"The younger the patient, the worse the prognosis in diseases of childhood. This is in consequence of the feeble resistance of the infantile organism to all diseases particularly those which are of an acute nature."

-- L. Emmett Holt

If the science of neonatology has come of age, the study of the immunobiology of the newborn is barely past infancy. Although we have come a long way from the concept of the newborn as "immunologically null," significant gaps still remain in our understanding of the neonatal host defenses. Infectious diseases during this period of immunologic immaturity, with the attendant increase in morbidity and mortality, have been the major concern of pediatricians for a long time. So, it is not surprising to see that developments in immunology have been closely intertwined with major breakthroughs in microbiology over the last century. However, these milestones were few and far between till the 1950's. In 1950, the thymus was still considered an enigmatic organ to be irradiated at birth, gammaglobulin estimation was still a research tool, no function was ascribed to the lymphocyte and immunodeficiency diseases were unknown.

Aside from the high mortality associated with infections, several other observations have suggested that the host defenses in the developing fetus and the newborn may be quite different from those in the older child. First, the microorganisms incriminated in neonatal infections are generally different from those producing similar disease in the older child; the neonate may also fail to demonstrate fever, leukocytosis and local inflammation in
response to infection. Agents such as rubella, cytomegalovirus, and toxoplasma which produce minimal or no disease after birth, can be devastating to the unborn child. On the other hand, neonates are relatively immune to measles, mumps, paralytic poliomyelitis, etc., due to the passive protection afforded by transplacentally acquired maternal antibodies. Other areas of investigation by neonatal immunologists include the study of the protective role of breast milk and transient diseases of the newborn acquired by transplacental passage of antibodies, viz. hyperthyroidism, thrombocytopenia, neutropenia and anemia. Another question that continues to interest scientists worldwide is the mechanism whereby the immunologically disparate fetus continues to avoid rejection by the maternal uterus. The fascinating saga of Rh disease and its conquest by immunologic intervention is a complete story in itself and is described by Dr. Zipursky in this book.

The practice of variolation as active immunization for smallpox in ancient China and India was probably the earliest milestone in immunology. However, modern day immunology owes its beginning to Edward Jenner (c. 1749-1823) and his cowpox vaccine in 1798. It was from this observation of the first attenuated virus vaccine that Louis Pasteur (c. 1822-1895) coined the term vaccination (L. vacca-cow) which has become an integral part of our language. Pasteur's work from 1881-1885 launched the germ theory of disease and resulted ultimately in the production of attenuated vaccines against anthrax, cholera and rabies. In 1882, Ilya Illich Metchnikoff (c. 1845-1916) wondered about the role of "wandering" cells in a starfish larva. These cells could ingest solid particles by a process he later called "phagocytosis." He proposed the "cellular theory of immunity," which embroiled him in prolonged controversy with the "humoralists." The "humoralists," led by Paul Ehrlich (c. 1854-1915), believed that chemical substances in serum (antibodies), rather than cells, were the key to immunity. Both groups were proved correct when Wright and Douglas in 1903 showed enhancement of phagocytosis by a serum substance (opsonin), demonstrating the intricate balance and interdependence between both these limbs of the immune response. The sharing of the Nobel prize in 1908 by Ehrlich and Metchnikoff saw a happy ending to this story.

Von Behring (c. 1854-1917) and Kitasato in 1870 were the first to describe diphtheria antitoxin (antibody), which could neutralize the fatal toxin and also, when injected into an unimmunized animal, this antitoxin containing serum could passively transfer protective immunity. Robert Koch (c. 1843-1910), in the same year, described delayed hypersensitivity reaction to tuberculin, since then called Koch's phenomenon. Buchner (1893) described a heat labile serum factor (complement) and in 1894 Pfeiffer and Bordet showed the destruction of cholera vibrio by interaction between specific antibody and complement; a phenomenon they called bacteriolysis. Ehrlich proposed his side chain receptor theory of antibody synthesis in 1897 which led to a drastic change in the understanding of immunobiology and stimulated a lot of subsequent research. In addition, he was the first to describe neutrophils, eosinophils, basophils and mast cells, and it was he who first used the term complement. Other significant milestones in the development of immunology include Landsteiner's (c. 1863-1943) discovery of human ABO blood groups in 1900; Von Pirquet's (c. 1874-1929) description of serum sickness (allergy); identification of lysozyme by Fleming (c. 1881-1955) in 1922; and the demonstration by Tiselius and Kabat in 1938 that the antibody activity of serum is localized in the gamma globulin fraction of serum proteins.

During this period in the development of immunology, there were a few developments of particular significance to the neonate. Epstein in 1891 made the first clinical adaptation of Koch's phenomenon of delayed hypersensitivity to tuberculin, when he used it for the diagnosis of tuberculosis in children. Paul Ehrlich in 1892 demonstrated the transmission of immunity to the infant through maternal milk and showed this transfer of immunity to be species specific. Fischl and Von Wunscheim in 1895 found diphtheria antitoxin in fetal blood. This was the earliest record of antibody in cord blood and this antibody was seen in the sera of infants born to...
Schick-negative mothers at levels equal to or greater than those in the mother. In 1905, Ernst Moro found that
the blood of breast fed infants is more bactericidal than that of the artificially fed infants.[3] Calmette and Guerin,
working in the Pasteur Institute, after 13 years of subculturing, developed an avirulent preparation of the vaccine
in 1920, which was later to be named in their honor. In July 1921, this BCG subculture was given orally by
Weill-Halle to a newborn child born in a household with an open case of tuberculosis. The child remained free
of tuberculosis. A series of 120 children were vaccinated successfully in June 1922, following which mass
vaccination began, before any controlled human studies were done to test the efficacy of the vaccine. Tragedy
struck in 1930. In Lubeck, Germany, 251 of 412 infants born from December 1929 to April 1930 were
vaccinated orally during the first 10 days of life. Of these 251, 72 died of tuberculosis in the next few months
and another 135 developed tuberculosis but recovered; none of the 161 unvaccinated were affected. In the
ensuing trial, it was discovered that the vaccine had been contaminated by the virulent Kiel strain of tubercle
bacilli, owing to negligence in the preparation of the vaccine. In the resultant controversy, the use of the vaccine
diminished greatly to be revived again only after World War II, amid enactment of strong laws and guidelines in
the production of the vaccine.[4] Another observation that was to have a profound effect on our understanding of
the host defenses in the developing fetus was the report by Sir Norman Gregg from Australia.[5] He showed that
rubella virus infection during pregnancy resulted in severe congenital defects in the newborn.

The year 1952 was a landmark in the history of modern immunobiology. Colonel Ogden Bruton studied a male
child with repeated bacterial infections and found an absence of gamma globulins upon electrophoresis of his
serum proteins.[6] Interestingly this child's agammaglobulinemia was probably an acquired rather than a
congenital form, since his bouts with infections began following the development of measles at 3 years of age.
Thereafter, the field of immunology which had shown only sporadic activity for decades finally erupted in a
burst of activity and, within a few years, a new science had evolved. Hitzig described the "Swiss
agammaglobulinemia" in 1953 and, in the same year, Billingham, Brent and Medawar demonstrated neonatal
induction of tolerance.[7] Glick and Change made the fortuitous observation in 1956 that antibody production in
chickens depended upon the presence of the Bursa of Fabricius. Miller in England and Good and his colleagues
in Minnesota almost simultaneously (1961-2) elucidated the role of the thymus in the immune response.[8-9] As
Steihm and Fulginiti contend, the story of pediatric immunology, subsequently, is "A Tale of Two Cities," that
of Boston and Minneapolis in the 1960's under the leadership of Good, Janeway and Gitlin.[10]

The following discussion will deal with the advances made in the understanding of host defenses in the newborn
in the last two decades and some special issues pertinent to the newborn. The four limbs of the immune
response, viz. humoral and cellular responses, the phagocytic system and the humoral mediators, will be
described individually for the sake of simplicity in description.

HUMORAL IMMUNE RESPONSE

A rather fortunate accident was responsible for elucidating the role of the Bursa of Fabricius in chickens. Glick,
in 1954, was studying the role of bursectomy on the subsequent growth of newborn chickens. Chang used some
of these bursectomized chickens, while demonstrating normal antibody production to his class. To his chagrin,
he found that 6 chickens died immediately after injection of salmonella O antigen, while 2 survivors showed no
antibody response. Further experiments confirmed their accidental finding of the role of bursa upon antibody
synthesis.[2] A clear understanding of humoral immunity in the newborn is complicated by the contribution of maternal
antibodies to the immune system of the fetus and newborn. Hence a discussion of transplacental passive immunity is warranted before a description of the B-cell system in the neonate.

**Passive Maternal Transfer.** As described earlier, the first demonstration of transplacental transfer of antibodies was in 1895 when Fischl and Von Wunscheim found diphtheria antitoxin in fetal blood. Immunoglobulins of the IgG class are acquired passively by the fetus beginning at about the third month of gestation. At term, the IgG concentrations in the cord blood exceed those in the maternal sera (110%), and this IgG affords passive protection against many bacteria and viruses in the first six months. The process of transplacental transfer is an active one and is dependent upon the presence of a special determinant on the Fc portion of the IgG molecule. The quantity of gammaglobulin in cord blood has a direct relationship to gestational age; hence prematurely born infants have lower serum IgG levels than term infants. IgG declines exponentially in the neonate, reaching its nadir between 2-4 months of life, when it starts to rise again owing to antibody synthesis by the infant.[11]

Immunoglobulins of other classes, viz. IgM, IgA, IgD, and IgE, do not cross the placental barrier; consequently antibodies of these classes are absent in a newborn. The increased susceptibility of the neonate to gram negative bacteria may be explained by the fact that antibodies against these are primarily IgM antibodies. There are some advantages to this selective transfer of IgG. Maternal allergy producing IgE antibodies and ABO isoagglutinins of IgM class do not gain access to the child.

Recently, maternally acquired measles antibodies (IgG) have been shown to interfere with active immunization of the child under 12 months of age which, consequently, has resulted in shifting the optimal age for measles immunization to 15 months.[12]

**Development of B-Cells.** The development of B-cells is a two-stage process: first, the antigen independent differentiation of the stem cell into the pre-B cell, and next, the maturation of these pre-B cells into immunocompetent B-cells. This latter process is dependent upon antigenic stimulation. Both steps require active interaction with T-cells. Pre-B cells have been visualized in the bone marrow of abortuses of 13 to 16 weeks gestation, but not in the spleen or peripheral blood. B-lymphocytes with IgM, IgG and IgD can be seen in the fetal liver at 12 weeks and in the peripheral blood thereafter. The sequence of appearance of these immunoglobulins is IgM first, then IgG, and then IgA. IgD appears after IgM, at some time coincident with the appearance of IgG and IgA. In the B-cells, the immunoglobulins first appear within the cytoplasm and only later are expressed on the surface of these lymphocytes. Hence, the fetal B-cells are ready for immunoglobulin synthesis after the 8th week of gestation, although animal studies demonstrate that the ability to produce antibodies to various antigens occurs in a stepwise fashion. This may be related to T-cell regulation of antibody synthesis or to immaturity of antigen processing by macrophages. However, at birth, the neonate has only small amounts of self derived immunoglobulins. This observation is related in part to the lack of antigenic stimulation during fetal life. Thus, animals raised in germ free environments produce very small amounts of immunoglobulins. Conversely, infants born after intrauterine exposure to infectious agents have increased levels of immunoglobulins, particularly IgM, and sometimes IgA.[1]

**B-Cell Function in the Newborn.** At birth, the newborn is exposed to a variety of antigens and noxious stimuli which provoke an antibody response. Immunoglobulins of M, A, and E classes can be detected in all neonatal sera. These are all of fetal origin unlike the IgG which is maternally derived. The neonate has a higher percentage of B-cells than the adult. Antibody producing plasma cells are not seen in the first 3-5 weeks of life, so, it appears that the site of antibody production in the neonate is the spleen rather than the regional lymph nodes.
Following exposure to an antigen, the neonate responds by production of IgM and later IgG antibodies, just like the adult. However, the transition from IgM to IgG is longer. An adult starts to produce IgG 5-15 days after an infection, whereas an infant may elaborate only IgM for 20-30 days. This prolonged IgM to IgG transition may be present up to 6 months of age. The postnatal rise of various immunoglobulins proceeds at varying rates. IgM rises rapidly in the first 3-4 weeks of life and slowly thereafter, reaching adult values by 2 years of life. The IgG globulins attain adult levels by five to six years of age and IgA by 10 years. Secretory IgA on mucosal surfaces in 11 S form develops rapidly after antigenic exposure and can be detected as early as 10-20 days.

CELLULAR IMMUNE RESPONSE

The lymphocytes are the major cells involved in the immune response. The lymphocytes were first described by Hewson (c. 1739-1774) in the late 18th century, and stained and studied by Paul Ehrlich in 1879. Ehrlich concluded mistakenly that these were non-motile cells that did not differentiate and served no special purpose. In the early 1950's the clinical significance of the lymphocyte became clear.

The story of the thymus is fraught with tragedy. Arnold Palatauf, in 1899, based on a sketchy analysis of five autopsies, proposed that an enlarged thymus with marked lymphoid hyperplasia was anatomic evidence of a constitutional weakness and was responsible for the sudden death of his young patients, the so-called "status thymolympathic." This view was readily embraced and accepted for a good part of this century, as more and more reports of this "disease" appeared all over the world. Over 800 papers had been published by 1922 relating to Palatauf's work. Friedlander, in 1917, started irradiation of the thymus in newborns to prevent sudden death, despite lack of supportive proof. The final blow came in 1950 when thyroid carcinoma appeared in people who had received "preventive" irradiation.

At this time, the role of the thymus in the regulation of the immune response started to become apparent. In 1954, a 54-year-old man was seen at the University of Minnesota Hospital with recurrent pneumonia, and was found to have low gammaglobulins and a mediastinal tumor which was a benign thymoma. During the following 3 years, he developed at least 17 life-threatening infections and finally succumbed to a bout of fulminant hepatitis. This observation, coupled with Glick and Chang's work with bursectomy in neonatal chickens led to the studies of thymectomy in neonatal mice by Good and co-workers in Minnesota and Miller in England, which finally clarified the function of the thymus gland.

Passive Transfer of Cellular Immunity. The issue of transfer of cellular immunity to the newborn has been the subject of various studies. Unlike maternal IgG, the cellular elements from the mother do not pass through the placental barrier in any predictable way. Direct transfer of sensitized T-cells has been demonstrated only rarely. However, in vitro studies have demonstrated that cord serum inhibits the proliferation of maternal T-cells in response to non-specific mitogens. Studies of passive transfer of cutaneous reactivity to tuberculin by giving sensitized lymphocytes to neonates have been contradictory. Only one study has demonstrated successful transfer of tuberculin skin reactivity to the fetus following exchange transfusion.

The transfer of maternal lymphokines across the placenta to affect fetal lymphocytes also has been clearly shown. Hence a passive transfer of cellular immunity to the fetus across the placenta appears unlikely. However, it is more likely that fetal T-cells may be sensitized by transplacental passage of antigen.
Development of T-Cells. Lymphocytes are first seen in the yolk sac at about 3-6 weeks of fetal life. They are next seen in the liver and bone marrow and then in the thymus and spleen at about the ninth week. Thymus dependent lymphocytes precede the appearance of antibody bearing lymphocytes in the fetus. These lymphocytes begin to appear in the thymus soon after, filling the cortex after 14 weeks and then migrating to the medulla.[16]

Functional testing of these lymphocytes after 11 weeks shows the ability to form rosettes with sheep RBC; and response to mitogen stimulation occurs by the end of the first trimester. Hence, it appears that the fetus develops cellular immunity by that time.

T-Cell Function in the Newborn. Quantitative assessment of T-cells in the newborn using various techniques shows that the percentage of T-lymphocytes in the cord blood is decreased, while in the peripheral blood it may be normal or decreased. However, the total number of T-cells in the cord blood is greater than that in adults, owing to the absolute lymphocytosis in the newborn.[17] There is no information about the distribution of the different subpopulations of T-lymphocytes in the newborn.

Conventional wisdom, for many years, has indicated that the newborn had a deficient cellular immunity. This was based on the observation that newborns showed poor skin test response to antigens to which they had been exposed. The diminished delayed hypersensitivity responses have now been explained by decreased inflammatory responses in the neonate.

Functional assessment of T-cells in the newborn shows variable results. Antigen recognition by T-cells in mixed lymphocyte cultures is present and so is antigen binding and graft versus host reactivity. Interferon production is normal while cell mediated cytoxicity and lymphokine production may be normal or decreased.

Proliferative responses to mitogenic stimulation by cord lymphocytes have been studied with variable results. They have been found to be greater than, equal to, or less than that of adult lymphocytes, making interpretation difficult. These variable responses may be related to the presence of other modifying factors at this age. Hence, the overall function of T-cells in the newborn appears to be normal.[1]

HUMORAL MEDIATORS

The inflammatory response is amplified by a number of humoral mediators, plasma derived and tissue derived. Of these, the complement system and the coagulation and kinin systems have been studied most extensively.

Development of Complement. Complement development occurs early in fetal life, with synthesis of most components occurring by 8-11 weeks of gestation. C3, C5, C6, and C9 are synthesized by the liver primarily with some synthesis in the thymus, while C2 and C4 are produced by macrophages. Complement development precedes immunoglobulin synthesis, suggesting a more primitive role of complement in the phylogeny of the immune response. There is very little or no placental transfer of complement.[18]

Complement in the Neonate. The total hemolytic activity of complement in the term neonate is only about 50% of maternal levels, and so is Factor B. Deficiencies of various complement components, C3 through C9, have been demonstrated. The triggering component of the classical complement pathway, C1q is decreased to 75% of adult levels. Levels of complement proteins increase rapidly after birth, reaching adult levels by 3-6 months of
Newborn serum is known to be deficient in complement related functions. For example, the opsonic activity shows marked deficiencies, greater toward gram negative than gram positive organisms. These opsonic deficiencies occur in addition to the IgM deficiency in the neonate. Fresh sera have been found to be defective in generating chemotactic activities. These quantitative and qualitative complement deficiencies may well be partly responsible for the rapid and often fulminant course of neonatal infections.[18]

PHAGOCYTES

Metchnikoff in 1882, while examining a transparent starfish larva saw some "wandering cells" which were able to ingest dye, carmine and, in subsequent experiments, gathered around a rosethorn he introduced into the starfish. He named these wandering cells phagocytes (eating cells) and began work which would consume him for over two decades and embroil him in great controversy. He traced the phylogeny of phagocytes through protozoa to metazoa to higher animals and, in the process, described two types of phagocytes: macrophages (neutrophils, eosinophils) and macrophages (histiocytes, monocytes, living cells in spleen, liver and bone marrow).

After establishing the central role of phagocytes in the immune response, he went on to propose that deficiencies in phagocytosis might lead to impairment of host defenses. Metchnikoff's genius, however, went unrecognized for decades, and it took 83 years for the first description of a defect in phagocytes of children with chronic granulomatous disease to be published by Holmes et al., in 1966.[19] Subsequent discoveries have more than fulfilled Metchnikoff's prophecies. The following discussion will present the development and function of the polymorphonuclear leukocyte (PMN) and monocyte-macrophage (MNL) in the neonate.

Development of Phagocytes. Hematopoiesis in the developing embryo occurs during 3 periods: in the mesoblastic stage, hemocytoblasts appear in the yolk sac around the nineteenth day of gestation; the hepatic stage begins by the seventh week and, by the third month, hematopoiesis is seen in the spleen and thymus; the final myeloid stage begins by the fourth month. Granulocytopenesis begins around the second month, but there are few circulating granulocytes in the first half of gestation; with their numbers exceeding 1000/mm³ only after the sixth month. Tissue macrophages begin to appear in the 3 to 4 week embryo and circulating monocytes are seen by 16 to 20 weeks.[20]

Phagocyte Function in the Newborn. The process of destruction of foreign matter by phagocytes consists of the distinct steps of cell movement or chemotaxis, ingestion or phagocytosis and intracellular killing.

Hunter (c. 1728-1793) in 1774 first recognized the presence of leukocytes at the site of inflammation. Metchnikoff's historic work on chemotaxis and phagocytosis, as noted earlier, began in 1882. Massart and Bordet in 1890 found that injured cells release chemical substances that attract granulocytes. However, the study of leukocyte locomotion had to await the development of time lapse cinematography in 1917 for observation of leukocyte movement toward bacteria (Commandos). Boyden devised the first quantitative in vitro study of neutrophil chemotaxis in 1962.

The neonatal PMN's show significant deficiencies of chemotaxis in vitro, when compared to adult cells.[21]
Neutrophil movement is studied in vivo by the Rebuck skin window technique. When newborns are examined by this method, two distinct differences appear consistently. First, the shift from the early granulocytic response to a monocytic one is slower and less intense. Secondly, many infants up to 3 weeks of age show a marked eosinophilia at inflammatory sites.[22]

Assessment of phagocytosis by neonatal PMN has shown variable results in different studies, based on the methodology. However, it appears that under conditions of stress, such as sepsis, the newborn PMN may have defective phagocytic activity. Intracellular killing of bacteria following phagocytosis is an event involving a burst of oxidative metabolism, resulting in the formation of superoxide anion and other oxygen radicals. Bactericidal activity of neonatal PMN has been found to be variable by various investigators. Intracellular killing activity of the neonatal PMN is impaired under stress. Neonatal PMN has also been found to have markedly decreased deformability, implying increased rigidity of PMN cell wall. The defective chemotaxis of the neonatal PMN, may thus be due in part to this increased cell wall rigidity.[1]

Functional analysis of the monocytic cells (MNL) in the newborn has provided conflicting data. The movement of MNL in the newborn has been found to be increased, normal, or decreased under different circumstances. Overall, it appears that neonatal MNL has normal chemotactic activity. Similarly phagocytosis and bactericidal killing by MNL in the newborn have been found to be normal.'

IMMUNOLOGY OF BREAST MILK

Mammalian species produce breast milk which is suited to the specific nutritional needs of their youngsters. The chemical nature of various milks has been well studied in the last two hundred years. Recent immunologic studies have revealed some fascinating information which shows that breast milk boosts the host defenses of the neonate.

Up to the turn of this century, infants were exclusively breast fed, since it was considered not only the best but the safest food for them. Despite the universal practice of breast feeding, very little information is available about the advantages of breast feeding in the medical writings of the eighteenth and nineteenth centuries, except the mention of high mortality associated with "dry nursing" of infants. In fact, much effort was wasted by the medical practitioners of the day in establishing criteria for the selection of wet nurses on the basis of their hair color and temperament.[14]

Artificial feeding of infants was looked upon with horror because of the attendant mortality, as high as 85-99% in foundling homes of Paris and Dublin in the late eighteenth century. Similar trends in mortality in artificially fed infants persisted throughout the nineteenth century in the, overcrowded cities of the U.S. and Europe, leading Holt (c. 1855-1924) to remark:

"In my practice, it is exceedingly rare to find a healthy child who has been reared in a tenement house and who has been artificially fed from birth."[23]

Much of this mortality, associated with cow's milk, of course, resulted from bacterial contamination, a problem which was resolved only after pasteurization was instituted-and Chicago was the first city in the world to require it, in 1908.[14] However, not all the reduction in morbidity and mortality in neonates can be attributed to improved sanitation, health care, and affluence. Careful analysis of several old studies from Europe and U.S.,
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and some recent ones from developing countries, comparing mortality and morbidity of bottle fed and breast fed infants, showed significant protection from respiratory and intestinal infections in breast fed infants. Indeed, this information has considerable significance for the developing world.[24]

As mentioned earlier, work by Ehrlich and Moro provided some information about the contribution of breast milk to the neonatal immune response. Recent improvements in immunology coupled with advances in technology, have seen a remarkable understanding of the functional qualities of breast milk.[25]

The infant at birth has only one type of immunoglobulin, IgG, acquired transplacentally. Analysis of breast milk proteins shows that they contain a high level of IgA and some IgM and IgG-immunoglobulins which do not cross the placenta. There is little correlation between serum and milk antibodies in several other areas. Quantitative differences exist between the antibody titres to the same antigens at the two sites. Qualitatively, different classes of antibodies appear in the breast milk and serum following challenge with the same pathogen, e.g. antibody to poliovirus in the serum resides in the IgG class primarily, whereas in the colostrum it is in the IgA class. The third difference is within the IgA class itself. In breast milk 80% IgA is of the dimeric secretory type and only 20% resembles the monomeric serum IgA.

The immunoglobulin characteristics of breast milk, therefore, resemble those of the mucosal sites in the intestinal and respiratory tract. High titres of antibody are present in the colostrum which drops sharply over the next few days. There is no information to suggest that milk immunoglobulins are absorbed in sufficient quantities to contribute to the serum immunoglobulins of the newborn. However, secretory IgA can bind microorganisms and prevent their penetration of the intestinal mucosa. IgA can also lyse certain enteric bacteria in the presence of complement and lysozyme. In addition to the specific antibodies, breast milk also contains nonspecific humoral factors such as lysozyme, lactoferrin and lactoperoxidase.

Colostrum and breast milk contain $1-2 \times 10^6$ leukocytes/ml. Macrophages make up 90% of these white cells; they form the primary line of defense against many pathogens. The other 10% of colostral cells are small lymphocytes with about equal proportions of B and T cells. The function of these lymphocytes is not precisely known, though an interesting relationship has been observed between the colostral B cells and antibodies, and the mucosal immune system. Recent work has demonstrated the existence of an immunologic broncho-mammary and entero-mammary axis, as evidenced by the following observations. First, a majority of B cells in colostrum differentiate into IgA secreting plasma cells just like the B cells at mucosal sites. Secondly, most of the antibodies secreted by breast milk are directed against enteric and respiratory pathogens. Indeed, experimental studies show that highest titres of antibodies develop in the breast milk following immunization by the oral and intratracheal routes rather than by the parenteral route.[26]

It is evident then, that in the course of evolution each mammal has developed special characteristics in the milk which fulfill not only the nutritional needs but also provide other biologic advantages for its nursing newborn.

IMMUNOLOGIC RELATIONSHIP OF FETUS AND MOTHER

Generations of physicians have been intrigued by the special relationship of the fetus with the mother during pregnancy. The lack of rejection of the antigenically disparate fetus (with at least half of its antigenic determinants inherited from the father) has prompted a lot of research. Lewis Thomas went so far as to liken the process of labor and delivery to an allograft rejection. Sir Peter Medawar, in 1954, proposed:
1. The fetus is antigenically immature;
2. The uterus is an immunologically privileged site;
3. Maternal immune response is suppressed during pregnancy, or
4. An anatomic barrier exists between the mother and her fetus. [2]

None of the hypotheses, when considered individually, provides a plausible explanation for the paradox. Using sensitive research methods, fetal tissues have been shown to possess transplantation antigens, although these might be weak in nature. Experimental studies designed to study the concept of the uterus as an "immunologically privileged site" have been unsuccessful, since uterine horns show normal rejection of tumor allografts. Although the maternal immune response is impaired during pregnancy, this in itself is insufficient explanation for the maternal fetal relationship. Successive pregnancies occur successfully even when the mother is immune, or hypersensitive to fetal/paternal antigens. Maternal blood circulates in contact with the fetal trophoblast, which serves as an anatomic barrier between mother and fetus. This syncytiotrophoblastic layer of cells has been found to be lacking in transplantation antigens. The absence, or dearth of antigenicity of the trophoblast may well be the most likely, if not the total, explanation for the preservation of the fetal allograft in the mother. [27]

A rather fortuitous discovery to emerge from the study of immunogenetics of pregnancy is the recent observation that repeated spontaneous abortions may occur when both parents share antigens of the major histocompatibility complex. Hence, male-female heterozygosity is beneficial rather than detrimental, to the outcome of pregnancy. [28]

The development and function of the neonatal and fetal immune response are summarized in Table 1. It is obvious then, that the newborn rather than being immunologically null, has a fairly well developed and sophisticated immune response. Lacking in antigenic challenge while in utero, the newborn promptly responds to heavy antigenic challenge after birth. Subtle maturational deficiencies in complement activity and immunoglobulin content, coupled with serious defects in phagocytic function, result in a diminished inflammatory response in the newborn. Current research is directed towards evaluating the T cell subpopulations, B-T cell interaction, role of macrophages in modulating the immune response and study of natural killer cell activity in the newborn. Some fruitful results from these studies have already begun to appear. Transient hypogammaglobulinemia of infancy, it was recently shown, occurs as a result of a transient deficiency of the helper T cell population. [29] The recent demonstration of increased survival of septic newborns by granulocyte transfusion opens up new horizons in immunologic intervention in neonates with severe infections. [30]

**Table 1**

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<th>Immune Response of Fetus and Newborn</th>
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<tr>
<th>Week</th>
<th>Cellular Immunity</th>
<th>Humoral Immunity</th>
<th>Complement</th>
<th>Phagocyte</th>
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<tr>
<td>Week 8</td>
<td>Lymphocytes in peripheral blood</td>
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<td>Synthesis of complement components begins in liver</td>
<td>Hematopoiesis in yolk sac</td>
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<td>Rosette formation</td>
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<td>Hepatic stage begins</td>
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<td>Granulocytes in peripheral blood</td>
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<td>Week 12</td>
<td>Mitogen stimulation</td>
<td>IgM bearing B cells in liver</td>
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<td>Graft versus host reactivity</td>
<td>IgG and IgA bearing B cells</td>
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<td>Week 16</td>
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<td>Myeloid stage beings</td>
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<td>Monocytes in peripheral blood</td>
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<td>Week 20</td>
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<td>PMN count 1000/mm³</td>
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<td>Week 24</td>
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<td>Week 40 - Birth</td>
<td>Maternal IgG - above normal</td>
<td>C1Q - 75%</td>
<td>PMN:</td>
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<tr>
<td>T cell number</td>
<td>T cell percentage below normal</td>
<td>IgM, IgA - require antigenic challenge</td>
<td>C3 - 56%</td>
<td>Chemotaxis - below normal</td>
</tr>
<tr>
<td>T cell percentage - below normal</td>
<td>Antigen recognition below normal</td>
<td>C4 - 55%</td>
<td>Phagocytosis - normal or low</td>
<td></td>
</tr>
<tr>
<td>Antigen recognition - below normal</td>
<td>Lymphotoxin production below normal</td>
<td>C5 - 60%</td>
<td>Bactericidal activity - normal or low</td>
<td></td>
</tr>
<tr>
<td>Interferon production - below normal</td>
<td>Interferon production - below normal</td>
<td>CH50 - 50%</td>
<td>Deformability - below normal</td>
<td></td>
</tr>
<tr>
<td>1 Year</td>
<td>IgG - 60%</td>
<td>Most components reach adult level</td>
<td>MNL Function - normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IgM - 75%</td>
<td>(of adult levels)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IgA - 20%</td>
<td>(of adult levels)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

REFERENCES


