The Immunological System of the Child*

Part I: Development of Immunity in the Child

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It is a great privilege to be asked to lecture in honour of Sir Leonard Parsons, who certainly, both for his contributions to medical knowledge and his personal characteristics, will always be remembered as one of the giants of paediatrics in the English-speaking world, and I want to express my deep appreciation to Professor Hubble and this Faculty for this invitation.

In these lectures I hope to share with you some ideas which are the product of the past 20 years of clinical experience, clinical investigation, experimental studies, and discussions with very able colleagues, particularly David Gitlin, Fred Rosen, John Craig, and Gordon Vawter. I also owe much to the generosity of professional friends in other institutions who have shared their ideas and often their unpublished manuscripts with me. Here I would like to pay special tribute to Robert Good of Minnesota, Walter Hitzig and Silvio Barandun of Switzerland, and Professors Nicholas Martin and the late John R. Squire of Britain. These people deserve part of the credit for any good ideas in these lectures but should not be held responsible for any bad ones.

This is an exciting time for the immunologist. Immunology had a first great upsurge in the late nineteenth and early twentieth centuries, when Metchnikoff put forward the cellular theory of immunity, and Pasteur, Koch, Pfeiffer, Ehrlich, Bordet, von Pirquet, Schick, and others developed the basic concepts of active and passive immunity and allergy.

Then there was a quiescent phase, while such great scientists as Landsteiner worked quietly, trying to give chemical meaning to biological concepts. Heidelberger and his school created quantitative immunochemistry, a very important achievement at a time when the serum therapy of pneumococcal infections was being developed under the leadership of Avery and Cole at the Rockefeller Institute. This work was so dominant during the 20's and 30's

that immunology became, for a time, as Dr. René Dubos once put it, 'the science of pneumococcal polysaccharide'.

With the advent of improved techniques in protein chemistry, permitting the isolation and characterization of the antibody proteins as γ globulins, and the explosion of biological knowledge, which has come as genetics has been placed on a chemical foundation, immunology has acquired a firm base in biochemistry and molecular biology. By now we recognize that the metabolic activities of cells, which determine their physiological function, are the direct result of the amounts and types of proteins which they synthesize, under the direction of the 'genetic code' inscribed in the nuclear DNA. This knowledge has led to the development of methods to control the biochemical activities of cells with drugs and physical agents, and has placed the treatment of many diseases on a more rational basis. Although the usual function of antibody proteins is to protect against pathogenic micro-organisms, we have learned that some diseases may be due to the action of harmful rather than protective antibodies. For immunological investigation, using the tools and theories of the molecular biologist, has become concerned not just with resistance to infection, but with the much broader problem of the response of the host to all foreign substances, which may include not only an invading parasite, but the foetus *in utero* whose blood group is incompatible with that of its mother, the drugs used in the treatment of disease, the organs which we hope to transplant from other individuals, or even the patient's own blood cells, tissues, or proteins in the so-called auto-immune diseases.

Paediatricians are still deeply concerned with problems of infection, since, even in highly developed civilizations, the prevention and treatment of infectious diseases occupies the major portion of their time. But inasmuch as allergy, maternal-foetal incompatibility, the need for homotransplantation for the replacement of malformed or

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diseased organs, and the supposed auto-immune diseases are most common in the child and young adult, paediatrics is particularly dependent upon advances in immunology to provide a scientific understanding of clinical phenomena.

In these lectures I shall try to show how much insight has been gained into basic immunological processes from studies upon a relatively rare group of diseases, which, however, provide opportunities for understanding human biology that cannot be adequately duplicated in the laboratory. My first lecture will concern the development of immunity in the child, and my second, the immunological deficiency diseases which have only been recognized in recent years and which have helped us to elucidate some of the ways in which the normal child combats the infectious agents that are part of his normal environment.

Human Adaptations to an Environment Containing Pathogenic Micro-organisms

Every human infant emerges from his 9 months' sojourn in the normally sterile intrauterine environment into a world swarming with potentially pathogenic micro-organisms. The miracle is that, in most instances, he is able to adapt himself successfully to this infective environment. This is due to a series of inherited defensive mechanisms which have developed with the evolution of the vertebrates. Paediatrics quite properly begins with the parents; so let us first examine these mechanisms of resistance to invasive infection by pathogenic bacteria in the human adult. We shall concentrate mainly on bacterial infections in these lectures, because, though viral infections are numerous and important, in most instances the mortality from common infectious diseases, even of viral origin, is the result of invasive bacterial infection. Table I lists some of the structures and mechanisms which normally protect us from such invasion.

The major role played by intact normally functioning body surfaces in resistance to infection is taken for granted. The exact role of local pH, mechanical factors such as the ciliary action of the respiratory epithelium or the cough or sneeze reflex, antibacterial substances such as lysozyme in certain secretions, and the presence of phagocytic cells in the sub-mucosa and subcutaneous tissues are hard to define but clearly important. Once the surface defences have been breached by trauma or by damage from chemical or viral agents, the *clearing mechanism*, consisting of the various phagocytic cells, both wandering and fixed, constitutes a second line of defence. Then the local *inflammatory reaction* comes into play with its complex series of steps

leading to hyperaemia, vascular stasis, and exudation of cells and plasma proteins into the area of infection. This is followed by the reabsorption into the circulation of the products of their interactions with each other and with the tissues. Substances are released, such as endogenous pyrogen (Wood, 1958), that affect the heat-regulating centre in the hypothalamus and produce fever, while others produce metabolic changes and stimulation of the myelopoietic tissues and result in leucocytosis. In the acute phase of the inflammatory reaction, there is a rise in blood fibrinogen and a consequent increase in erythrocyte sedimentation rate, and a rise in α_2 -glycoproteins including the C-reactive protein which appears in the blood during fever (Petermann, 1960). Many of

TABLE I
Factors in Resistance to Invasive Infection

A. <i>Non-specific Resistance</i>
1. Surface protection
Skin, mucous membranes
2. Clearing mechanism
a. Wandering phagocytes (PMNs, monocytes)
b. Fixed phagocytes (R-E system)
3. Reactive mechanism
a. Local inflammation
b. Acute phase reaction in blood
c. Stress reaction
B. <i>Specific Immunity</i>
1. Primary response
2. Secondary response
C. <i>Enhancement of Non-specific Response by Specific Immune Reactions</i>
1. Delayed hypersensitivity reaction
2. Interaction of complement components with antigen-antibody complex

these responses are kept within reasonable bounds by the outpouring of glucocorticoids from the adrenal cortex as part of the general reaction to stress (Kass, 1960). Not only do the corticosteroids help to dampen the fires of fever and inflammation, but they affect a shift in metabolism to the provision of energy at the expense of many body proteins.

Meanwhile the immunological system of the body is brought into play and begins to respond to chemical constituents of the invading micro-organisms that it recognizes as foreign. These *antigens* set in motion a series of cellular and biochemical responses in the affected lymphoid tissues, which ultimately result in the establishment of a state of *delayed hypersensitivity* to certain constituents of the bacterial cell and in the *synthesis of antibody globulins* which combine specifically with particular antigenic groupings on the bacterial surface. This hypersensitivity is a form of cellular

TABLE II
Immunoglobulins

Class	Molecular Weight (sed. constant)	Average Adult Plasma Conc. (mg./100 ml.)	Placental Transfer	Turnover Half-time (days)	Antibodies
γ_M (β_{2M} , γ_{1M})	1,000,000 (19S)	50-70	0	3-5	'Natural', anti-O, isoagglutinins
γ_A (β_{2A} , γ_{1A})	170,000-500,000 (7S-12S)	50-150	0	2	
γ_G (γ_2 , γ)	170,000 (7S)	800-1,100	+	20-40	Anti-H, antitoxins, antibacterial, antiviral

immunity usually elicited clinically by the skin test 24-48 hours after intradermal injection of antigen; and the tuberculin test is the best known example. In general, the first contact with a particular species of micro-organism leads to a rather slow response, often requiring several weeks for these changes to become recognizable. This so-called *primary response* is in considerable contrast to the secondary response, when the host encounters an organism or an antigen to which it has previously responded. Under these circumstances, the rate of the response is accelerated and the amount of antibody formed is greatly enhanced.

There is an interplay of specific and non-specific factors when, as a result of a delayed hypersensitivity reaction to the antigen or of the union of antigen and antibody with fixation of complement, active enzymes and other cell constituents are released, which alter vascular permeability and enhance local inflammation in response to the infection. The total system of interactions between plasma and tissue proteins and blood and tissue cells initiated by bacterial invasion is enormously complex and defies total analysis in most clinical situations, though the preceding generalizations probably reflect our present knowledge with some accuracy.

Components of the Immunological System

Gradual refinement of the techniques of protein chemistry and immunology has led to recognition of three major classes of antibody molecules in the blood plasma of the normal human adult. These

γ - or immunoglobulins have been given several different names in the past, but are now known as γ_M (or IgM), γ_A (or IgA), and γ_G (or IgG) globulins (*Bull. Wld Hlth Org.*, 1964). Table II gives the properties, distribution, and functional relations of these immunoglobulins in the blood of the average adult.

The antibody response has been the subject of a vast amount of investigative work during the past decade. Table III presents an oversimplified picture of the sequence of steps which occurs following the presentation of an antigen to the antibody-forming tissues (Smith and Eitzman, 1964). In some way the formation of γ_G -antibody shuts off the synthesis of γ_M -antibody, whereas if the former is blocked the synthesis of γ_M continues (Sahiar and Schwartz, 1964). One of the puzzling mysteries is why the so-called 'natural' or bactericidal antibodies to the Gram-negative enteric bacilli remain γ_M -globulins in most individuals and why γ_G type antibodies to the O-antigens (endotoxins) of the organisms are only formed in the blood of a few subjects and in low titres, whereas continued antigenic stimulation by most other antigens leads to high titres of γ_G -type antibodies (Michael and Rosen, 1963).

Appreciation of the differences between the primary and secondary response to a specific antigen is of great paediatric importance, because so often in infancy we are dealing with the infant's first contact with a particular organism, whereas in later childhood or in adult life, the response is altered by previous contact with at least some of the antigenic constituents of the infecting organism. Table IV contrasts these responses. A very important difference is that the primary response must establish the state of delayed hypersensitivity, whereas the secondary response occurs in an individual in whom this state already exists. Although it is likely that, in most infections, the antigenic constituent which induces delayed hypersensitivity is different from the antigen or antigens giving rise to antibody formation, and the cells involved are also different, nevertheless these two immune responses are closely

TABLE III
Antibody Response

- (1) Recognition of antigen as foreign
- (2) Multiplication of reacting cells
- (3) Differentiation into secretory cells
- (4) Synthesis and secretion of immunoglobulins
 - (a) γ_M —initial (plasmacytoid cells)
 - (b) γ_A —transitional
 - (c) γ_G —final (plasma cells)

linked in most infections, and each plays a role in the host response and the consequent manifestations of disease.

The cells that participate in specific immunological responses are lymphoid cells. There is increasing evidence that the small lymphocyte is the cell responsible for the delayed hypersensitivity reaction and for the closely linked phenomenon of homograft rejection (Gowans, McGregor, and Cowen, 1963). The strongest evidence for this is the passive transfer of delayed hypersensitivity such as that to tuberculin from one subject to another by the injection of a small number of lymphoid cells. The long duration (up to 1-2 years) of such passively transferred hypersensitivity might be due either to the demonstrated long life of certain lymphoid cells (up to 2 years) in the body (Norman, Sasaki, Ottoman, and Fingerhut, 1965), or to the ability of such lymphoid cells to instruct the host's own cells to respond through Lawrence's *transfer factor* (Lawrence, 1959).

TABLE IV

Contrast Between Primary and Secondary Immune Response

Primary

- (1) Delayed hypersensitivity must be established (lymphocytes)
- (2) Differentiation $\longrightarrow$ plasmacytoid cells
- (3) Synthesis γ_M -immunoglobulin
- (4) Low titre of antibody

Secondary

- (1) Delayed hypersensitivity reaction occurs
- (2) Multiplication or differentiation $\longrightarrow$ many plasma cells
- (3) Synthesis γ_G -immunoglobulins
- (4) High titre of antibody

The formation of humoral antibodies is associated with a series of morphological transformations in the lymph nodes draining the site of infection or antigen deposition. Local lymphadenopathy, a commonly observed clinical phenomenon, reflects these microscopical changes. There is swelling of the reticulum, enlargement of the germinal follicles, development of secondary follicles, and the appearance of scattered plasmacytoid and plasma cells in the margins of the follicles (Gitlin, Janeway, Apt, and Craig, 1959). These plasma cells have been shown by Gitlin to contain specific antibody by immunofluorescence. It is clear that antibody formation involves the transformation of certain responsive lymphoid cells into secretory cells producing large quantities of antibody protein. The exact cell that is transformed, the exact stimulus to its transformation, and the exact mechanism that

leads to the appearance of numerous plasma cells, particularly in the secondary response, either by transformation of an increased number of pre-plasma cells or by the multiplication of precursors or of the transforming cells themselves, all remain to be clarified. Pyroninophilic cells forming γ_M -globulins are PAS positive, indicating the formation of high carbohydrate globulins (γ_M - and γ_A -globulins contain approximately 10% carbohydrate), and have a plasmacytoid or transitional cell morphology (Cruchaud, Rosen, Craig, Janeway, and Gitlin, 1962), while pyroninophilic cells forming γ_G -globulins are PAS negative (γ_G -globulins contain only about 2% carbohydrate) and have the classical plasma cell morphology. That these are indeed secretory cells is borne out by the demonstration in plasma cells of clearly defined endoplasmic reticulum by electron microscopy (Feldman, 1964).

The lymphoid system includes the tonsils, the lymph nodes in the subcutaneous, mesenteric, retroperitoneal, and mediastinal spaces, and the lymphoid follicles of the spleen and the intestinal tract. For this system to function properly, a normal thymus appears to be necessary at least during foetal life and perhaps for some time thereafter (Janković, Waksman, and Arnason, 1962; Good, Dalmaso, Martinez, Archer, Pierce, and Papermaster, 1962; Miller, 1961). This organ, which has been in search of a function for so many years, is clearly related to the integrity of the immunological system, but whether it functions primarily as a source of immunologically competent lymphocytic cells, as a source of a hormone required for their normal function, or as a site where lymphoid cells, perhaps derived from the haematopoietic tissues, are properly 'instructed' before their distribution throughout the body, remains to be determined. The experimental work of Miller (1961), of Waksman's group (Janković *et al.*, 1962), and the phylogenetic and experimental studies of Good and his colleagues (1962), taken together with clinical observations to be presented in the next lecture, all point to the thymus in foetal and early neonatal life as an essential component of a normally functioning immunological system. Fig. 1 presents a schematic representation of the present state of our knowledge on the development of immunological competence.

Maternal-Foetal Relationships and Development of Immunity in Infancy

The transfer of passive immunity against certain common diseases, such as measles, from mother to infant has been recognized for many years (Vahlquist, 1958). Among the domestic animals with a multi-layered placenta, like the cow, sheep, and pig,

FIG.—Development of the immunological system in man (after R. A. Good).

absence of such immunity at birth and the amazingly rapid oral transfer of immunoglobulins in the colostrum during the first days of life has been clearly demonstrated. On the other hand, the human placenta is very different in structure, and consequently the relation between mother and foetus also differs. By about 10-12 weeks of age human foetal blood contains traces of all the major proteins present in adult plasma, but the relative concentrations are very different. γ -globulins can first be detected in the 3rd or 4th month of foetal life, and thereafter their concentration in foetal plasma rises until it is equal to, or even a little higher than, the maternal level at term.

There is considerable evidence that the normal foetus synthesizes little if any γ -globulin during pregnancy. Experimental work by Dancis showed this in guinea-pigs (Dancis and Shafran, 1958). Observations on human infants born to hyper- γ -globulinaemic and a- γ -globulinaemic mothers are also compatible with this conclusion (Bridges, Condie, Zak, and Good, 1959).

The antibodies present in the infant's blood at birth appear to have been transferred from mother to foetus, and reflect the mother's antibody pattern. This process presumably involves an active transport mechanism across the placenta, though Brambell has provided evidence that, in the rat at least, the antibodies diffused from the chorio-allantoic vessels into the amniotic fluid, are swallowed by the foetus and absorbed from its gastrointestinal tract (Brambell and Halliday, 1956).

Using plasma proteins labelled with radioactive iodine, Gitlin, Kumate, Urrusti, and Morales (1964) studied the transfer of a number of different human plasma proteins near term, and were able to show that, whereas there was some transfer of all proteins tested from maternal to foetal circulation, the rate was much higher for γ -globulin than for any other protein.

Although the foetus does not ordinarily synthesize γ -globulin in appreciable quantities, it is capable of doing so when infected, and antibodies of foetal as well as of maternal origin appear in the blood of foetuses infected with rubella (Alford, Neva, and Weller, 1964), syphilis (Silverstein, 1962), or toxoplasmosis (Eichenwald and Shinefield, 1963).

Although the newborn infant's γ -globulin level, as well as its pattern of antibodies, closely approximates that of its mother, transfer of maternal immunoglobulins is quite selective. Sherman, Hampton, and Cooke (1940) found that the blood of one infant born to a highly allergic mother, whose serum not only contained atopic reagents but also blocking antibodies as a result of hypersensitization treatment, contained the blocking antibodies but not the atopic reagents. More recent work has demonstrated that, while the γ -globulins of the mother are readily transferred to the foetus, γ_A - and γ_M -globulins are not. The so-called 'natural antibodies', bactericidal anti-O antibodies against the endotoxic somatic antigens of the enteric bacilli, are not usually found in cord blood, even though usually

present in the mother's blood. These antibodies are 19S γ_M -globulins (i.e. macroglobulins) in most instances. In a few infants, low titres of bactericidal antibodies were found, but on ultracentrifugal examination of the mother's and infant's serum a portion of the maternal antibody and all of the infant's antibody was in the 7S rather than the 19S globulin fraction and hence was γ_G -globulin, thus explaining this unusual transfer of bactericidal antibody (Gitlin, Rosen, and Michael, 1963).

γ_G -globulin containing most of the antibodies of the mother increases steadily in the blood of the foetus during the last 6 months of gestation. After birth, this passively acquired γ_G -globulin falls away as it is diluted by growth and katabolized. The synthesis of γ -globulins by the infant begins in response to immunization and contact with infectious agents and is characterized by an initial rise of γ_M -globulins, then the appearance of γ_A and finally of γ_G -globulins, which gradually become the major fraction of the immunoglobulins, as continuing and recurrent contact with various antigens occurs (West, Hong, and Holland, 1962). Presence of γ_G maternal antibody to specific antigen may completely inhibit or depress an antibody response in the infant. This has been clearly demonstrated in the case of living attenuated measles virus vaccine, when it is given in the first 6 or 8 months of life (Stokes, Reilly, Hilleman, and Buynak, 1960). The total γ -globulin concentration of the infant's blood, which is the summation of all the processes described above, changes much during infancy, and the normal γ -globulin level between 1 and 6 months of age is quite low by adult standards.

The shifting pattern of chemically different groups of immunoglobulins in the infant's serum with development has its morphological counterpart in the appearance of the lymphoid tissues from which they are derived. According to Good and Papermaster (1964), who have made an exhaustive study of the evolution and development of the lymphoid system, development of the thymus slightly precedes that of the lymph nodes and of the spleen during foetal life. Lymphocytes begin to appear in the lymphoid tissues by about the 16th to 20th week, but even at birth the lymph nodes are small, with rather minimally developed follicular architecture and no plasma cells. During the first two or three months of extrauterine life, there is rapid enlargement of the lymph nodes and lymphoid follicles, which become much more heavily populated with lymphocytes, and first plasmacytoid and then plasma cells begin to appear in appreciable numbers as the infant begins to form immunoglobulins in response to antigenic stimuli from his environment.

Immunological Development and Interpretation of Clinical Phenomena in Infancy

Although there are many mysteries still to be unravelled, such as the curious vulnerability of male infants to infection in early life (approximately twice as many males as females develop neonatal sepsis, neonatal meningitis, or primary staphylococcal pneumonia), knowledge of immunological development does provide partial explanations for some of the recognized peculiarities of infectious disease in infancy.

There is only one period in life—the first two weeks—when humans are subject to primary septic infection with bacteraemia or meningitis, due to the colon bacilli. These infections may occur in later life but almost always as a result of dissemination from a local focus like an obstructed urinary tract, or of serious debilitation of the patient with superinfection following massive antibiotic therapy. It may be coincidental, but the first fortnight happens to be the time when the newborn infant is without the protection of 'natural antibody', since he does not ordinarily receive these γ_M -globulins from his mother, and has not had time to form his own in response to the enteric organisms which rapidly populate his own bowel after birth. Since this is a universal immunological deficiency in newborns, why don't they all succumb to colon bacillus sepsis? One is tempted to speculate that the integrity of the gastro-intestinal mucosa, its phagocytic cells, and the gradual rate of population of the gut by colon bacilli permit the infant's own immunological responses to cope with them. It is an established fact that colon bacillus sepsis in the infant is usually associated with urinary tract infection or a history of some obstetrical complication in the mother, which might result in exposure of the infant to greater numbers of more virulent organisms in the amniotic fluid or placental blood (Haggerty, 1961). Proof for such speculations is extremely difficult to obtain, and since no satisfactory preparation of γ -immunoglobulins is available, a controlled study of passive protection of newborn infants with complicated obstetrical histories has not been made. Ordinary preparations of γ -globulin do not contain 19S γ_M -antibodies but only γ_G -globulins.

The rather peculiar and specific manifestations of bacterial infections in infancy and early childhood seem to be the result of the fact that in almost every instance these represent primary infections giving rise to a primary type of response. Later in life the response is modified by the previous establishment of delayed hypersensitivity to one or more components of the bacteria, which gives rise to a more

violent local reaction, and partial immunity to related antigens frequently results in a secondary type of antibody response and consequently a more short-lived disease. Clinicians have long been familiar with the differences between the primary or childhood type and the reinfection or adult type of pulmonary tuberculosis. We forget that these same differences are seen in pyogenic infections even though humoral antibodies undoubtedly play a far greater role in recovery from them than in tuberculosis. The major clinical characteristics of primary tuberculosis are a relative paucity of symptoms with a rather extensive lesion, but a far greater tendency for dissemination of the infection than in the more highly tuberculin sensitive adult.

Primary pyogenic bacterial infections often have similar characteristics. Although most children pass through their initial infections with *β -haemolytic streptococci*, *H. influenzae*, *Pneumococci*, *Meningococci*, or *Staphylococcus aureus*, with little more than subacute upper respiratory tract disease, the frequency with which the relatively rare instance of dissemination and meningitis occurs is far greater than at any other period in life (Haggerty and Ziai, 1964). This is quite analogous to the frequency of miliary tuberculosis and tuberculous meningitis in childhood, and I believe reflects the inefficiency of the primary response in a heavily infected subject.

Staphylococcal pneumonia and empyema, a disease that only occurs as a secondary complication of measles or influenza in older children and adults, occurs as a primary disease in infants between the ages of 1 and 12 months of age (Hendren and Haggerty, 1958). Presumably several factors are operative—presence of a virulent strain of staphylococci, loss of passively transferred maternal immunity during the first month or two of life, lack of delayed hypersensitivity to staphylococcal products, and the slow immune response of an infant exhibiting a primary response to antigenic stimulation. We must remember that probably hundreds of infants become carriers and are immunized by this same virulent strain of staphylococcus for every one that exhibits this severe clinical disease, but the clinical picture of primary pneumonia and empyema is unique to this age period. All subsequent staphylococcal infections will occur in a subject who has already some degree of hypersensitivity to staphylococcal products and a partial immunity.

Summary

Immunological competence depends upon (a) an intact thymus, certainly during foetal life and perhaps for a certain period in early extrauterine life; (b) an adequate supply of immunologically competent

lymphoid cells, which populate the lymphoid follicles of lymph nodes, gut, and spleen.

The immune response to infection consists of two important specific phenomena; (a) *the development of delayed hypersensitivity* to certain chemical constituents of the infectious agent, a phenomenon mediated by small lymphocytes; (b) *the formation and secretion of specific antibodies* to certain antigens of the infectious agent by cells which become differentiated into cells of the plasma cell series during this process.

The primary or initial response to an antigen results in the formation of γ_M (19S macroglobulin) antibodies, which have a short half-life, by PAS positive plasmacytoid cells, and the subsequent formation, by typical plasma cells, in low titre of intermediate molecular weight antibodies and ultimately of 7S γ_G -globulins with a longer half-life. The primary response is slow and requires time for the establishment of delayed hypersensitivity and for the formation of antibodies in relatively low titre.

The secondary response usually occurs in an individual with established delayed hypersensitivity, and results in a rapid increase in the number of plasma cells and in the appearance of a high titre of specific γ_G -immunoglobulin antibodies in the blood.

The foetus can form antibody *in utero* if infected, but normally does not, and the infant is born with γ_G -antibodies passively transferred from his mother and a transient deficiency of γ_M - and γ_A -immunoglobulins, which do not normally cross the placenta.

After birth, as the level of maternal γ_G -globulin falls by dilution and katabolism, the infant begins to form his own immunoglobulins in response to immunization and contact with micro-organisms in his environment.

The newborn infant is peculiarly vulnerable to invasive infections with Gram-negative bacilli during the first two weeks of neonatal life, possibly because of the transient deficiency of γ_M -globulins.

The infant is unusually susceptible to invasive infection with most pyogenic bacteria from about 1-2 months to about 18-24 months of age, because these are primary infections occurring in an infant without previously established delayed hypersensitivity, in whom antibody formation is slow.

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