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MATERNAL ANTIBODIES, CHILDHOOD INFECTIONS, AND AUTOIMMUNE DISEASES

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RECOVERY from an infectious disease or an encounter with a nonmicrobial antigen is usually followed by the development of resistance to that disease or a rapid and heightened immune response on reexposure to the antigen. These effects, termed immunologic memory, are explainable by the generation of increased numbers of precursor lymphocytes during the initial encounter and the induction of a special "memory" quality of individual T and B cells.[1-4] Alternatively, memory could result from the persistence of low levels of antigen in lymphoid tissues, which keep T cells activated and maintain protective amounts of antibodies.[5,6] In this article, I will discuss how the antibody repertoire of the mother influences the susceptibility of her child to infectious agents and autoimmune diseases.[7-10] Her immune repertoire reflects not only her cumulative immunologic memory but also the protective immunity present in her neighbors — herd immunity. I will argue that a mother's immunologic memory can influence the ability of early childhood infections to serve as physiological vaccines not only in her own child but also in generations to come.

TRANSFERABLE MATERNAL IMMUNE PROTECTION

The period shortly before and after birth may be the key to understanding immunologic memory.[6,8-10] During this phase of development the immune system is relatively incompetent. For this reason, transferable maternal immunologic memory is essential for the survival of the fetus, newborn, and infant. Moreover, the attenuation of infection by transferable maternal immunity permits microbial agents to immunize the child under optimal conditions (this key function of transferred maternal antibodies is also essential for the survival of birds and fish). Although maternal antibodies can protect the offspring, maternal T cells cannot, because of differences in tissue antigens (HLA in particular) between the mother and her fetus. These differences raise the possibility of an attack on the fetus by maternal T cells, but this danger is avoided by the absence of HLA antigens in areas of placental contact[11,12]; conversely, the risk that fetal lymphocytes will attack the mother is likewise low, because of the incompetence of fetal T cells. Thus, antibodies alone serve to transmit the mother's immunologic experience to the fetus and infant; these, and not T cells, protect the child while its own immune system matures.

The importance of the protection afforded by maternal antibodies is clearly seen in agammaglobulinemia.[8,9,13] Infants incapable of producing immunoglobulins are protected by maternal antibodies for the first 3 to 12 months after birth (Fig. 1). Maternal IgG antibodies enter the fetal circulation through the placenta, whereas IgA antibodies in milk remain largely within the infant's gut, where they influence the intestinal flora. How can antibody levels in plasma and milk be kept high enough to protect the child?[9,10] Various mechanisms cause a constant boosting of the immune responses by microbes. Examples are periodic reinfection by polioviruses,[14] the persistence of low levels of disabled measles virus,[15,16] and controlled subclinical infection by persistent hepatitis B virus (HBV).[17]

Protective antibodies against all relevant infectious agents cannot be produced during pregnancy without harming the fetus. In fact, infections that threaten the survival of the fetus or newborn are rare not only because of transferred maternal immunity but also because of herd immunity. Herd immunity reflects the equilibrium between susceptible and immune individuals in a population or species.[5] It reduces the probability that an infected person will spread the infection widely to susceptible, uninfected people. By evolutionary necessity, women must become immune to life-threatening infectious agents before they become pregnant if they are to transfer their protective antibodies to the next generation during pregnancy. Therefore, the outcome in a given child of any of the classic infectious diseases of childhood depends on the mother's history of infectious disease before pregnancy — her accumulated immunologic experience — which in turn is partly dependent on herd immunity (Fig. 1).[5,14,18]

THE HOST–PARASITE EQUILIBRIUM

It is not surprising that all protective vaccines induce long-lasting neutralizing-antibody responses. Current vaccines that are not sufficiently protective include those against mycobacteria, most parasites, and herpesviruses and human papillomaviruses. Neutralizing antibodies alone are not sufficient to eliminate infections with these kinds of microbes, since these agents can persist outside lymphoid tissues in neurons, epithelial cells, or granulomas. Moreover, such infectious agents are often only weakly cytopathic, if at all,

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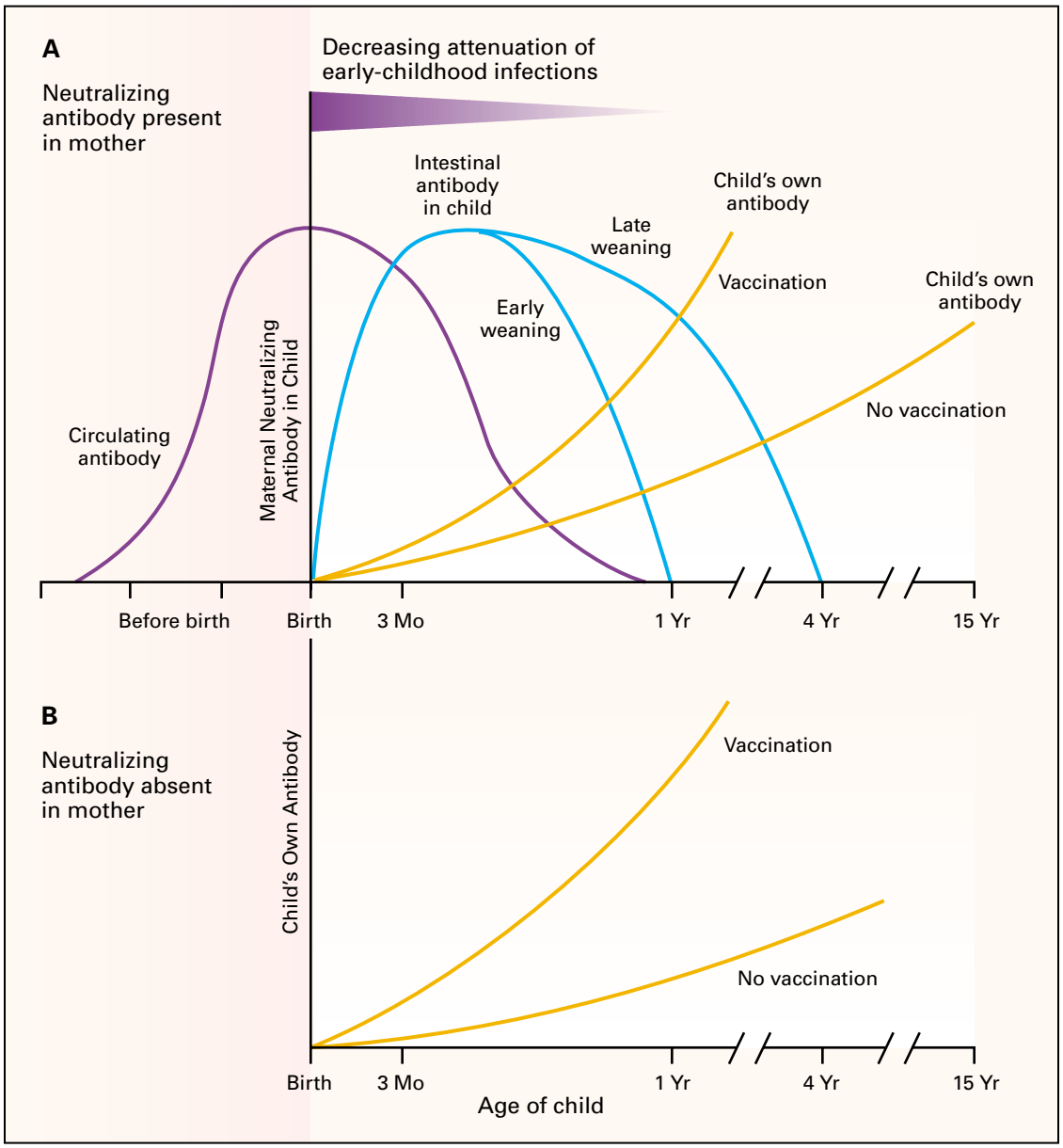

Figure 1. Protective Effect of Maternal Antibodies in Serum and Milk.

In Panel A, maternal neutralizing antibodies cross the placenta to protect the offspring and attenuate systemic infections for 6 to 12 months after birth. The timing of weaning — early or late — influences the levels of intestinal antibodies derived from breast milk and the rate of attenuation of gastrointestinal infection. In Panel B, the absence of specific neutralizing antibodies in maternal serum leads to the absence of a protective effect.

and the infections they cause are chronic and are usually not lethal. In almost all these instances, immunologic control of the invader requires both antibodies and T cells.[19-25] Chronic HBV infection is an exception, because neutralizing antibodies alone protect efficiently; a carrier mother who lacks neutralizing antibodies readily transfers the virus to her infant during labor and delivery.

In many cases, the microbe and its host are in a delicate equilibrium: an ongoing immune response results in low levels of the infectious agent, and a low level of the microbe helps maintain protective immunity. This balanced state of chronic infection and concomitant immunity is accompanied by a heightened degree of macrophage activation by cytokines (e.g., interferon-γ and tumor necrosis factor) and activa-

tion of natural killer cells.[22,23] The result is the enhancement of innate immunity — the initial nonspecific disposal of infectious agents. For some agents, such as mycobacteria and many parasites, a chronic low-level infection may represent an exquisite coevolutionary balance of mutual benefit.

THE ROLE OF HYGIENE

The neutralizing antibodies that a mother transfers to her fetus may not always eliminate a particular infectious agent, but they do attenuate infection during the initial months of life, thereby creating optimal conditions for the natural immunization of the child against that agent as a result of infection. However, the development during the past century of high standards of hygiene in the developed world has decreased the level of exposure to common infectious agents during childhood to the extent that many infections now occur only after maternal antibodies in the child have waned. Moreover, hygienic conditions may hamper the induction and maintenance of protective maternal antibodies before pregnancy. This situation will be aggravated if vaccination programs are inadequate and thus reduce opportunities to boost immunity to important pathogens. The failure to maintain high levels of neutralizing antibodies will eventually diminish herd immunity, thereby increasing the risk of the spread of an infectious agent, and reduced levels of neutralizing antibodies during pregnancy in one generation will influence the initial host–parasite equilibrium in succeeding generations. The latter change will, over time, increase susceptibility to serious childhood infections among populations and exacerbate other infections that are currently mild.

Transferred maternal immune protection can have an important influence on emerging or new infectious diseases in susceptible populations. The excessive morbidity and mortality of emerging infections may be due largely to the lack of transferred maternal antibodies during infancy, when they could attenuate the infection.[14,26] For this reason, the relation between maternal immunity and emerging infections may be of general importance now and in the future. If the transmission of immunologic memory from mother to offspring does indeed influence disease susceptibility in the next generation, then the use of vaccines that are as efficient as wild-type infections in evoking protective immunity, at least during the reproductive period, may be crucial, because they will have a species-wide influence.

The experience with poliovirus may be instructive here (Fig. 2).[14] Because levels of neutralizing antibodies against poliovirus are determined by infection and vaccination, better hygiene has delayed the occurrence of natural infection with the virus in both the developed and developing worlds.[14] The consequence of this delay is that antibodies in maternal serum and milk (poliovirus infections occur through the gut) do not protect adequately against infection for a sufficient length of time; hence, infections late in childhood are not attenuated and can result in severe, acute disease. Similar problems may be anticipated in the case of measles, mumps, and other infections, for which levels of maternal antibody are insufficient to attenuate late infection in children. The effectiveness and influence of many types of childhood vaccinations across more than one or two generations have not yet been established.[26-33] Goals of global vaccination and breast-feeding of infants are therefore relevant not only in the developing world but also in developed countries, and vaccines must be improved, many more vaccines must be developed, and vaccination schedules must be stringently followed.

MATERNAL IMMUNITY AND AUTOIMMUNE DISEASES

With the advent of the era of increased hygiene, we humans have entered a dramatic new environment. The characteristics of an infection differ depending on whether it occurs early in life or later, after maternal protection has disappeared. Moreover, maternal protection influences infections with typical pathogens as well as with agents that are not usually life-threatening, particularly gastrointestinal and respiratory viruses that are not cytopathic or only poorly cytopathic. If such an infection is not noticed clinically, then the immune response it evokes may well be regarded as an autoimmune disease (Fig. 2).

Let us assume that type 1 diabetes or cardiomyopathies are caused by coxsackievirus B, at least in some patients. Let us also postulate that levels of maternal antibodies are insufficient to protect the child against this virus.[34] Since coxsackievirus B infections are not usually lethal, the virus may spread from the gastrointestinal tract to other sites, including pancreatic islet cells or cardiac myocytes, depending on the degree of protection offered by the mother's neutralizing antibodies in plasma or milk (Fig. 2). Coxsackievirus B can be cytopathic to islet cells or indirectly cause their destruction in the course of an antiviral immune response. In any case, prolonged release of islet-cell or myocyte antigens into lymphoid tissues may induce autoimmune T-cell and autoantibody responses that eventually become self-perpetuating, particularly if lymph follicles form in the target organ.[35] Perhaps this kind of mechanism explains the increased incidence of juvenile diabetes, cardiomyopathies, and other autoimmune diseases in industrialized countries in the 20th century.

The host–parasite relations that evolved over thousands of years, when life expectancy was 30 years or less, may have changed too rapidly in the past 100 years. Perhaps the prolongation of life, coupled with the occurrence of many fewer infectious diseases during childhood, will, on balance, have disadvantages

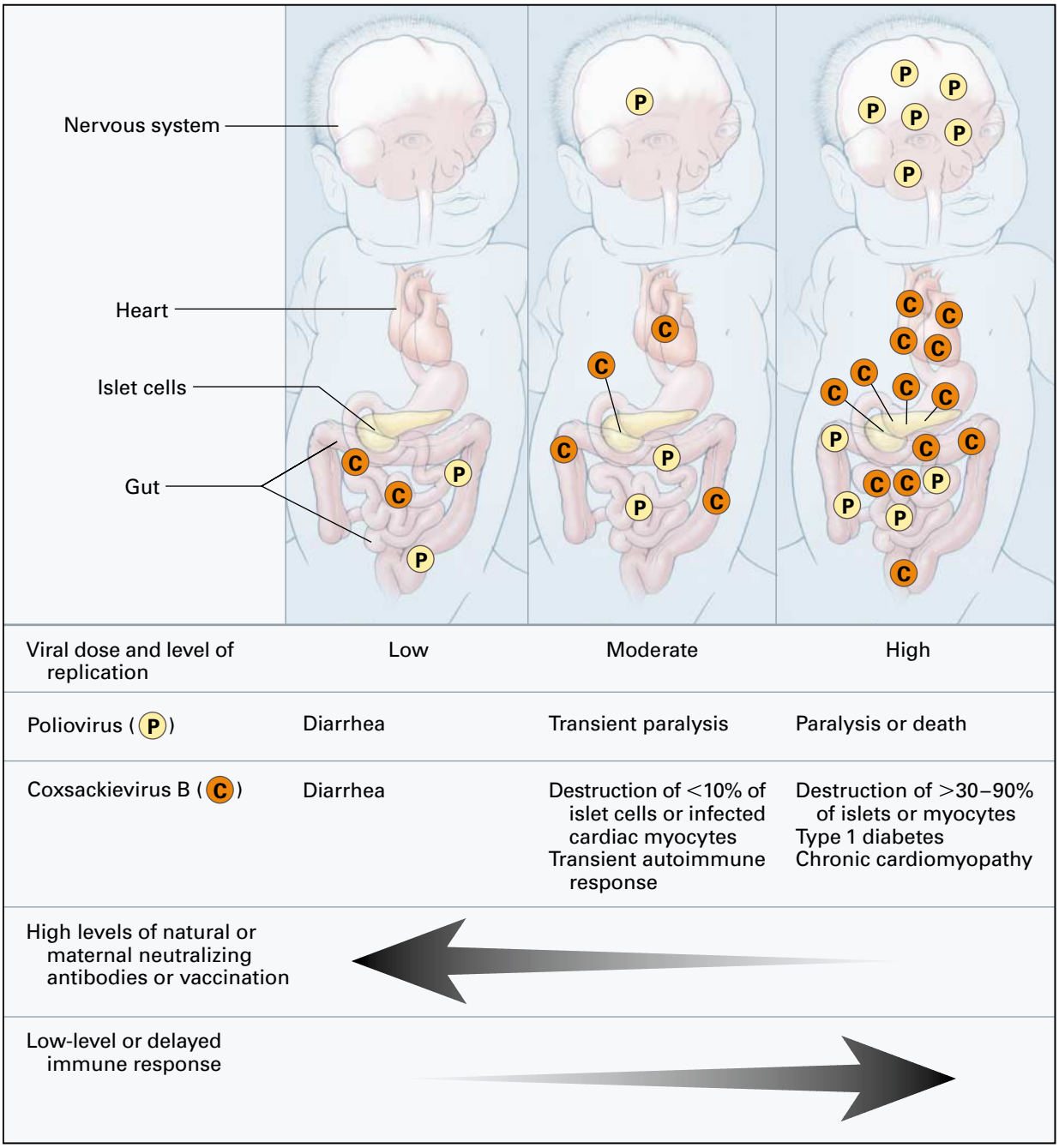

Figure 2. Influence of Viral Dose, Time of Infection, and Resistance Mechanisms of the Host on Infectious Disease.

The host in this example is an infant three to eight months old. The extent and duration of infection that leads to the destruction of host cells depend on various factors. The presence of effective maternal antibodies or immunity as a result of vaccination, activated macrophages, or natural killer cells will limit the damage. The presence of immune defects or immunosuppression will allow much more widespread and potentially fatal damage to occur, either directly by the agent (e.g., poliovirus) or indirectly by immunopathology or autoimmunity (e.g., coxsackievirus B).

that are revealed not only later in life but also in coming generations.

CONCLUSIONS

The protection against infection afforded by vaccination is one of the great successes of medicine. Vaccines have prevented more deaths than any other medical measure so far. Protective immunity is about survival within an evolutionary context. It is particularly important early in life, because the immune system is immature at birth. Successful vaccines induce optimal levels of neutralizing antibodies against acutely cytopathic agents. In contrast, long-lasting cell-mediated immunity is much more difficult to induce through vaccination: the required balance between attenuation and persistent stimulation of effector T cells by microbial antigens has not yet been achieved with vaccines. The aim should be to develop strategies that create a persistent low level of infection and of infectious antigens in order to maintain sufficient levels of activated T cells and IgG antibodies. This may not be easy to achieve, but the development of DNA-based vaccines may bring us closer to the goal.

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