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SOME DEVELOPMENTAL ASPECTS IN RELATION TO IMMUNITY AND ALLERGY*

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The newborn animal emerges bacteriologically sterile and immunologically pristine into an environment rich in microorganisms and antigenic materials. He is dependent initially on a dowry of maternal antibodies for protection against the microbial insults of the extrauterine environment. Immunologic development is not a single process which suddenly matures at birth. Like any other developmental phenomenon, it is a continuation of the process which has started early in prenatal life and continues to mature well into the postnatal life.

Immunity

The term 'immunity' is generally applied to the resistance offered by the host to an infective agent. It helps in the elimination of the latter. Recently, it has been applied in a very wide sense to cover all processes whether protective or not, which come into force following the introduction of a foreign agent to the host's milieu. Immunity may be specific or nonspecific.

Nonspecific immunity. Several factors influence this. It may be species dependent, e. g. several diseases including syphilis, meningococcal meningitis, leprosy, and measles affect human beings but have not been propagated in animals. Hereditary factors may be important. For example, the sickle cell trait offers a protective resistance to *P. falciparum* infection through an as-yet-unknown mechanism. Similarly racial and individual immunity plays a part in warding off disease manifestation even after infection has been introduced. Other factors possibly affecting host resistance in a nonspecific way are, age, nutrition, metabolic disturbances, tissue enzymes, complement, interferon, phagocytosis by fixed and wandering macrophages.

Specific immunity. When specific mechanisms exist which check the invasion and growth of a particular organism, specific immunity is said to be operating. This may follow active immunization through natural or artificial infection, or passively acquired again through natural or artificial means. The advantages of active immunity are several, including a longer duration of protection, an absolute or greater protection, absence of harmful serum reactions, lack of suppression of natural antibody formation, etc.

Development of Immune Competence

The three factors which interact in immunogenesis are, the presence of cells capable of a specific immune function, the exposure to antigens and the consequent formation of

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antibodies. The cells concerned with immune competence include the macrophages which process the antigen and to some extent digest it, making it immunogeneic ; the small lymphocytes which are concerned with delayed hypersensitivity and specific cellular immunity responses ; lymphoid cells which on stimulation get converted to plasma cells elaborating antibodies ; and cells producing interferon and other nonspecific protective substances either on mucous membranes or into tissue fluids.

The thymus is the master organ controlling the optimal development of immune function. It originates from the third and fourth branchial clefts, together with the parathyroids, which explains the occasional occurrence of defects involving both these organs, manifesting as recurrent severe infections in early life and tetany. It is likely that lymphocytes derived from the bone marrow populate the thymus, which also secretes a hormone-like substance having a maturing influence on other lymphoid tissues throughout the body. The thymus itself contains few if any antibody forming cells, as shown in several mice experiments. In the face of involuting agents like radiation and steroids, the organ shrinks remarkably.

The antibodies are elaborated by the plasma cells, which get their stimulus through the immunologically competent small lymphocytes. The antibodies formed can be classified into five immunoglobulin groups : IgG, IgA, IgM, IgD. and IgE. The last named is the most recent discovery, and is the reaginic antibody concerned with the allergic phenomena. These antibodies differ in their molecular weight, aminoacid structure, electrophoretic inability, sedimentation rate and antigen-binding capacity. Their levels differ at various ages and in different communities, perhaps related to the amount of antigenic exposure. IgM is lacking in the neonatal period and this to some extent explains the increased frequency of Gram negative infections in this age period. In subsequent periods, low levels of IgM may occur singly or in combination with defects of other Ig classes. Clinically, it has been reported to be associated with generalized nonprogressive vaccinia following smallpox immunization. IgG levels in the newborn period run parallel to the maternal levels, since, this Ig diffuses across the placenta through active transport. By about 3 months, most of the maternal IgG has decayed, and the infant has started producing its own, but by the time the latter reaches an adequate level, a short period of transient physiological hypogammaglobulinemia exists which may lead to severe frequent infections, expecially in the premature whose endowment of maternal IgG is relatively small. IgA is principally concerned with immunity at cell and mucous membrane surfaces, and its role in protective immunity and in disease states is still a fascinating lacuna of knowledge.

Immunological tolerance as a developmental phenomena.

The competence of the fetus to react to foreign substances is limited, especially in the first few weeks of intrauterine life. It is therefore, 'tolerant' to such antigens because the mechanisms by which it recognizes it as 'foreign' have not developed. This may be based on the lack or small

numbers of immunologically competent cells or due to the presence of modifying metabolic factors such as cell permeability, existence of hydrolytic enzymes, maturation of lysosomal function, competition for protein synthesis pathways, etc.

Autoimmunity

The term 'autoimmunity' is used to imply the formation of antibodies to the individual's own tissues by antibody forming cells, which are pathologically stimulated or altered. Examples of this are Hashimoto's thyroiditis, autoimmune hemolytic anaemia, rheumatoid arthritis, lupus erythematosus, etc. Some recent work indicates that autoimmune diseases may be based on an inherent lability of lysosomes which break down releasing hydrolytic enzymes which make one's own tissues antigenic. This is supported by the observation that agents which stabilise the lysosomes also help the disease process, whereas others which labilise the lysosomes worsen the disease. Other theories which might explain autoimmune diseases, are the hapten mechanism wherein a chemical becomes attached to a body constituent and forms a new 'foreign' antigen, breakdown of anatomic or physiologic isolation of certain tissues exposing them to immunologically competent cells, or the existence of abnormal clones of such cells.

Infections during Infancy and Childhood

In the perinatal period, several infections follow a course and have complications vastly different from a similar infection in a mature individual. This is based on poorly matured immune mechanisms. Examples of this are provided by toxoplasmosis, congenital syphilis, herpes simplex, etc. In this age period, Gram negative infections are more common, which is perhaps related to a deficiency of IgM. In general, there is a greater tendency to blood invasion, dissemination and more severe residual effects, than is seen in older children and adults. Some infections, on the other hand, may be milder and less serious in the young. The examples of this are chicken pox and mumps.

Besides these physiological handicaps of the small infant, infections during this age period may be based on a partial or complete, single or combined immunity deficiency state. With the ubiquitous microbes in our environment, it is a wonder why only some of us contract infections whereas others do not. Such defects of immunity may be genetic and may manifest themselves at birth or in the first few months of life, or be acquired due to unknown or known causes.