

Evolutionary Process and the Ecology of Human Immune Function

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ABSTRACT Evolutionary principles inform central design features of human immune defenses and provide key insights into this complicated host defense system. This article explores the selection pressures and adaptive responses that have elaborated the immune system over the course of evolution and discusses their implications for understanding contemporary immune development and function. Special attention is given to the challenges posed by diverse, rapidly evolving pathogens and the mammalian response to these challenges. The process of lymphocyte diversity generation and subsequent clonal selection is quintessentially Darwinian: pathogens provide selection pressure that drives differential replication of host immune cell lines, resulting in changes in genetic frequencies within an individual's population of lymphocytes. The immune system also incorporates nongenetic transgenerational processes in the transfer of antibodies from mother to offspring through the placenta and breast milk. The consequences of these observations for human development, health, and the ecology of immune function are considered throughout the life cycle. Specifically, evolutionary processes provide insight into autoimmunity, thymic function, lymphocyte development, infectious disease risk, and lactation. While much work in evolutionary medicine focuses on the discordance between evolved biology and rapidly changing cultural environments, with respect to the immune system, evolutionary processes may be most revealing when applied within individuals. *Am. J. Hum. Biol.* 11:705–717, 1999. © 1999 Wiley-Liss, Inc.

Evolutionary processes are central design features of human immune defenses, and cast new light on the development and function of this complicated host defense system. Attempts have been made to elaborate the evolutionary origins of immunity (Edelman, 1987, 1994; Langman, 1989), but few have given explicit attention to the evolutionary principles that operate within the system itself. In the present article, this theme is explored and it is suggested that evolutionary processes may provide a useful organizing framework for understanding the ecology of human immune function.

Evolutionary medicine (Williams and Nesse, 1991) has contributed to our current understanding of the immune system and infectious disease. Anthropologists and evolutionary biologists have provided insights into the implications of the major histocompatibility complex for HIV transmission and

AIDS (Hoff and Peterson, 1990), the evolutionary significance of allergy (Profet, 1988; Armelagos and Barnes, in press), the adaptive functions of fever and nonspecific inflammatory processes (Kluger, 1986), and the adaptive behavioral responses to infectious disease and immune activity (Hart, 1990). This work complements a large body of literature focusing on the evolution of pathogens (Bull, 1994; Ewald, 1994; Levin and Bull, 1994) and the implications of host–pathogen dynamics (Anderson and May, 1991; Rowe, 1994; Mittler et al., 1996).

Nevertheless, the relevance and importance of evolutionary principles to the on-

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togeny of immune function remain relatively unexplored. The present analysis seeks to highlight and partially address this gap with a discussion of the evolutionary processes that shape the function of the immune system, not across generations, but within an individual's lifetime. The conceptual tools typically employed to analyze competition, adaptation, and phylogenetic change at the population level can be used to enrich our understanding of immune development and function. This article focuses on pathogen defense, rather than the equally important repair and maintenance functions of the immune system. First, the degree to which the immune system incorporates evolutionary processes into normal development and function is highlighted. The implications of these evolutionary processes are then considered; specifically, the potential for self-reactivity, the apparently anomalous developmental trajectory of lymphatic tissue, and the ecology of breastfeeding. The present analysis is viewed as suggestive for future research on, rather than as a definitive account of, the relationship of evolutionary principles to immune function.

THE PHYLOGENY OF IMMUNITY

The immune system is comprised of several interdependent subsystems. Nonspecific defenses such as mucus, cilia, enzymes in tears and saliva, phagocytosis, and acute phase proteins provide the body's first line of defense against infection. In contrast to this generalized protection, humoral-mediated and cell-mediated immune responses are activated by and directed against specific antigens. B lymphocytes and the antibodies they produce are definitive components of humoral-mediated immunity, and are primarily involved in the defense against extracellular pathogens such as bacteria and parasites. Cell-mediated immune responses employ several T cell subsets that protect against intracellular pathogens such as viruses and perform critical regulatory and activational functions.

What does an evolutionary perspective contribute to the understanding of this complex, multifaceted system? Few immunologists pose this question, although a small group of comparative immunologists study defense systems across phylogenetic lines—looking at nonmammalian species such as

insects, worms, and sharks—to investigate the evolutionary origins of mammalian complexity (Reinisch and Litman, 1989; Travis, 1993). The struggle between host and pathogen is recognized as omnipresent among life forms, and the diversity of host defense strategies is explored to help identify the events and trade-offs that led to the development of specific immunity, a defining attribute of vertebrate defense systems. Vertebrate defense systems possess a striking degree of homogeneity. From cartilaginous fish to mammals, all elements of the immune system are present in some form (Du Pasquier, 1992; Marchalonis and Schluter, 1994). All vertebrates will reject tissue grafted from nonisogeneic individuals of the same species, demonstrating the ability for self/non-self differentiation. Frogs, fish, and humans each have extensive, differentiated lymphatic tissues, display major histocompatibility complex class I and class II molecules on all cells, and have B cells that produce antibodies with a vast range of antigen-binding specificities (Du Pasquier, 1992).

This homogeneity has been a boon for experimental immunology, allowing it to successfully use rat and mouse models to illuminate the human immune system. The evolutionary conservatism of the vertebrate immune system is a testament to its plasticity, the elegance of its design, and its robustness in functioning in the world's diverse disease ecologies. Why is this the case? Why is the immune system so highly conserved, while other physiological systems are more specifically adapted to our mammalian ancestry or hominid roots? The answer lies largely in the design of a host defense system with specific ontogenetically mediated functional properties that themselves recapitulate evolutionary processes within the individual in which the system operates.

CLONAL SELECTION AND SOMATIC EVOLUTION

Consider the adaptive challenges facing the immune system. Table 1 compares the replication rates, absolute numbers, and frequency of mutation in pathogens and hosts, highlighting the disadvantages of large, long-lived mammalian hosts vis-a-vis pathogens. Viruses and bacteria multiply rapidly, with short intergenerational intervals on the order of minutes or hours

TABLE 1. Evolutionary potential of pathogens, human hosts, and lymphocytes

	Pathogen	Host	Lymphocyte
Intergeneration interval	Short	Long	Short
Number	High	Low	High
Mutations	Frequent	Infrequent	High diversity/somatic mutation

(Zinkernagel et al., 1985). The high number of infecting organisms thus generated also creates a greater opportunity for mutation. Mutation, along with genetic mechanisms such as plasmid transfer, amplify production of diversity and the potential for evolution of forms capable of evading existing host defenses. The human host, in contrast, is relatively long-lived, and produces few offspring at an intergeneration interval of 15 to 30 years. As such, the opportunity for production of diversity through mutation and subsequent evolution in response to pathogen selection pressure is relatively low. On a population level, the host can never match the pace of pathogen evolution.

Propitiously, the evolution of specific immunity has leveled the playing field. Like pathogens, T and B cell intergeneration times are short, on the order of 12 to 24 hours. Like pathogens, their numbers are high—approximately 10^{12} in humans (Roitt et al., 1993)—and activated B cells can produce more than 2,000 antibody molecules per second (Kuby, 1994). Like pathogens, mutations are frequent, and the tremendous range of diversity displayed by lymphocyte receptors helps counter the high rate of mutations in pathogens. B cells and their antibody receptors are estimated to display over 10^8 different antigen specificities, while T cell receptors have an even wider range, at 10^{15} different specific receptors (Kuby, 1994; Paul, 1993).

From an evolutionary perspective, pathogens clearly have a tremendous advantage relative to long-lived hosts such as humans. However, specific immunity, comprised of a large number of mobile cells with great proliferative potential and high diversification, provides a fighting chance. The process of specific immunity, considered below, reveals how evolution has designed a system that evolves itself, and suggests trade-offs involved with this type of ontogenetically mediated host defense system.

Until rather recently, the mechanism for generating antibody diversity to match the seemingly infinite diversity of potential antigens remained something of a mystery.

Antibodies are comprised of four polypeptide chains, two light and two heavy, both identical, linked by disulphide bonds, that combine to form a variable region with two antigen binding sites and a constant region on the opposite end that interacts with cells of the immune system (Paul, 1993; Kuby, 1994). The variable region of the antibody produced by each clonal line is unique, possessing a specific molecular configuration and attendant binding specificity, while the constant region binds to receptors that facilitate the destruction of the invading pathogen through phagocytosis or complement activation. Although the human body contains approximately 100,000 genes, the B cells in any individual can produce over 100 million distinct antibody proteins (Kuby, 1994). Obviously, antibody diversity cannot be explained by simple genetic inheritance, and immunologists have debated for years the merits of germ-line versus somatic-variation theories of antibody diversity.

Current understanding joins these theories. Antibody genes are inherited as diverse multiple copies of discrete gene segments that are randomly assorted somatically to compose a complete antibody gene only in the developing B lymphocyte (Tonegawa, 1983) (Fig. 1). Genes for heavy chains are built from three gene segments (variable [V], diversity [D], and joining [J]), and light chains, from two (V and J). Random selection among “minigene” sequences coding for immunoglobulin segments and assembly of the 3 or 2 segments, respectively, produces approximately 16,000 different heavy chain combinations, and 1,200 potential light chain combinations. These variants, once assembled into a final configuration of duplicate heavy and light chains, create 1.9×10^7 possible antigen binding sites (Kuby, 1994). Diversity is further enhanced by the imprecise joining of gene segments and random additions of up to 15 nucleotides at the joints of the VDJ coding sequence during gene assembly. The process of generating diversity in T cell receptors is comparable, involving the random

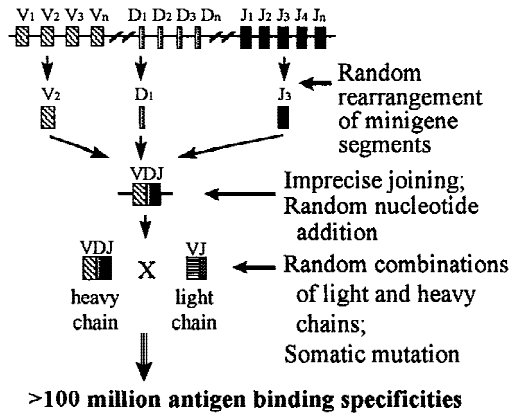


Fig. 1. Mechanisms of generation of antibody diversity.

rearrangement of minigene segments, imprecise joining, and random addition of up to six nucleotides at each joint. All lymphocytes within an individual share the same set of germ-line antigen receptor minigenes, but stochastic developmental processes in cell differentiation create exponential diversity in antigen binding abilities.

Lymphocytes reside primarily in lymphatic tissue, specifically, spleen and lymph nodes. Lymphatics drain virtually all parts of the body, and thus the fluid filtered through lymph nodes exposes resident lymphocytes to a representative sampling of incident pathogens and toxins. Furthermore, lymphocytes circulate regularly in blood and lymph. Approximately 1 to 2% of the total lymphocyte population recirculates each hour, enhancing the opportunity for lymphocytes to come in contact with the maximum number of pathogens (Roitt et al., 1993). The size of this population remains relatively stable, despite high rates of lymphocyte production by primary lymphoid organs, reflecting the limited lifespan of recirculating lymphocytes and suggesting a process of differential survival (Sprent, 1993a,b). Upon binding an antigen matching its receptor and receiving the appropriate co-stimulatory signal, the selected lymphocyte becomes activated and undergoes mitosis, passing on its genes to a generation of daughter cells sharing the same antigenic specificity (Fig. 2). These clones further replicate and differentiate into effector cells and memory cells. In this way, an antigen itself sets into play a process of somatic evo-

lution: it selects and activates the specific immune defenses the body enlists to eradicate it.

In the process of somatic mutation, the evolution of response specificity is even more finely tuned: receptor genes of B cells subsequently exposed to the same antigen are one million times more likely to mutate than other genes (Gearhart, 1993; Kuby, 1994). Individual nucleotides are randomly replaced, resulting in slight differences in antigen binding affinities from the parental generation. Random generation of diversity produces antibodies of higher and lower binding affinities, but the antigen itself selects those clones that bind the most specifically and tightly, driving the evolution of more effective antibodies in a process of "affinity maturation."

These processes follow quintessentially Darwinian principles. The prerequisites of evolution by natural selection—heritability, population variation, and differential reproductive fitness—are clearly met. Specific lymphocyte cell lines compete for access to antigens. Antigens bind only a fraction of the population, and only these cells replicate and have their unique receptor genes represented in the next generation. Changes in the gene frequency of the lymphocyte population ensue from the selection pressure provided by antigen exposure. A recent series of experiments that borrow models from population ecology have confirmed that resource competition and population diversity are critical determinants of

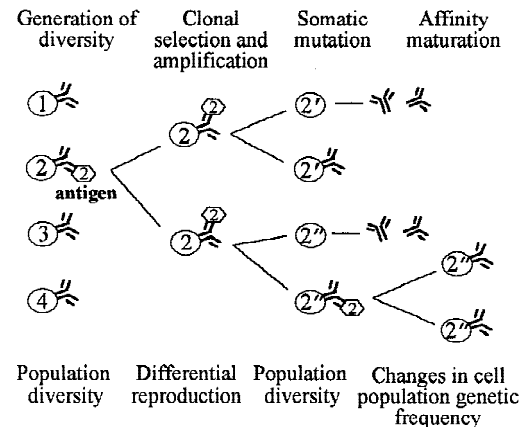


Fig. 2. Clonal selection and the somatic evolution of lymphocyte populations.

the composition of peripheral lymphocyte populations (McLean et al., 1997).

From the perspective of the individual lymphocyte, clonal selection, amplification, and fine tuning comprise bases for fitness maximization and adaptation to the internal molecular ecology of the organism itself. From the perspective of the individual organism, these mechanisms comprise a somatic process of adaptation to the external disease ecology. The development of the nervous system employs analogous processes in the proliferation of diversity and selective retention of axonal and dendritic connections (Changeux, 1985; Rakic, 1995), but these events do not result in heritable genetic modifications within nerve cells. Only the immune system embodies a truly Darwinian process of descent with modification over multiple generations of lymphocytes within individual organisms. The capacity to generate acquired specific immunity through ontogenetic processes is transmitted intergenerationally, while specific immunity itself is not.

SELF-REACTIVITY

What are the implications of a host defense system that recapitulates evolutionary processes? How does the body prevent individual lymphocyte cell lines from maximizing their own fitness at the expense of the fitness of the individual, as occurs with the uncontrolled cell growth of cancer? An obvious consequence of incorporating random processes into the generation of lymphocyte diversity is the possibility of self-reactivity. Indeed, one might expect self-antigens to drive the clonal selection of a population of self-destructive lymphocytes and antibodies, as is the case with several autoimmune diseases (Frank et al., 1995).

Selection events during the ontogeny of lymphocytes minimize such a possibility (Fig. 3). Lymphocyte progenitors are produced in bone marrow and migrate to the thymus, where maturing T cells undergo a process of positive and negative selection that ensures not only that they are competent to participate in antigen recognition mechanisms, but also that they can distinguish self from non-self. Only those T cells that can bind to major histocompatibility complex molecules, but do not react so strongly as to induce self-reactivity, are released from the thymus into circulation. It has been estimated that over 97% of matur-

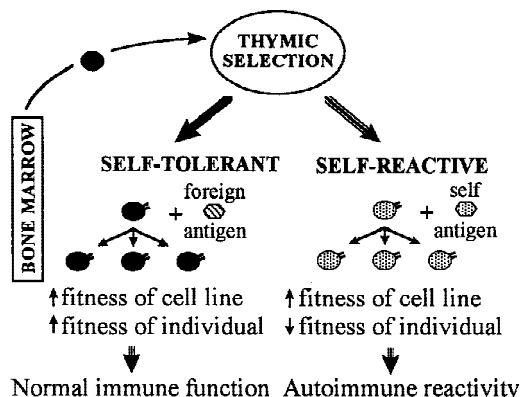


Fig. 3. Lymphocyte maturation in the thymus and the development of self-tolerance.

ing T cells are destroyed during this selection process (Sprent, 1993a). Positive and negative selection in the thymus, therefore, significantly reduces the risk of self-reactivity peripherally.

A host defense system based on the random generation of diversity and clonal selection capitalizes on the capacity of cells to act in their own selfish interest. The realities of cancer and autoimmune disease indicate that the fitness interests of cells may not always coincide with those of the individual, and further remind us that the application of evolutionary processes within the body entails considerable risk. Maturation events in the thymus minimize this possibility: clonal deletion ensures that the surviving cell lines will replicate only in response to exogenous antigens, not self antigens. In this way, the fitness interests of T cells are wed to those of the individual during T cell ontogeny, because a cell line must bind exogenous antigen in order to reproduce, and is thereby constrained to promote the fitness of the individual as well as that of the specific cell line. Buss (1987) argues that this is a central theme in evolution, such that the development of multicellular organisms depends on successful resolution of potential conflicts between selection at the level of the individual and the level of the cell. From this evolutionary perspective, thymic selection can be conceptualized as a mechanism by which convergence of interests is imposed on T lymphocytes during their ontogeny.

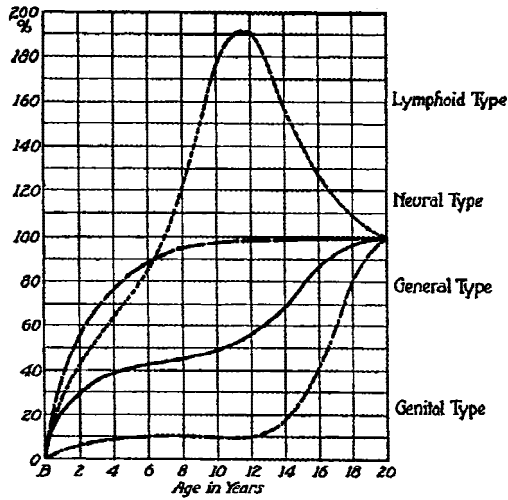


Fig. 4. Divergent developmental trajectories of lymphatic, nervous, and reproductive tissues. Reproduced from Scammon (1930), with permission from the University of Minnesota Press.

THE DEVELOPMENT OF IMMUNE FUNCTION

In addition to self-reactivity, evolutionary processes cast new light on our understanding of the development of immune function. The anomalous developmental trajectory of the immune system has attracted considerable attention for decades (Fig. 4), for it appears to contradict the general view of development as a cumulative incremental process, the gradual attainment of an adult state. While most organ systems have yet to reach their functional peak in childhood and adolescence, lymphoid tissues appear to attain twice the mass of adults by late childhood or puberty. They regress in size through the remainder of the second decade, declining to adult mass at around 20 years (Scammon, 1930). Given their importance throughout life, this apparently characteristic lifespan feature of degeneration and loss of function in immunologic structures has puzzled developmentalists and immunologists.

The pattern of regression of lymphatic tissues illustrated in Figure 4 is driven by development of the thymus, a primary lymphoid structure and processing center for T lymphocytes. Immature lymphocytes migrate to the thymus from stem cells in bone marrow, and undergo a process of maturation and differentiation within thymic cortical

and medullary structures prior to their release into circulation. The thymus appears to be the first body organ to exhibit the progressive functional loss characteristic of aging (Muller-Hermelink et al., 1982; Steinmann et al., 1985). The decline in thymic size with age has been universally reported by postmortem studies since the turn of the century (reviewed in Cardarelli, 1989).

A recent, methodologically sound study reveals the following pattern of development (Fig. 5): functional tissue within the thymus—represented here by cortical volume—is at its peak in infancy, and begins decreasing continuously from the first year of life to about age 40, at which time the rate of regression slows considerably. Previous, less carefully operationalized studies have reported that thymic size peaks at around age 15, and fueled unconfirmed speculation that thymic regression may be related to endocrine changes associated with puberty (Muller-Hermelink et al., 1982; Tosi et al., 1982). However, these studies do not differentiate functional immunological tissue from nonlymphatic connective and adipose tissues, and may confound the regression of thymic lymphatic tissue with the growth patterns of nonlymphatic tissues. Precise measurement of the tissues most relevant to the development of specific immunity reveals that the atrophy of functional thymic tissue is a continuous process that commences in the first year of life.

This pattern of early thymic regression is puzzling, especially since the thymus has

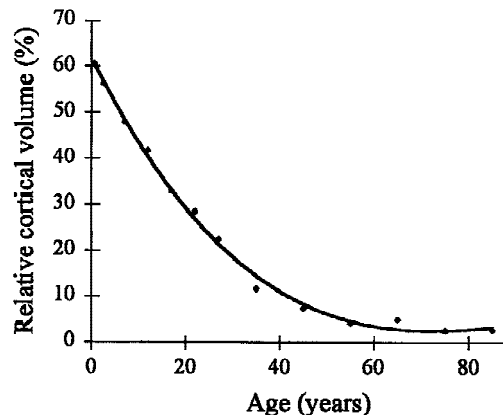


Fig. 5. Regression of thymic tissue with age. Data from Steinmann et al. (1985).

been labeled the “master gland” of the immune system (Cotman et al., 1987). It has supported conceptualization of the thymus as a clock for immunological aging and human senescence (Kay, 1979; Fabris, 1992), and has attracted substantial clinical attention as a possible avenue for intervention. Indeed, considerable research has investigated the possibility of stopping, or even reversing, this pattern of development. Articles with titles such as “Neuroendocrine-thymus interactions: Perspectives for intervention in aging” (Fabris et al., 1988), or “Thymic involution with aging: Prospects for correction” (Hadden et al., 1993), clearly construct thymic regression as a pathological phenomenon.

A Darwinian perspective, by contrast, makes this developmental pattern intelligible. As exemplified earlier in the discussion of clonal selection and somatic evolution, the immune system is about more than tissues; it is about information. The development of specific immune defenses requires engagement by the individual with his or her environment to gain the antigenic experience that drives clonal selection and evolution of specific lymphocyte cell lines. Antigen exposure thus represents access to information about non-self that becomes incorporated through evolved specificity and memory cell formation. This is a time-dependent learning process. From such a perspective, it is not the size of the thymus or other immune tissues that is relevant. Rather, it is the information that they package in adapting the individual to the local disease ecology.

The apparently anomalous trajectory of thymic development is actually a necessary component of this learning process. The thymus releases a diverse population of lymphocytes into circulation where antigens will drive the survival and evolution of specific cell lines. The degree of peripheralization expands with age as the thymus regresses, creating a relatively self-sufficient T-cell population that recirculates through blood, lymph, lymph nodes, and spleen (Sprent, 1993b), and thus distributes information in the form of differentiated cells, across strategic sites throughout the body. This rise in peripheral distribution and regulation may be modeled as a negative function of the age-related regression in thymus parenchyma (Fig. 6). The fact that neonatal thymectomy leads to fatal wasting disease at-

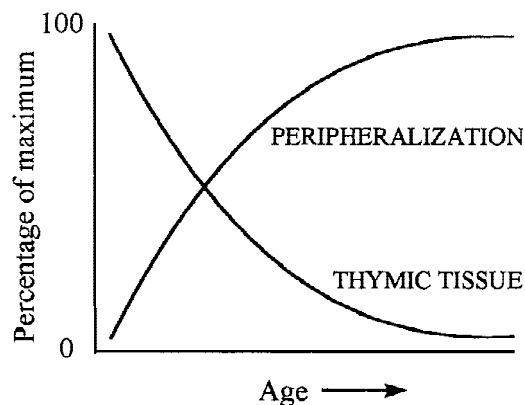


Fig. 6. Complementary developmental patterns of thymus lymphatic tissue and immune peripheralization.

tests to its essential role in proper immune function, but the degree of immunodepression following thymectomy is inversely proportional to age, indicating that the centrality of the thymus is age-dependent (Cardarelli, 1989).

The properties of peripheral T lymphocytes support this model. Like the thymus itself, peripherally circulating T lymphocytes have been shown to carry receptors for glucocorticoids, sex steroids, growth hormone, and prolactin (Shkhinek, 1985; Schuur and Verheul, 1990; Gala, 1991). Further, activated lymphocytes actually produce measurable quantities of substances similar, if not identical, to ACTH, TSH, GH, prolactin, hCG, gonadotropin, and beta-endorphin (Cotman et al., 1987; Gala, 1991; Fabris, 1992). Thus, peripheral lymphocytes have been referred to as a “minihypophysis” (Fabris, 1992) for their ability to integrate information and manipulate the paracrine environment. In a sense, the thymus becomes redundant, and its regression is part of the developmental design of a distributive system characterized by peripheral and locally mediated regulation. Consequently, the thymus is probably not a “master gland” of the immune system, and its apparently anomalous pattern of early regression represents not senescence or pathology, but a necessary developmental trajectory.

It is also possible that this trajectory is not universal. Current understandings of thymic development are based on anatomical studies conducted exclusively within

Western populations residing in environments with relatively low pathogen loads. However, the thymus receives and integrates information from all the major neuroendocrine axes, and in turn provides feedback that modulates neuroendocrine and thymic activity (Kelley et al., 1987; Fabris, 1989; Goya, 1992). Physical growth, sexual maturation, metabolism, nutrition, and stress are but a few of the factors that affect the thymus, and therefore potentially shape its development. From the perspective of life history theory, the thymus seems a logical place to expect observable impacts from trade-offs among functions serving the demands of growth, reproduction, and maintenance. If the thymus is sensitive to the context within which it develops, then one might expect different rates of regression and peripheralization in different ecological situations, particularly in high versus low pathogen environments. However, informed a priori predictions based on an adaptationist framework are currently problematic, as these types of ecologically and evolutionarily informed questions have yet to be asked with respect to the development of immune function.

An information-based conceptualization of immune development is consistent with age-related susceptibility to infectious disease. Given their immunological naivete, infants and children are most vulnerable because each pathogen is a novel pathogen, resulting in a slower, less intense specific immune response to each novel exposure. Around the world, children under the age of 5 suffer from infectious disease 8 to 24 times more frequently than any other age group (World Bank, 1993). Such suffering is a high price to pay, and one might expect that survival advantages would be conferred upon individuals who can accelerate the learning process and thereby minimize the period of immunological naivete and vulnerability. In adaptationist terms, therefore, three hypotheses can be proposed concerning expectable design features in the ontogeny of specific immunity: 1) The generation of lymphocyte diversity should be elevated in infancy to provide maximum opportunity for clonal selection and somatic evolution of T and B cells; 2) lymphocyte proliferative potential in response to antigen stimulation should also be maximized at this point in time; and 3) the rate of memory cell formation should be maximized early in life as

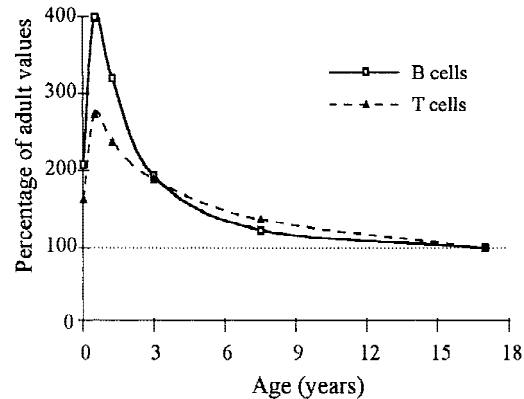


Fig. 7. T and B lymphocyte numbers, by age. Data from Hicks et al. (1983b).

lymphocytes evolve in response to antigen selection pressure.

These hypotheses find support in the clinical literature. Several laboratories have documented the following consistent age-related pattern of lymphocyte development: T and B cell numbers peak during the first 6 months of life, then decline steadily with age until adulthood (Fig. 7) (Hicks et al., 1983b; Denny et al., 1990; Hannel et al., 1992). Correspondingly, T and B cell proliferation in response to *in vitro* mitogen stimulation is maximal postnatally, and declines in childhood and adolescence (Hicks et al., 1983a). The pattern of memory cell formation is also as predicted: based on the high prevalence of CD45RA expression on CD4+ cells, infant T cells are almost exclusively naive. As the infant and child gain antigenic experience, the proportion of memory T cells (roughly approximated by the prevalence of CDw29 expression) expands, while the proportion of naive cells shrinks (Fig. 8) (Pirenne et al., 1992). As hypothesized, the immune system apparently has been designed to maximize lymphocyte diversity and responsiveness early in life, thereby accelerating the somatic evolution process that minimizes the high costs of immunological inexperience and adapts each individual to the local disease ecology.

THE IMMUNE SYSTEM AND INHERITANCE OF ACQUIRED CHARACTERISTICS: PASSIVE IMMUNITY

Evolution has provided another partial solution to the problem of early immunologi-

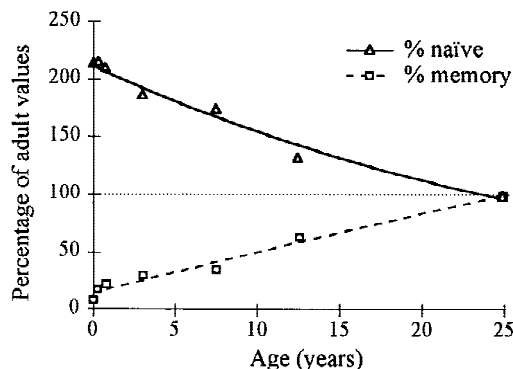


Fig. 8. Relative proportions of naive and memory T cells, by age, as approximated by the proportion of CD45RA and CDw29 expressing CD4+ cells. Data from Pirenne et al. (1992).

cal naivete via materno-fetal transfer of passive immunity. Although fetal immunoglobulin production remains limited during the course of gestation, immunoglobulin G (IgG) levels rise significantly as a result of active placental transfer. Trophoblast surface receptors specific for the constant region of IgG molecules transport IgG exclusively into fetal circulation, leading to fetal levels as high as or higher than maternal levels at term (Saxon and Stiehm, 1989; Billington, 1992). With a half-life of approximately 21 days, maternal IgG provides significant passive immunity to neonates for 6 months or longer, covering a period when the infant's developing defenses are seriously compromised (Saxon and Stiehm, 1989; Hoshower, 1994). Maternal antigen experience, accumulated over a lifetime of infection and/or vaccination, defines the specific antibodies a mother transports to the fetus, providing protection against such pathogens as rubella, tetanus, diphtheria, polio, measles, mumps, streptococcus, hepatitis B, meningococci, and others, depending on the local disease ecology (Wilson, 1990; Lewis and Wilson, 1992). Obviously, individual and cultural management of maternal antigen exposure has direct implications for infant health and development.

Similar considerations make breastfeeding a critical immunological issue. At parturition, the breast replaces the placenta as the neonate's primary source of nutrition and passive immunity. Breast milk contains high concentrations of nonspecific defense factors such as lactoferrin, lysozyme, and

complement proteins that inhibit bacterial growth in the neonatal gastrointestinal and respiratory tracts (Weisz-Carrington, 1987; Ogra and Fishaut, 1990). Specific defense is afforded primarily by IgA, the predominant immunoglobulin in human breast milk, coating the infant's gastrointestinal tract and binding soluble antigens, thus providing the first line of specific defense against pathogen invasion. The secretory protein attached to IgA in breast milk protects the immunoglobulin from proteolytic action of digestive enzymes, allowing it to work along the length of the gastrointestinal tract to neutralize microbial enzymes, toxins, and viruses, and inhibit pathogen colonization and penetration of the mucosal membrane (James, 1993; Gregory, 1994).

Consistent with the specificity afforded by IgG transport prenatally, sIgA molecules in breast milk reflect maternal antigenic experience. Lymphocytes stimulated by antigens in the maternal gastrointestinal tract enter circulation and migrate to mucosal and secretory tissues, including the mammary glands, where they differentiate into plasma cells and produce specific antibodies (Hanson and Brandtzaeg, 1989; Keller, 1992). Secretory antibodies against a range of viral, bacterial, and microbial enteropathogens have been detected in human breast milk and shown to reduce the morbidity and mortality of infection (Pickering and Ruiz-Palacios, 1986; Hoshower, 1994). For example, in rural India mothers infected with *Giardia* produce significantly higher levels of anti-*Giardia* sIgA than noninfected mothers. As a consequence of this passive immunity, infants of infected mothers are more than two times *less* likely to become infected with *Giardia* than infants of noninfected mothers (Nayak et al., 1987). Assuming that maternal infection increases the infant's risk of pathogen exposure, the protective effect of sIgA is doubly impressive.

Passive immunity conferred by two routes, placental and lactational, affords not only protection, but also the possibility of buffered exposure. While maternal antibodies directly recognize pathogens and bolster infant immune defenses, the infant's immune system is also being exposed to the antigens that stimulate its own immune response and, hence, the acquisition of specific immunity. This is a different evolutionary process at work in the immune system, a

mechanism for inheritance of acquired characteristics mediated by physiology and behavior. Through transplacental IgG and sIgA in breast milk, the mother shares her immunologic experience with her infant, and provides a degree of specific immunity not quickly attainable by the inexperienced infant immune defenses. Natural selection has designed a system that incorporates Lamarckian processes to a limited degree, by allowing transient inheritance of acquired maternal characteristics via transgenerational transfer to the infant. Operative only during a brief but high-risk period, and hence of high fitness value, maternally acquired protection specific to the local disease ecology buffers the infant while it builds up its own repertoire of defenses through a Darwinian process of somatic evolution. This is not a complete solution, as evidenced by high rates of infant mortality due to infectious disease, but its effectiveness is clearly demonstrated by the reduced morbidity and mortality risks of infants who do receive sustained passive immunity through breast-feeding.

Appreciation of these evolutionary processes suggests testable hypotheses regarding breast-feeding behavior, infectious disease risk, and infant health. Earlier, it was emphasized that the human immune system is not unique, but represents a pan-mammalian, perhaps pan-vertebrate system. However, with respect to passive immunity and infancy, the human species may be unique in its ability to defeat this elegantly dynamic system. From the perspective of evolutionary ecology, one would predict that pathogen exposure is a primary, but not exclusive, determinant of the duration of exclusive breast-feeding due to the protective effects of breast milk (Fig. 9) (McDade and Worthman, 1998). Therefore, a positive correlation between pathogen risk and the duration of exclusive breast-feeding might be hypothesized. There are upper limits to the duration of breast-feeding, including energetic demands on the mother and of the growing infant, constraints on maternal activity, and costs to future reproductive potential. Hence, one might expect mothers to optimize the duration of exclusive breast-feeding with respect to the local disease ecology and the costs of breast-feeding.

However, the local cultural environment constructs the ecology of breast-feeding, cre-

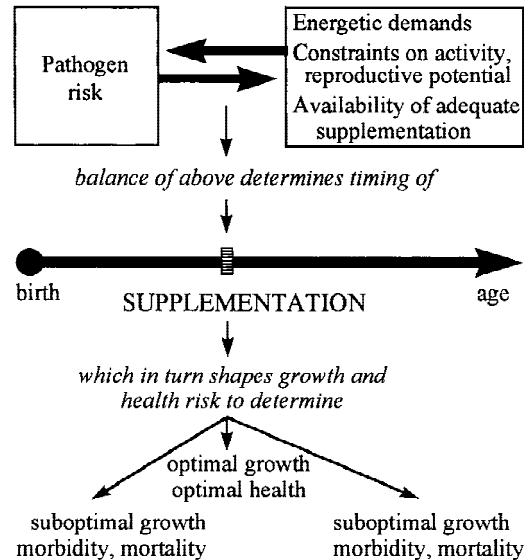


Fig. 9. Evolutionary ecological model of breast-feeding and the timing of supplementation.

ating physical, social, and ideological supports for and constraints on this activity. Maternal workloads, the manipulation of fertility, availability of supplementary foods, gender relations, social networks, beliefs about breast milk and its alternatives, and emic understandings of child development interact to titrate the duration of exclusive breast-feeding. Breast-feeding is a culturally contingent behavior. Evolution has designed a system of passive immunity that affords protection for infants during their period of greatest vulnerability, but certain cultural environments may deny or limit this protection.

Therefore, high rates of infant mortality and morbidity might be predicted in cultural and ecological contexts characterized by a poor "fit" between the duration of exclusive breast-feeding and pathogen exposure. Pathogen burden is rarely reported as a culturally acknowledged and salient variable in the breast-feeding equation, but pathogen risk is biologically salient in its effect on infant health. When supports for breast-feeding are weak and constraints are strong, the duration of exclusive breast-feeding is short. However, in relatively low pathogen environments such as the U.S., infant morbidity is still low. The passive immunity from breast milk is not critical since pathogen exposure is low. If the duration of

breast-feeding is short in high pathogen environments, the infant is left unprotected by passive immunity, and a large margin of morbidity and mortality is likely. In these situations, failure to breast-feed during the first 5 months increases the risk of diarrhea by a factor of nearly 5, and raises the risk of mortality by a factor of 25 compared to exclusive breast-feeders, regardless of levels of hygiene and socioeconomic status (Feachem and Koblinsky, 1984). This is not an adaptive situation and emphasizes the importance of passive immunity to infant health.

The inexperience of the infant immune system presents a challenge to mothers and the cultures within which they live. Evolution has met this challenge in designing a system that incorporates mechanisms for intergenerational transfer of immunocompetence to provide critical protection during the highest period of infant vulnerability. The health consequences of defeating this system are contingent on the local disease ecology, while additional ecological, social, and ideological factors provide support for and constrain breast-feeding in different cultural contexts. Hence, both the probability and costs of impaired passive immunity are mediated through culturally determined behaviors and ecologies.

CONCLUSION

Within human biology there is growing interest in immunology and the factors that shape immune function and infectious disease risk (e.g., Hoff and Peterson, 1990; Hoff et al., 1991; Shell-Duncan 1993, 1997; Flinn et al., 1996; McDade et al., 1996, 1998; Ulijaszek 1997). A framework for investigating the ecology of human immune function has been presented that highlights evolutionary processes as central design features of this complicated host defense strategy. Short intergeneration intervals, large numbers, and high mutation frequencies give pathogens a fundamental evolutionary advantage with respect to long-lived mammalian hosts. Given the high stakes for individual survival, it is perhaps not surprising that evolution has responded in kind to this adaptive challenge, creating a facultative, experience-based system that, on the level of ontogeny, evolves itself. Stochastic processes create tremendous diversity in lymphocyte genotypes and receptor phenotypes, allowing pathogens to provide the selection pressure that drives the evolution of specific

cell lines, thereby adapting the individual to the local disease ecology. With an appreciation of these evolutionary dynamics, one can predict that the developmental trajectories of immune tissues are not necessarily "anomalous" or "pathological," and that culture can interfere in potentially destructive ways when immune defenses are not fully developed.

Evolutionary medicine has focused heavily on human physiological systems with reference to the environments in which they originally evolved, the environments of evolutionary adaptedness (EEA) as represented by a foraging subsistence strategy. It has emphasized discordances between evolved human biology and rapidly changing cultural environments as the bases for a wide range of contemporary health issues. By contrast, with respect to the immune system, it is suggested that evolutionary principles may be most illuminating when applied within individuals in contemporary environments rather than across generations. Evolution has designed an elegant host defense system in its own image, and consideration of these processes provides insight into the developmental ecology of immune function and susceptibility to disease.

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