to it (F. S. Rosen, S. V. Kevy, and C. A. Janeway, unpublished observations). Although these patients cope with viral infections much better than they do with bacterial infections and can be vaccinated without risk, hepatitis has caused death in several

patients, at least one of whom never received any injections of γ -globulin (Good and Page, 1960).

The pathology of congenital α - γ -globulinaemia differs from that of thymic alymphoplasia; the thymus appears relatively normal and lymphocytes are usually present in normal numbers in the blood, as well as in somewhat reduced numbers in the lymph nodes and the *lamina propria* of the bowel (Gitlin and Craig, 1963). The lymphoid tissues are somewhat small, and their architecture is distorted, with poor follicular structure. Upon antigenic stimulation there is swelling of the reticulum, giving rise to lymphadenopathy, but no formation of secondary follicles or of plasma cells, as is usually seen in lymphoid hyperplasia.

Diagnosis of this disease, even in the male sibs of known cases, is not possible for 6-9 months, until the child's γ -globulin level has fallen below 200 mg./100 ml. as a result of katabolism of the maternal globulins, though it can be strongly suspected if γ_M or γ_A globulins are not apparent upon immunoelectrophoresis after 4 months of age. Definitive diagnosis depends upon a consistent family history, the demonstration of a severe deficiency of all three immune globulins after 6 months of age (Fig. 2), abnormal architecture, and absence of plasma cells in a local lymph node after antigenic stimulation and failure to form detectable serum antibodies in response to immunization. Once the diagnosis has been made, these children are committed to γ -globulin replacement therapy, presumably for life. The dose required seems to be a loading dose of

300 mg./kg., which may be given in divided doses over a period of a week or so and a maintenance dose of 100 mg./kg. month thereafter, with occasional checks to be sure that a blood level of over 200 mg./100 ml. is being maintained (Janeway and Gitlin, 1957).

From an immunological standpoint, these patients are capable of developing delayed hypersensitivity but form antibodies very poorly. They may reject homografts but somewhat more slowly than normal subjects.

Acquired a- γ -globulinaemia. The antibody deficiency syndrome may develop at any time in life. Cases occurring after the first two years fall into two main groups—those that are primary or idiopathic, and those that are secondary to a variety of processes which affect the lymphoid system, such as radiation, immunosuppressive therapy, or lymphomatous disease. In about one-third of the cases of chronic lymphatic leukaemia significant hypo- γ -globulinaemia with a tendency to recurrent infections develops, and in many instances of myeloma there is an antibody deficiency syndrome, despite increased levels of myeloma γ -globulin (Good, Kelly, Rotstein, and Varco, 1962) (Table IV).

TABLE IV

Summary of Idiopathic Acquired A- γ -globulinaemia

1. Both sexes—rarely familial
2. Onset—any age
3. Course:
 - Recurrent bacterial infections
 - Respond to antimicrobial therapy
 - Prophylactic γ -globulin effective
4. Complications:
 - Bronchiectasis mainly
 - Sprue-like syndrome common
5. Pathology:
 - Thymus normal
 - Lymph nodes—poor follicles, no plasma cells
 - Circulating lymphocytes normal
6. Immunology:
 - Delayed hypersensitivity + +
 - Homograft rejection +
 - Antibody formation $\pm$

Idiopathic acquired a- γ -globulinaemia. This may develop at any age in those of either sex. Although there is seldom a positive family history, several instances of two cases developing in the same family have occurred, thus suggesting that a genetic factor may sometimes play a role (Wollheim, 1961; Charache, Rosen, Janeway, Craig, and Rosenberg, 1965). The clinical manifestations of this disease closely resemble those of congenital a- γ -globulinaemia, but recurrent sinusitis and pneumonia are the principal infections, frequently leading to bronchiectasis before the disease is recognized. Arthritis is less common in adults than in children, but a sprue-

like malabsorption syndrome occurs much more often in older patients.

In general, as in congenital a- γ -globulinaemia, there is a deficiency of all three immunoglobulins, though the total γ -globulin level is often somewhat higher, and evidence of some antibody formation may be obtained after antigenic stimulation or infection (Fudenberg, German, and Kunkel, 1962). Replacement therapy with γ -globulin in the same dosage as for congenital a- γ -globulinaemia is effective in preventing most severe infections except in those patients with bronchiectasis, who, like immunologically normal subjects with this disease, are subject to recurrences of pneumonia.

The pathology of idiopathic acquired a- γ -globulinaemia is quite comparable to that of congenital a- γ -globulinaemia, with a normal thymus, some hypoplasia and disorganization of lymph node architecture, and a paucity of plasma cells. However, in some of these patients, proliferation of the reticulum cells may lead to generalized lymphadenopathy, hepatosplenomegaly, and ultimately a picture resembling lymphoma. Much has been made of the association between thymic lesions, particularly thymoma, antibody deficiency syndrome, and malignancy of the lymphoid system (MacLean, Zak, Varco, and Good, 1956).

The Dys- γ -globulinaemias

We have used the term dys- γ -globulinaemia to describe any condition characterized by abnormal variations in the relative amounts of the immunoglobulins. Myeloma and macroglobulinaemia, which are primarily seen among adult patients, would certainly fall into this group and are often associated with the antibody deficiency syndrome, but, as a paediatrician without experience with these clinical entities, I shall omit them from consideration here.

Transient dys- γ -globulinaemia and hypo- γ -globulinaemia in infancy. *Neonatal dys- γ -globulinaemia.* This condition, with an adult level of γ_G -globulin, but only trace amounts of γ_M - and γ_A -globulins occurs normally in the first few weeks of life and may perhaps predispose to colon bacillus sepsis under special circumstances. Hypo- γ -globulinaemia is likewise a normal phenomenon from the second to sixth month of life, but in a few infants *delayed maturation of immunological function* may occur, leading to a persistence and deepening of hypo- γ -globulinaemia for several months longer than is usual, with increased susceptibility to infection, requiring the administration of γ -globulin.

This *transient hypo- γ -globulinaemia of infancy* is fortunately rare.

True *dys- γ -globulinaemia*, due to a delay in the normal sequence of immunological maturation or to an abnormal sequence, may occur as a transient phenomenon for months or several years, and require a period of γ -globulin therapy in order to maintain the health of the child. Peetoom, Cohen, and Smeenk (1966) in the Netherlands have found a group of non-allergic children with frequent severe respiratory infections who could be identified by unusually low levels of γ_M - or γ_A -globulins or by failure of the level of these globulins to rise within a few days after infection (Smeenk, Cohen, and Peetoom, 1966). Infections could be prevented by administration of γ -globulin, and as soon as the level or the response of the immunoglobulins to infection became normal, recurrent infections ceased, and γ -globulin was no longer necessary. Giedion and Scheidegger (1957) described a boy in whom, despite a normal level of electrophoretic γ -globulin, there were recurrent severe infections, whose blood contained normal amounts of γ_G - but no γ_M - or γ_A -globulin. By the age of about 5 his infections ceased, and the immunoglobulins in his blood became normal. We have studied a boy of 4 who is now completely normal, who was shown by A. Ross and B. Rose in Montreal at 2 years to have increased macroglobulins with a severe deficiency of 7S γ -globulin, whose frequent infections were well controlled by γ -globulin injections and tetracycline drugs for a two-year period until he became normal (C. A. Janeway and F. S. Rosen, unpublished observations).

Congenital dys- γ -globulinaemia. The commonest form of dys- γ -globulinaemia which we have observed is among children with the antibody deficiency syndrome which has begun in early life. These children have a typical history of recurrent severe infections, but on examination of their blood, the level of γ -globulin, instead of being below 50 mg./100 ml. as in the unusual case of congenital a- γ -globulinaemia, is found to be between 200-400 mg./100 ml. Further analysis usually shows that the 19S fraction by ultra-centrifugal analysis, corresponding to γ_M -globulin, is increased several times, whereas there is less than 50 mg./100 ml. γ_G -globulin (Rosen, Kevy, Merler, Janeway, and Gitlin, 1961). This condition has persisted in several children for all the years they have been followed. In one such child tonsillar hypertrophy necessitated tonsillectomy and the tonsil was filled with PAS positive plasmacytoid cells containing γ_M -globulin. It is interesting that the few instances of

cyclic neutropenia we have observed in congenital a- γ -globulinaemia and the two instances of florid warts have been in this dys- γ -globulinaemia group (C. A. Janeway and F. S. Rosen, unpublished observations).

Acquired dys- γ -globulinaemia. Several instances of a clinical picture resembling idiopathic acquired a- γ -globulinaemia have been observed in adults, where laboratory studies have shown γ -globulin levels in the 200-400 mg./100 ml. range, deficiency of γ_G -globulin, abnormally high concentrations of γ_M -globulin, and PAS positive plasmacytoid cells in their lymphoid tissues (Rosen and Bougas, 1963; Hinz and Boyer, 1963).

Finally, one of our patients, followed for a number of years with typical congenital a- γ -globulinaemia, showed a marked increase in γ_M -globulin following the successful chemotherapeutic treatment of tuberculosis. He developed a severe autoimmune disease affecting liver, kidney, and blood, which responded to splenectomy. The spleen contained many PAS positive plasmacytoid cells, and the level of γ_M -globulins declined after its removal. However, several years later there was a recurrence of fatigue, fever, jaundice, abdominal pain, and colitis associated with a rise in γ_M -globulins, and the finding of many PAS positive plasmacytoid cells in the gall-bladder which was removed at an exploratory operation. He succumbed to this recurrent disease in a few months for reasons that are far from clear (C. A. Janeway and F. S. Rosen, unpublished observations).

My excuse for presenting these last examples in a rather anecdotal fashion is to indicate that, though we have learned a lot in the past 12 years, there are still many bewildering clinical phenomena involving the immunoglobulins, which we cannot satisfactorily explain.

Summary

The child who is brought to the physician because of recurrent infection will most frequently have an over-anxious mother or some local factor predisposing to infection.

If the infections are severe, repeated, often recurrent but vary in location, some failure of the mechanisms of resistance is strongly suggested, either neutropenia, absence of the spleen, or a specific deficiency of the immunological system.

There are a variety of inherited and acquired conditions where there is a failure of the immunological system, associated with pathological lesions in the lymphoid tissues and occasionally in the thymus, and with abnormalities of the immuno-

globulins and sometimes of the peripheral lymphocytes.

There are three well-defined clinical entities with immunological deficiency:

(a) *Thymic alymphoplasia* is the most severe of the antibody deficiency syndromes, since it includes an inability to manifest delayed hypersensitivity, and a severe deficiency of lymphocytes with failure to form antibodies.

(b) *Congenital α - γ -globulinaemia* is a sex-linked recessive disease, in which the patients can develop delayed hypersensitivity but are severely defective in antibody formation.

(c) *Acquired α - γ -globulinaemia* is either secondary to various processes which injure or infiltrate the lymphoid tissues or occurs idiopathically at any age in either sex in a form which is clinically and pathologically very similar to congenital α - γ -globulinaemia.

In addition there are several poorly understood conditions such as Wiskott-Aldrich syndrome, ataxia telangiectasia and diffuse granulomata, as well as a variety of dys- γ -globulinaemias, which may be transient, congenital, or acquired.

Although replacement therapy with γ -globulin is effective in protecting from infection all patients with the antibody deficiency syndrome except those with thymic alymphoplasia, it is our hope that, as knowledge of the interrelationship of the thymus, the lymphoid follicles throughout the body, and the peripheral lymphocytes increases, we may some day be able to activate or restore the immunological system to normal function by other methods.

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