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Life History Theory and the Immune System: Steps Toward a Human Ecological Immunology

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ABSTRACT Within anthropology and human biology, there is growing interest in immune function and its importance to the ecology of human health and development. Biomedical research currently dominates our understanding of immunology, and this paper seeks to highlight the potential contribution of a population-based, ecological approach to the study of human immune function. Concepts from life-history theory are applied to highlight the major challenges and demands that are likely to shape immune function in a range of ecological contexts. Immune function is a major component of maintenance effort, and since resources are limited, trade-offs are expected between investment in maintenance and other critical life-history functions involving growth and reproduction. An adaptationist, life-history perspective helps make sense of the unusual developmental trajectory of immune tissues, and emphasizes that this complex system is designed to incorporate information from the surrounding ecology to guide its development. As a result, there is substantial population variation in immune development and function that is not considered by current biomedical approaches. In an attempt to construct a framework for understanding this variation, immune development is considered in relation to the competing life-history demands that define gestation, infancy, childhood, adolescence, and adulthood. Each life stage poses a unique set of adaptive challenges, and a series of hypotheses is proposed regarding their implications for immune development and function. Research in human ecological immunology is in its earliest stages, but this is a promising area of exploration, and one in which anthropology is well-positioned to make important contributions. Yrbk Phys Anthropol 46:100–125, 2003.

Research on human immune function has proliferated in the past 25 years, leading to fundamental insights into basic physiology, as well as strategies for the prevention and treatment of a wide range of diseases. The complexity of the immune system is daunting, and current biomedical research elaborates this complexity by focusing almost exclusively on cellular- and molecular-level processes. The majority of this research uses animal models, with human research participants drawn primarily from clinical settings. Complementary population-based research in international health has observed consistent, bidirectional associations between undernutrition and infectious morbidity, sparking interest in immunocompetence as a potentially important mediator (Chandra, 1988; Gershwin et al., 2000; Hoffman-Goetz, 1986; Pelletier et al., 1995; Suskind and Tontisirin, 2001).

The significance of these contributions should not be overlooked, but something is missing. Human physiological systems are products of natural selection, designed to develop and function in whole organisms that are integral components of surrounding social and physical environments (Oyama, 1985; Williams and Nesse, 1991). The immune system is no exception, and considerable insight may be gained from an ecological, adaptationist perspective. Correspondingly, anthropologists have become increasingly interested in field studies of immunity and their significance to the study of adaptation and human ecology (Barnes et al., 1999; Campbell et al., 2001; Flinn, 1999; Hoff, 1999; Hurtado et al., 1997, 2003; Lubach et al., 1995; McDade et al., 2000b, 2001a; McDade and Worthman, 1999; Shell-Duncan, 1993; Shell-Duncan and Wood, 1997; Ulijaszek, 1998; Williams-Blangero et al., 1999).

There are a number of compelling reasons to pursue anthropological research in immunology. High global rates of infectious disease (particularly in many populations of anthropological interest) immediately come to mind as a primary selective force, and as a major public health burden (Barrett et al., 1998; Inhorn and Brown, 1990; Sattenspiel, 2000). Although immune processes provide protection

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against infectious disease and some forms of cancer, they also contribute to allergy, asthma, and autoimmune disease, as well as the pathophysiology of cardiovascular disease (Bjorksten, 1994; Fergusson et al., 1997; Libby et al., 2002; Ross, 1999). Populations differ in their risk for these diseases, and an anthropological perspective on immunity may shed some light as to why.

In addition, anthropologists have played a pivotal role in demonstrating the relevance of cultural and ecological contexts to variation in developmental and health outcomes. Often these outcomes serve as proxies for underlying physiological processes, and a number of scholars have called for increased attention to the specific mechanisms that link contexts to outcomes (Dressler, 1995; Goodman and Leatherman, 1998; Panter-Brick, 1998; Panter-Brick and Worthman, 1999; Worthman, 1993). The immune system represents such a mechanism. It also presents an opportunity to further our understanding of development, plasticity, and adaptation: central concepts for biological anthropology.

The primary objective of this paper is to draw attention to the potential contribution of a population-based, ecological, adaptationist approach to the study of human immune function. The importance of immunogenetic perspectives is recognized (e.g., Tishkoff and Williams, 2002; Weiss, 1993; Williams-Blangero et al., 1999), but is beyond the scope of this review. Rather, concepts from life-history theory are employed as an organizing framework to highlight the major challenges and demands that are likely to shape immune function in a range of ecological contexts. The approach is also unambiguously developmental, with an explicit discussion of the immunological issues and life-history trade-offs confronting humans at major life stages from gestation through senescence.

LIFE HISTORY THEORY AND THE IMPORTANCE OF MAINTENANCE

As the body's key defense against microbial invasion and uncontrolled cellular replication (i.e., cancer), the immune system is of pivotal importance to organismal survival, and thus evolution. This is a costly defense system (see below), both in terms of the resources it consumes to perform its functions, and in the consequences it has for well-being when immune processes are misdirected. Other critical physiological and developmental systems also require resources, and natural selection should favor the optimal allocation of resources across these systems in a way that maximizes fitness. Life-history theory is the branch of evolutionary thought concerned with variation in these allocation strategies, and this section presents a brief overview of central principles and concepts.

Life-history theory provides a comparative evolutionary framework for understanding reproductive and developmental strategies, both within and across species (Charnov, 1993; Stearns, 1992). It is assumed that resources are limited, and that energy is allocated to three primary life functions: growth, reproduction, and maintenance. Excess resources can also be invested in storage for future use. According to the "allocation rule," these functions are mutually exclusive, with resources invested in one no longer available for use in another (Hill and Hurtado, 1996). In a world with unlimited resources, the optimal life-history strategy would be to start reproducing at birth, and to continue reproducing at a high rate for an infinite lifespan (Partridge and Harvey, 1988). Obviously, physiological and ecological constraints make such a strategy impossible, and instead, the organism attempts to allocate its limited resources in the context of these constraints in order to maximize reproductive value.

A consideration of trade-offs is therefore central to the life-history approach. These trade-offs can be encoded at different levels: genetically, as the result of natural selection; developmentally, as the phenotype responds adaptively to early environments within a limited range of plasticity; or more immediately, with short-term responsiveness to shifting environmental demands (Lasker, 1969). The lines separating these levels of adaptation are not hard and fast, and all three are likely to operate with respect to setting up the trade-offs involved in human immune function. With respect to the application of life-history theory to comparisons across human populations, it is generally assumed that individuals inherit the ability to respond adaptively to a range of ecological pressures within a certain range of plasticity, and that developmental processes mediate population differences in life-history strategies (Hill and Hurtado, 1996; Stearns and Koella, 1986).

Life-history analyses focus on age-specific schedules of mortality and fecundity and related traits, including lifespan, age at first reproduction, body size, and growth rate, among others. Currently, age-specific rates of mortality are given special attention as major drivers of life-history strategies (Charnov, 1993; Promislow and Harvey, 1990). Although primarily applied as a comparative tool to explain life-history variation across species, recent applications to humans underscore the utility of life-history theory for exploring phenotypic variation in aspects of human growth, development, and reproduction (e.g., Bribiescas, 2001; Chisholm, 1993; Hawkes et al., 1997; Hill and Hurtado, 1996; Kaplan et al., 2000; Worthman, 1993).

Controlling for individual differences in energy availability, or efficiency in energy utilization, is a fundamental methodological challenge for within-species applications of life-history theory (Hill and Hurtado, 1996). For example, since resources are limited and can only be used for one function, the allocation rule predicts that an increased investment in growth will come at a cost to investment in maintenance (and vice versa), assuming no change in investment in reproduction. Therefore, at the pop-

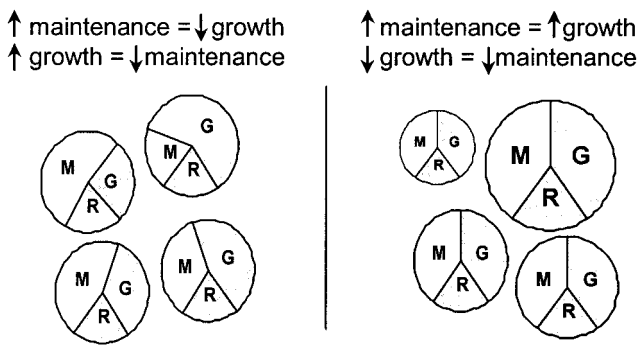

Fig. 1. Problem of phenotypic correlation. An individual's life-history strategy at a given point in time is indicated by relative proportions of energy allocated to maintenance (M), growth (G), and reproduction (R). Size of circle indicates total amount of available resources. **Left:** All individuals have access to same resources, and reproductive effort is held constant, resulting in negative correlations between M and G. **Right:** Individuals differ in level of available resources, resulting in positive correlation among M, G, and R.

ulation level, one would expect to see a negative correlation between investment in growth and maintenance (Fig. 1). However, individuals are not identical in their access to resources, or in the efficiency with which they use these resources. Therefore, individual variation in resources leads to *positive* correlations among growth, maintenance, and reproduction at the population level, thereby obscuring anticipated trade-offs. This is the problem of phenotypic correlation.

For example, in a population of children, we might expect to see a trade-off between investment in growth and immune function: children who invest more energy in fighting infection will have less energy available for growth, and simple statistical analyses should reveal a negative association between measures of immune function and growth in our population. However, resources are not likely to be equal in this population, and some children may have better access to food than others. Therefore, when we correlate our measures of immunity and growth in this population, we may find a positive association, since children with good food access will grow better and have better immune function than children with poor food access. While the expected life-history trade-off still operates at the individual level (energy applied to immunity cannot be used to fuel growth for all the children), we may not see the trade-off at the level of the population.

This issue emphasizes the need to control for phenotypic correlations in life-history analyses of human populations (or any within-species analyses). In addition to resource access, with respect to immune function, individual differences in genetically encoded major histocompatibility complex antigens may increase susceptibility to certain diseases (Weiss, 1993). A consideration of individual differences in phenotypic quality (both in terms of measurement and statistical analysis) is critical for a meaningful evaluation of life-history trade-offs (Hill and Hurtado, 1996). However, phenotypic correlation is likely to be less of an issue in low-resource settings, where life-history trade-offs are more severe and variation in resource access is reduced.

Currently, maintenance is a relatively underexplored area of life-history investigation (for exceptions, see Charnov, 2001; Hawkes, 2003; Kirkwood, 1981; Kirkwood and Rose, 1991). In theory, it is recognized that energetic investment in the preservation and repair of the soma is critical to survival, but in practice, the majority of analyses focus on events linked to reproduction or growth. No doubt this is due in large part to the obvious fitness implications of these events, and the relative ease with which they can be observed and measured. However, these functions are moot without adequate attention to survival, and recent work has emphasized the significance of maintenance costs and the mechanisms that mediate trade-offs with growth and reproduction (Kirkwood and Rose, 1991; Sheldon and Verhulst, 1996).

The immune system represents a major physiological system with primary responsibility for survival, and as such is an essential component of maintenance effort. The emerging field of "ecological immunology" recognizes the cost of this effort and its significance to life-history variation (Sheldon and Verhulst, 1996). For example, measures of immunity in birds suggest that certain ornaments are honest signals of parasite resistance and mate quality, and may therefore be important cues for sexual selection (Blount et al., 2003; Moller et al., 1999; Zuk and Johnsen, 2000; Zuk et al., 1995). While much of this research has focused on the potentially immunosuppressive role of androgens, other investigators have emphasized the more general point that immune activity is energetically expensive, and that trade-offs with growth and reproductive effort are inevitable (Buttgereit et al., 2000; Lochmiller and Deerenberg, 2000; Read and Allen, 2000). In addition, a recent series of comparative analyses across primate species has shown that investment in immune tissues is related to promiscuity and a slow life history (Nunn, 2002; Nunn et al., 2000). In contrast to biomedical or epidemiological approaches, the life-history perspective emphasizes that immunity is costly, and trade-offs are inevitable. Ecology is a major factor in defining these costs, leading Lochmiller and Deerenberg (2000, p. 94) to claim that "life history is as much a reflection of an organism's pathogenic environment as it is any other facet that may be driving complex evolutionary changes within a species."

HUMAN IMMUNE FUNCTION: A BRIEF OVERVIEW

An in-depth overview of human immune function is beyond the scope of this review, and a number of excellent introductory and advanced texts are currently available (Goldsby et al., 2000; Paul, 1998; Roitt et al., 2001). The immune system is notori-

TABLE 1. Major components of immune function, measures used in their assessment, and immunological significance of these measures

Component	Measures	Significance
Lymphoid organs		
Thymus, spleen, bone marrow, lymph nodes	Organ weight/histology; patterns of cell circulation; production of thymic peptides, cytokines	Developmental patterns; hematopoiesis; lymphocyte maturation/function
Nonspecific defenses		
Complement, acute-phase response, phagocytosis	Concentrations of complement, acute-phase, and other antimicrobial proteins; phagocytic cell counts, chemotaxis, lytic ability	Generalized antipathogen defenses; inflammatory response; antigen processing/presentation
Cell-mediated immunity		
T lymphocytes: CD4+ helper (Th1 vs. Th2); CD8+ suppressor/cytotoxic; naive vs. memory	Cell counts, proportions; proliferation in response to antigen stimulation; cytokine production; target-cell lysis; delayed-type hypersensitivity	Defense against intracellular pathogens; tumor surveillance; graft rejection; immunoregulation; atopy
Humoral-mediated immunity		
B lymphocytes; immunoglobulins (IgA, IgM, IgG, IgE, IgD)	Cell counts, proportions; proliferation and antibody production in response to antigen stimulation; immunoglobulin concentrations	Defense against extracellular pathogens and toxins; history of pathogen exposure

ously complex, and is in fact comprised of multiple interdependent subsystems that provide a relatively seamless network of antipathogen defenses (Table 1). Innate or nonspecific defenses (generalized defenses that provide resistance without recognizing specific pathogens) include anatomical barriers such as skin and mucosal membranes, antimicrobial soluble proteins (e.g., complement, lysozyme), and phagocytic cells that scavenge extracellular macromolecules. The inflammatory response (involving acute-phase proteins and the recruitment of phagocytic cells to the site of injury or infection) is a key nonspecific process that provides a first line of defense against pathogens while specific immune defenses come online.

T and B lymphocytes are the central mediators of specific immunity, which unlike aspects of innate immunity, recognize and target specific antigens (any substance that elicits a specific immune response) with exquisite precision, to the point that a single amino-acid substitution on the epitope (the site of recognition on the antigen) may prevent binding by a given T or B lymphocyte receptor. Other hallmarks of specific immunity include an enormous range of diversity in antigen-binding receptors, the ability to recognize and respond more quickly to antigens upon second exposure (memory), and the ability to discriminate self from nonself.

Subsets of T lymphocytes (identified by the expression of membrane glycoproteins, e.g., CD4 or CD8) perform a range of regulatory, activational, and effector functions that are critical to eliminating intracellular pathogens and managing specific immune processes. B lymphocytes and the antibodies they produce are definitive components of humoral-mediated immunity, and are primarily involved in protection against extracellular pathogens. Antibodies belong to one of five immunoglobulin isotypes (IgG, IgA, IgM, IgE, and IgD), each of which possesses unique structural and functional properties. IgG is the predominant immunoglobulin in serum, while IgA (in its secretory form, sIgA) is abundant in external secretions, including mucus, saliva, breastmilk, and tears. IgM accounts for 5–10% of the total serum immunoglobulin concentration, and is produced when a new antigen is first encountered. IgE is a potent mediator of immediate hypersensitivity reactions, and is involved in antihelminthic defenses as well as symptoms associated with allergy and asthma. IgD is present in serum in very low concentrations, and its function is not well-understood.

Many aspects of immune regulation are self-limiting: antigens are responsible for activating a range of nonspecific and specific defenses, and once the antigen is cleared, these processes downregulate. In this sense, the immune system is characterized by a high degree of compartmentalized, autocrine, and paracrine activity. However, the interconnections among the immune, nervous, and endocrine systems are substantial, with innervation of lymphoid organs and receptors for all major endocrine axes on lymphocytes as well as lymphoid tissues. Indeed, these reciprocal connections are so pervasive, and so critical to immune development and function, that immune function is conceptualized as part of a seamless neuro-immune-endocrine network (Ader et al., 2001; Besedovsky and del Rey, 1991; Cotman et al., 1987; Imura et al., 1991; Millington and Buckingham, 1992). These connections provide a number of potential physiological mechanisms through which life-history trade-offs involving immunity may be mediated.

The complexity of immune function, the absence of simple feedback loops, a high degree of compartmentalized activity, and peripheral (rather than central) regulatory processes all pose serious challenges to any attempt to define "immunocompetence." Add to this the relative invasiveness of current methods of immunological assessment (requiring large volumes of blood, immediate access to laboratory facilities, and time-consuming protocols for sample processing and analysis), and it is

clear why field-based research in immunology has been more limited than studies of other physiologic and health-related outcomes.

Fortunately, the methodological options for population-level, field-based research are currently expanding. A number of immune factors can be measured in saliva that probe into mucosal defenses protecting the gastrointestinal tract, a major entry point for pathogens (Mestecky, 1993; Nishanian et al., 1998). However, mucosal immunity is a relatively distinct subsystem of defense, and salivary measures provide an indication of local rather than systemic immune activity. Immune factors in blood provide more information, and a number of methods have been developed for small quantities of whole blood collected from a simple finger stick. Blood collected on filter paper can be used to analyze C-reactive protein (acute-phase protein) and antibodies against Epstein-Barr virus (indirect measure of cell-mediated immunity) (McDade et al., 2000a,b), and whole blood smears on slides can be used to quantify white blood cell fractions and lymphocyte subsets (Lisse et al., 1990, 1997b). In addition, lymphocyte proliferation protocols have been developed that require less than a drop of whole blood, and recent advances in immunoassay technology support the simultaneous quantification of multiple cytokines (Bloemena et al., 1989; Carson and Vignali, 1999; Elsasser-Beile et al., 1991). These latter methods will require validation prior to application in the field, but they raise the possibility of using standard clinic-based immune measures in population settings. In addition, delayed-type hypersensitivity (involving the intradermal application of test antigens to the forearm) has been used with success in a number of sites as a semiquantitative measure of cell-mediated immunocompetence (Black et al., 1989; Shell-Duncan and Wood, 1997). Consideration of multiple immune measures in relation to one another, as well as in relation to outcome assessments of morbidity and growth, will facilitate the interpretation of these measures, and offer insights into the definition of immunocompetence.

Nutrition and the energetics of immune function

Nutrition is an important and intensively investigated determinant of immune function. Immune defenses (particularly antigen-specific defenses) are energetically expensive: fever requires a 13% increase in metabolic rate for each degree Celsius of increase in body temperature (Elia, 1992); protein synthesis kicks into high gear as part of the acute-phase response, and to facilitate lymphocyte proliferation, antibody production, and cytokine release (Beisel, 1984; Mata, 1992); and the thymus (central to T-lymphocyte development and function) is a relatively large organ early in life that contains over 10^{11} maturing T cells, 20–25% of which are created each day as a product of cell division. It is estimated that over 95% of maturing T cells are destroyed in the thymus as a result of rigorous selection procedures, making this a very expensive (and wasteful) developmental process (George and Ritter, 1996).

The energetic costs of these processes are substantial, particularly for those at the margins of nutritional adequacy. Research with humans is lacking, but a number of studies have documented the direct energetic costs of immune function in bumblebees, birds, and mice (Demas et al., 1997; Martin et al., 2002; Moret and Schmid-Hempel, 2000; Ots et al., 2001). In one bird study, immune activation was associated with a 29% increase in resting metabolic rate (Martin et al., 2002). A rough estimate of the energetic costs for children can be calculated based on the fact that malnourished children synthesize approximately 3.5 g of protein per kilogram of body weight each day, but in the presence of infection, the rate of protein turnover approaches 6 g per kilogram per day (Waterlow, 1984). With an energetic cost of 7.5 kcal per gram of synthesized protein (Butte et al., 1989), the upregulation of protein production costs the malnourished child 19 kcal per kilogram per day. For a 15-kg child, these costs translate into a debt of 37.5 g of protein and 285 kcal for each day of infection.

In addition to the direct metabolic costs, pathogens and associated immune responses may disrupt normal processes of nutrient digestion and absorption (Mata, 1992; Solomons, 1993). Recent research indicates that diarrhea may cause damage to the intestinal mucosa that impairs nutrient absorption well beyond the point of recovery, potentially leading to a pernicious cycle of infection and malnutrition (Lunn, 2000; Lunn et al., 1991). In addition, a number of studies have documented reductions in food intake during infection, despite increased energetic demands (Brown et al., 1990; Martorell et al., 1980; Mata et al., 1977). Although the importance of infection as a cause of undernutrition and poor child growth has been questioned (Black, 1991; Briend, 1990), the direct and indirect energetic costs of infection have been associated with deficits in weight gain of up to 30 g per day ill if access to energy- and protein-rich foods is not sufficient to fuel catch-up growth (Rowland et al., 1988; Scrimshaw, 1981; Walker et al., 1992; Zumrawi et al., 1987).

Likely as a result of their high energetic costs, cell-mediated immune processes are acutely sensitive to macronutritient deficiencies (Chandra, 1988; Gershwin et al., 2000). Dramatic declines in thymic weight, reduced T-lymphocyte numbers and proliferative responsiveness, suppressed delayed-type hypersensitivity, and poor vaccine response are all associated with undernutrition. In contrast, humoral-mediated immune processes remain relatively buffered from the effects of even severe malnutrition. B-lymphocyte numbers remain in the normal range, and immunoglobulin levels are frequently elevated in malnourished individuals, possibly reflecting increased parasite and gastrointestinal antigen exposure (Gershwin et al., 1985; Lunn, 1991). Stud-

ies of infants suffering from kwashiorkor or marasmus report severely depressed synthesis of serum albumin, but normal or slightly elevated immunoglobulin production, indicating preferential allocation of protein resources (Cohen and Hansen, 1962; El-Gholmy et al., 1970). Micronutrient deficiencies are also contributors to impaired immunity, although they rarely surface in the absence of macronutrient deficiency (Gershwin et al., 2000).

The physiological mechanisms mediating energetic trade-offs between immunity and other functions are far from clear, although recent research has drawn attention to leptin as a likely candidate. Leptin is similar in structure to interleukin-2 (a major cytokine involved in the regulation of immunity), and is produced primarily by adipocytes (Prentice et al., 2002). Its role as an endocrine indicator of energy status has been intensively probed, and a number of studies with animal models have indicated that leptin is critical to normal cell-mediated immune processes (Howard et al., 1999; Lord, 2002). A dramatic illustration of the importance of leptin comes from a series of studies with mice, which showed expected levels of cell-mediated immune suppression following starvation. However, injection of leptin during starvation provided full protection from the immunosuppressive effects of undernutrition: normal thymic architecture was preserved, and delayed-type hypersensitivity responses were comparable to nonstarved mice (Lord et al., 1998). Corroborative evidence in humans comes from the Philippines, where we found a positive association between leptin and thymopoietin (a measure of thymic activity) in 14–15-year-old girls (McDade and Kuzawa, in press). A positive association between leptin and thymic hormone production makes sense from an energetic perspective, and suggests a potentially important role for leptin in regulating central aspects of cell-mediated immune activity.

In sum, the ecology of nutrition is a critical determinant of human immune function. In particular, nutritional resources are likely to play a central role in setting allocations to maintenance effort, and in defining the intensity of life-history trade-offs.

DEVELOPMENT OF HUMAN IMMUNE FUNCTION

Figure 2 describes the developmental trajectory of major aspects of human immune function. The dramatically elevated numbers of T and B lymphocytes in infancy and early childhood immediately stand out, as does the increased proliferative potential of T and B lymphocytes in response to in vitro stimulation at this age. Thymic cortical volume is also highest in infancy, while remaining aspects of immunity demonstrate a more familiar developmental trajectory of incremental increase with age. It is commonly reported that the thymus peaks in adolescence and regresses following puberty (Muller-Hermelink et al., 1982; Scammon, 1930; Tosi et al., 1982), but careful anatomical analysis shows a steady decline in functionally significant cortical tissue beginning in infancy, with infiltration of nonlymphatic connective and adipose tissue keeping overall thymic volume relatively constant (George and Ritter, 1996; Steinmann et al., 1985). The anomalous developmental trajectory of central components of the immune system (lymphatic tissues in particular) has attracted considerable attention for decades (Scammon, 1930), although few teleological explanations have been offered. Rather, developmental perspectives within clinical immunology tend to focus on the attainment of specific functional capacities and their links to specific infectious agents and vulnerability to disease, particularly in infancy (e.g., Lewis and Wilson, 1995; Quie, 1990).

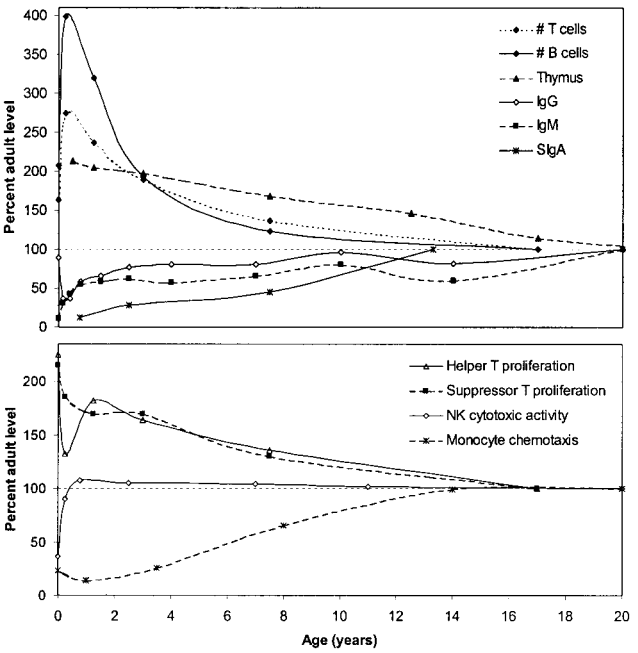

Fig. 2. Age-related changes in enumerative (**top**) and functional (**bottom**) measures of human immune function. All data are cross-sectional, and are from following sources: Hicks et al., 1983a,b; Klein et al., 1977; Pirenne et al., 1992; Steinmann et al., 1985; Stiehm and Fudenberg, 1966.

An adaptationist, life-history approach may provide some insights into the reasons underlying this developmental trajectory (McDade and Worthman, 1999). First, consider the obvious fact that infectious agents have a fundamental advantage with respect to their long-lived mammalian hosts: viruses, bacteria, and parasites reproduce themselves on the order of minutes, hours, or days, and produce large numbers of offspring that increase opportunities for mutation. In addition, genetic mechanisms such as plasmid transfer (sections of DNA that are transmitted horizontally, between individual microbes, or even across microbial strains) further amplify the production of diversity and the potential evasion of host defenses through the evolution of resistant forms. In contrast, the human host is relatively long-lived, and produces relatively few offspring at an

intergenerational interval of at least 15 years. Opportunities for the production of diversity and subsequent selection are therefore low, and as a result, on a population level, human hosts can never match the pace of pathogen evolution.

Natural selection arrived at an elegant solution to this challenge in favoring a system of pathogen defense that embodies evolutionary processes as central ontogenetic features. T and B lymphocytes (the defining cells of specific immunity) have properties that are analogous to pathogens in several important ways. First, the intergeneration interval is short, on the order of 12–24 hr. Second, the number of lymphocytes in an individual is high (approximately 10^{12} in humans), and activated B lymphocytes can produce over 2,000 antibodies per second (Paul, 1998). Third, antigen-binding receptors on lymphocytes display a tremendous range of diversity. Even though the human genome contains less than 30,000 genes, random rearrangement of minigene segments, imprecise joining of nucleotide sequences, random combinations of heavy and light peptide chains, and somatic mutation during cell replication can produce well over 100 million different antigen-binding specificities on B lymphocytes (Goldsby et al., 2000; Paul, 1998). The generation of large numbers of random variants increases the likelihood that any one will bind, or "recognize," a nonself antigen.

Once a diverse repertoire of T and B lymphocytes has been established, the development of antigen-specific immunity is a relatively straightforward Darwinian process (termed clonal selection) in which: 1) antigens bind to and activate specific lymphocytes with matching receptors, 2) selected lymphocytes undergo mitosis and pass on their genes to subsequent generations of daughter cells that share the same antigenic specificity, and 3) these lymphocytes orchestrate the process of antigen removal, and differentiate into long-lived memory cells (McClean et al., 1997; Paul, 1998; Roitt et al., 2001; Tonegawa, 1983). As with pathogens (or any organism, for that matter), population variation, heritability across generations, and differential reproductive success (the defining attributes of natural selection) are the primary forces that drive change in lymphocyte populations within an individual's lifetime.

In a sense, evolution has designed a system that itself evolves as part of its development. Pathogens clearly have a tremendous evolutionary advantage with respect to long-lived human hosts, but specific immunity (directed by a large number of mobile cells with great proliferative potential and high receptor diversity) meets this challenge head on. From the perspective of the lymphocyte, antigen-binding and subsequent activation/replication represent a selection process that leads to fitness maximization and adaptation to the internal molecular ecology of the organism. From the perspective of the individual sheltering these lymphocytes, this is a somatic evolutionary process that shapes the resident lymphocyte population, and adapts the individual to the external disease ecology.

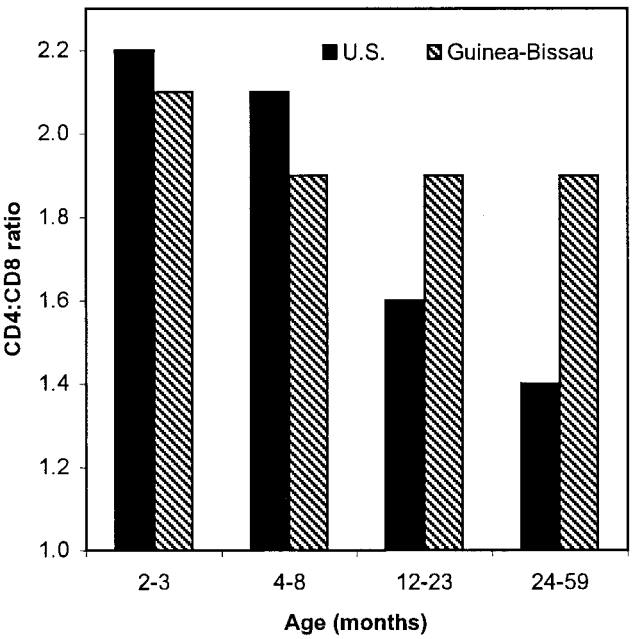

Fig. 3. Median ratio of CD4+ to CD8+ T lymphocytes with age in Gambia and United States. Data from Lisse et al. (1997).

An important implication of this design is that the development of immunity is context-dependent. Antigen exposure drives the ontogeny of specific immune defenses, and the intensity and diversity of this exposure will shape the trajectory of immune development and function. As such, one might expect substantial variation in a system that appears to be designed to develop in response to the surrounding ecology. Although research addressing this question is scant, a number of immune parameters were shown to vary significantly across context.

For example, a recent attempt to establish age-specific reference values for healthy children in West Africa reported a profile of lymphocyte development that differed substantially from norms derived in Western populations (Fig. 3). In the US, the ratio of CD4+ (helper) to CD8+ (cytotoxic/suppressor) T lymphocytes drops significantly in infancy and early childhood (Denny et al., 1992). In contrast, the CD4+:CD8+ ratio levels off at around 6 months of age in Guinea-Bissau, primarily due to a relatively higher number of CD8+ cytotoxic/suppressor lymphocytes (Lisse et al., 1997a). Children in this sample were healthy at time of blood collection, and anthropometric indicators of nutritional status were not associated with lymphocyte parameters. In addition, the overall number of lymphocytes, but not the total number of white blood cells (including lymphocytes as well as neutrophils, monocytes, eosinophils, and basophils), was elevated in Guinea-Bissau relative to the US, further hinting at a divergent developmental trajectory in this environment. A

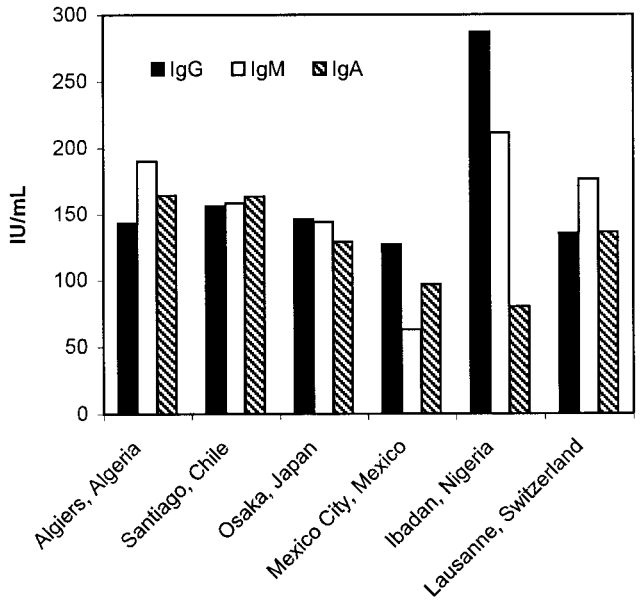

Fig. 4. Variation in concentrations of IgG, IgM, and IgA in healthy adult males from six populations (Rowe, 1972).

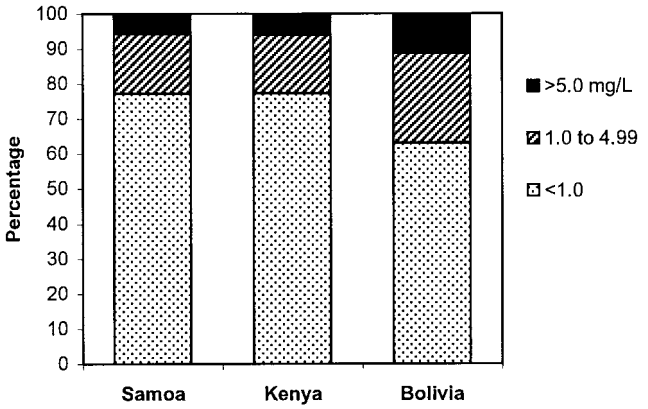

Fig. 5. Distribution of CRP concentrations (mg/L) measured in whole blood spots from 5–10-year-olds in Samoa (N = 363), northern Kenya (N = 298), and lowland Bolivia (N = 265). All samples were assayed with same ELISA protocol for maximum comparability.

similar pattern of elevated CD8+ cytotoxic/suppressor T lymphocytes in adolescence and young adulthood was documented in the highlands of Papua New Guinea (Witt and Alpers, 1991). Again, the authors noted that this pattern is difficult to explain in clinical terms, particularly since all participants in the study were healthy at the time of blood sampling, and mortality risk is lowest in the Eastern Highlands between ages 10–15 years.

Similar population variation in immunoglobulin concentration has also been documented. Children in the Netherlands demonstrate an age-specific pattern of immunoglobulin concentration that is similar to that reported in Figure 2, but with a significant sex difference such that girls show higher levels of IgM after age 4, and higher IgG after age 7 (Stoop et al., 1969). Age-matched Indian children in Surinam evaluated by the same research group produced 1.5–3 times as much IgA, IgG, and IgM at all ages (Zegers et al., 1973). Girls were characterized by developmental acceleration, attaining adult levels of all immunoglobulin classes by age 5, while boys continued to increase IgM and IgA production past age 10 prior to reaching adult levels. Along the same lines, a large study of Chinese children in Hong Kong reported a biphasic, rather than continuous, pattern of immunoglobulin development (Lau et al., 1992).

Enormous variation in adult immunoglobulin production was also reported in a survey of healthy young males (Fig. 4). Mean population values for IgG, IgA, and IgM ranged from 116–287, 80–164, and 63–211 IU/ml, respectively (Rowe, 1972). Nigerian men produced the highest IgG and IgM concentrations, but ranked among the lowest in IgA. In contrast, Swiss men had high IgM and IgA, but below-average IgG. While population genetic differences may account for some of this variation, research within a relatively genetically homogenous population in Nigeria reported significant differences in IgM, IgG, and IgA in urban and rural residents that cannot be explained by genetics, or by nutritional deficiency (Mohammed et al., 1973). Rather, these findings suggest a significant degree of responsiveness to distinct local disease ecologies.

In addition to specific immunity, there is substantial population variation in parameters of nonspecific immune processes. For example, C-reactive protein (CRP) is a central component of the acute-phase response, a nonspecific, systemic response to infection or injury that provides the body's first physiological line of defense against pathogens (Ballou and Kushner, 1992; Baumann and Gauldie, 1994; Fleck, 1989). CRP has important effector functions in activating phagocytes and complement, and in binding to bacteria, fungi, and parasites. It has been used as a measure of severity of infection or inflammatory activity, and has been associated with detrimental child-growth outcomes (Filteau et al., 1995).

The distribution of CRP concentration in 5–10-year-olds from three distinct populations is presented in Figure 5. In Samoa, 17.1% of children have moderately elevated levels of CRP, and 5.8% show substantial elevation (McDade et al., 2000b). Among Rendille pastoralists from the Marsabit district of northern Kenya, a similar profile of moderate (16.7%) and substantial (6.0%) elevation is present (McDade and Shell-Duncan, 2001). In contrast, CRP is substantially elevated for 11.3% of Tsimane children in lowland Bolivia, with moderate elevations in an additional 25.7% (McDade et al., 2003). From a public health perspective, elevated CRP among Tsimane children indicates a highly pathogenic environment. From a life-history perspective, elevated CRP represents a higher level of investment in nonspecific, antipathogenic defenses. It is not clear, however, whether CRP is increased solely in response to pathogen exposure, or whether immune

development has been biased in favor of generalized acute-phase processes in this environment, possibly at the expense of investment in other immune processes.

Current understandings of human immune development and function are based on data derived from industrialized, epidemiologically and nutritionally privileged populations. The full range of variation is currently not known, but there is enough evidence to presume that the trajectory of immune development presented in Figure 2 is not a universal one. In addition, a number of studies indicate important seasonal influence on immune parameters and disease risk (Boctor et al., 1989; Moore et al., 1997; Nelson and Demas, 1996; Shadrin et al., 1977; Shell-Duncan, 1995). The context-dependent nature of immune development makes such variation predictable (indeed expectable) and suggests a process of facultative adaptation through which various aspects of immunity may develop in response to the local ecology. Below, life-history theory is proposed as a framework for this developmental and ecological perspective on human immune function, and as a tool for generating hypotheses to guide future population-based research in a range of population settings.

LIFE-HISTORY TRADE-OFFS AND THE DEVELOPMENTAL ECOLOGY OF HUMAN IMMUNITY

Figure 6 presents the development of human immunity in relation to key selection pressures and competing life-history demands. Risk of death from infectious disease is presented as a major selection pressure with respect to the development of immunity, and as an indicator of the immune system's ability to provide protection against ubiquitous pathogen exposure. Although the resolution of these data is low (i.e., deaths are reported in large age blocks: less than 1 year, 1–4 years, 5–14 years, and 15–24 years), they provide a general indicator of mortality risk during major developmental periods. The populations represented in Figure 6 vary widely in their overall burden of infectious disease, but the age-related mortality trends are consistent within each population, suggesting that the concentration of infectious mortality early in life is a global phenomenon.

Height velocity is presented as a measure of age-specific energetic investment in growth. For the sake of simplicity, male and female data are averaged, even though the pubertal growth spurt typically occurs 1.5–2 years earlier in females than in males. The pattern of increase in body weight is roughly parallel to increases in height. Investment in growth effort is maximal early in life, with a prolonged period of relatively slow and steady growth in childhood, and an acceleration of height gain punctuating adolescence (Bogin, 1999; Tanner, 1990). It is recognized that there is substantial individual- and population-level variation in growth

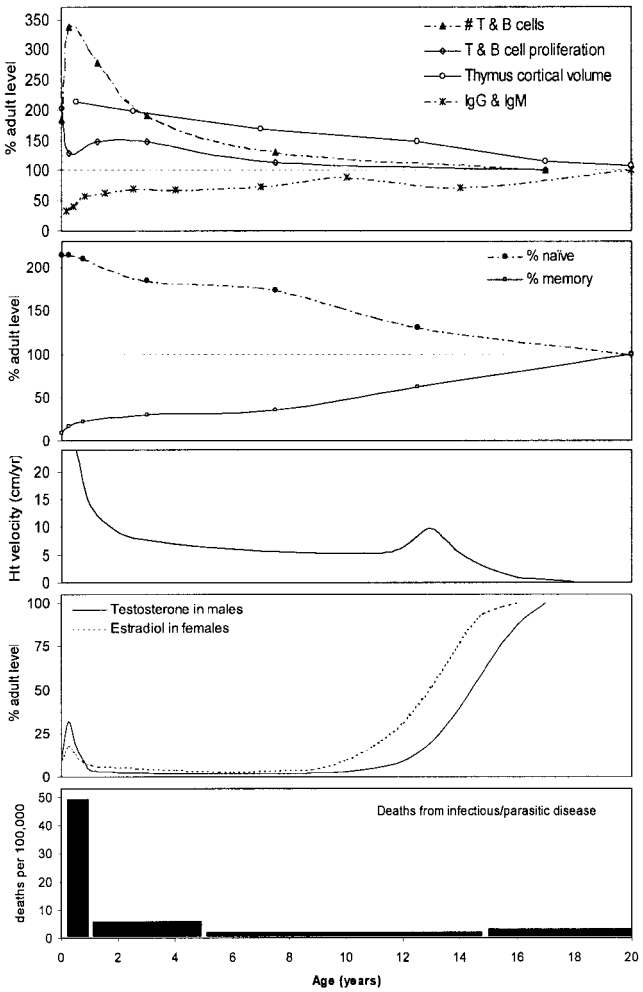

Fig. 6. Development of human immunity and competing life-history demands from birth to adulthood. Data are from following sources: mortality data compiled from WHO Mortality Database (February 25, 2003 release), using information from Argentina, Australia, Chile, Czech Republic, Hungary, Japan, Mexico, Ukraine, and USA; height velocity data derived from Tanner (1990); hormonal data modified from Worthman (1993). Immune data were compiled from same sources as in Figure 2.

that may substantially shift the pattern presented here (Eveleth and Tanner, 1990).

Production of gonadal steroids (testosterone in males, estradiol in females) is presented as a gross marker of investment in reproductive effort with age. Gonadal steroids are upregulated by hypothalamic-pituitary activity, and are primarily responsible for the physiological and morphological events that lead to the attainment of adult reproductive capacity (Bogin, 1999; Tanner, 1990). The hypothalamic-pituitary-gonadal (HPG) axis undergoes a burst of activity in the first 6–12 months of life, and then becomes quiescent through childhood until initiating activity associated with puberty. As with growth, there is substantial variation across individuals and populations in the actual timing and sequence of events associated with reproductive maturation (Worthman, 1987, 1999).

Below is a discussion of the immunological processes and life-history events that operate during fetal development, infancy, childhood, adolescence, and adulthood. While each life stage could be the subject of its own review, the emphasis here is on identifying key issues and generating hypotheses that can serve as a guide for future research.

Fetal development

Immune organs and cells begin to develop early in gestation: immature B lymphocytes are present in peripheral blood and in bone marrow by 12 weeks, and approach adult levels by 15–18 weeks; T lymphocytes appear in a differentiated thymus at 7–9 weeks, enter circulation after 12–14 weeks, and reach adult levels by 20–25 weeks; and complement proteins and monocytes are identifiable after 7 weeks (Blackburn and Loper, 1992; Wilson, 1990). The fetal immune system is capable of antigen recognition at 12 weeks, although specific immune reactivity remains depressed through gestation (Klein and Remington, 1990). Growth in overall body length and weight occurs primarily in the second and third trimester, following the completion of organ differentiation in the first trimester (Bogin, 1999). Given the relative sterility of the fetal environment in utero, pathogen exposure is minimized and the fetus can devote all available resources to growth and development in preparation for the transition to postnatal life.

Immunologically, the primary objectives of the embryo and fetus are twofold: first, avoid rejection by the mother and maintain a steady supply of nutrients; and second, develop antipathogen defenses in anticipation of life post-utero. Pregnancy represents an immunological dilemma in that the mother and offspring are not genetically identical, and the embryo/fetus runs the risk of being rejected as a foreign "allograft" by the mother's immune system (Blackburn and Loper, 1992). Indeed, mothers will reject tissue grafts from their own children, even though these same children were nurtured in utero for 9 months (Lederman, 1984). Despite its foreign antigenicity, the fetus escapes rejection through the joint efforts of the fetus and mother. Separate maternal and fetal circulatory systems minimize antigenic exposure, while masking substances and blocking antibodies may reduce fetal antigenicity. Specific aspects of maternal immune activity are also downregulated during pregnancy, further contributing to tolerance of the fetus at the expense of enhanced susceptibility to maternal infection (Blackburn and Loper, 1992; Thellin and Heinen, 2003; Weetman, 1999).

Parturition represents an abrupt delivery from a relatively sterile prenatal environment to one dense with microbes. Passive immunity (through the active transfer of maternal IgG across the placenta and into fetal circulation) provides a measure of protection that cannot be matched by the infant's own naive defenses (Billington, 1992; Wilson, 1990). The timing of transfer is critical: most IgG is delivered during the final trimester, and premature infants are relatively deprived of this passive immunity (Chandra, 1975b, 1991). With a half-life of approximately 21 days, maternal IgG provides passive immunity to neonates for 6 months or longer (Hoshower, 1994).

In addition, maternal antigenic experience (recorded over a lifetime of infection or vaccination) defines the specific antibodies the mother transports to her fetus. For example, in rural Thailand, where over 20% of adults are infected with *Giardia lamblia* and 80% show immunological evidence of previous infection, neonatal levels of *Giardia*-specific IgG antibodies are almost twice those present in American neonates from Denver where maternal exposure is infrequent and episodic (Janoff et al., 1990). Obviously, the individual and cultural determinants of maternal antigen exposure are important factors in shaping passive immunity.

Issue 1. Invest in the development of immune defenses. With respect to the prenatal development of immune tissues, one might hypothesize that undernutrition will be associated with reduced investment in immune function. Two lines of reasoning lead to this hypothesis. First, the rate of thymic development is rapid in the last trimester (Wilson, 1990), and insults during this critical period may have more serious consequences than those experienced later in life. Second, it has been suggested that disproportionate fetal growth following undernutrition (indicated by a relatively normal head circumference despite a smaller body size) may represent a biased investment in brain growth at a cost to organs in the trunk such as the thymus, with long-term implications for immune function (Godfrey et al., 1994). Extending this logic, long-term allocation decisions (in the form of relative levels of investment in different organ systems) may be made prenatally at least in part on the assumption that the quality of the prenatal nutritional environment will be a predictor of future environmental quality.

There is emerging evidence in support of the hypothesis that prenatal undernutrition may "program" immune function to a significant degree, with implications for immune development and function that last into adolescence and adulthood (McDade and Kuzawa, in press; Moore, 1998). Early research with murine models documented alterations in offspring immune function following maternal nutritional deficiencies (both macro- and micronutrient) that lasted into adulthood and even the next generation, despite ad libitum feeding of both F_1 and F_2 generations (Beach et al., 1982; Chandra, 1975a). Recently, we reported that prenatal undernutrition is associated with impaired antibody responsiveness and reduced thymic hormone production in Filipino adolescents (McDade et al., 2001a,b). Participants in this study were recruited in the third trimester of gestation and followed prospectively, allowing for

rigorous analysis of postnatal variables that may confound the association between prenatal undernutrition and adolescent immunocompetence.[1] Thus, current evidence supports the hypothesis that prenatal undernutrition decreases long-term immune investment, although the implications for infectious disease risk are not known.

The question also remains as to whether this represents impairment, or an adaptation to the constraint of prenatal undernutrition. It is possible that in response to this suboptimal environment, there is a differential allocation of resources within the immune system away from energetically expensive specific immune defenses, and toward less costly, nonspecific defenses such as inflammation and the acute-phase response. In addition, preliminary findings indicate that males may be more sensitive to prenatal undernutrition than females (Kuzawa and Adair, 2003; McDade and Kuzawa, in press), suggesting that these trade-offs may be sex-specific.

Infancy

For the purposes of this analysis, infancy is defined as the period from birth to 2 years. Immunologically, thymic cortical volume, the number of T and B lymphocytes, and lymphocyte proliferative potential are all maximized early in infancy, reaching levels that are 1.5–3.5 times higher than where they will be after adolescence (Fig. 6). However, the effectiveness of the immune system in infancy is hampered by the naivete of the T- and B-lymphocyte repertoire, thereby increasing potential vulnerability to infectious disease.

Rates of growth are most rapid in infancy, particularly in the first year of life when an infant may gain 20–25 cm in length and 5 or more kg in weight. In addition, brain development is prioritized at this point: infants are born with only 25% of their adult brain volume, but by 6 months brain size has doubled, and by 2 years it has reached 75% of adult volume (Tanner, 1990). The energetic costs of this growth trajectory are substantial: the brain accounts for more than 50% of metabolic expenditure in the first year of life (Holliday, 1986). In addition, the majority of early growth effort is devoted to the deposition of adipose tissue, which peaks at approximately 25% of body weight between 6–9 months. This pattern of fat deposition is unusual in comparative perspective, and may represent an energy buffer that can fuel brain metabolism despite the nutritional disruptions that often accompany weaning (Kuzawa, 1998). Except for an early burst of gonadal activity (the significance of which is not entirely clear), investment in reproductive development in infancy is virtually absent.

In comparison to other life stages, the energetic demands of infancy are intense: growth is maximized, immune activity is upregulated, and the reproductive axis is modestly active. For these reasons, it is not surprising that the risk of death from infectious disease is dramatically elevated in the first year of life. Given the intensity of competing life-history demands, trade-offs in infancy can be expected to be especially severe, particularly in low-resource settings.

Issue 1. Avoid death from infectious disease. Since specific immune defenses in infancy are naive, and infectious disease mortality risk is exceptionally high, selection pressure will likely favor an accelerated process of immunological learning to minimize mortality risk. More specifically, one might hypothesize that opportunities for clonal selection and somatic evolution of lymphocytes should be maximized in infancy.

Clinic-based findings from Western populations provide three lines of support for this hypothesis (Figs. 2, 6). First, early in infancy, circulating T- and B-cell numbers are 3–4 times higher than in adulthood (Hicks et al., 1983b). Elevated numbers of lymphocytes maximize antigen receptor diversity, and thereby enhance opportunities for clonal selection and somatic evolution of T and B cell lines. Second, lymphocyte proliferation in response to in vitro mitogen stimulation is maximal postnatally, and declines with age through childhood and adolescence (Hicks et al., 1983a). A lower threshold of proliferative responsiveness also encourages T and B cell selection and somatic evolution. Third, the rate of memory-cell formation is elevated in infancy (Pirenne et al., 1992). CD4+ cells in infancy are almost exclusively naive (as indicated by expression of the membrane molecule CD45RA). As the infant gains antigenic experience, the proportion of memory T cells (approximated by membrane expression of CDw29) expands rapidly, and the proportion of naive cells diminishes, reflecting an accelerated process of somatic evolution and incorporation of antigenic information specific to the local disease ecology.

Issue 2. Balance the costs and benefits of breastfeeding. In many ways, breastfeeding can be understood as a partial solution to the competing life-history challenges of rapid growth and immunological naivete. Following birth, the breast replaces the placenta as the infant's primary source of nutrition and passive immunity, and breast milk delivers the appropriate balance of macro- and micronutrients to fuel rapid brain and body growth through the first 4–6 months of life (Institute of Medicine, 1991;

[1]The Cebu Longitudinal Health and Nutrition Survey (CLHNS) is an ongoing population-based study of maternal and child health in the Philippines that began in 1983 with the recruitment of 3,327 pregnant women (Cebu Study Team, 1989). Home visits were made prior to birth, immediately following birth, and every 2 months for 2 years to collect in-depth data on child and maternal health, anthropometry, patterns of breastfeeding, dietary intake, rates of diarrhea and respiratory disease, household socioeconomic status and demographics, and environmental quality. Follow-up surveys were conducted in 1991, 1994–1995, and 1998–1999.

Pierse et al., 1991). High concentrations of nonspecific immune defenses such as lactoferrin, lysozyme, and complement proteins inhibit pathogen colonization and growth in the neonatal gastrointestinal and respiratory tracts, and pathogen-specific defenses are provided primarily in the form of secretory IgA (Goldman, 1993; Ogra and Fishaut, 1990). Secretory IgA is present in large quantities, and coats the infant's gastrointestinal tract and binds soluble antigens to provide the first line of specific defense against infection.

Like the IgG transported across the placenta in utero, sIgA molecules in breast milk are a product of prior maternal antigenic encounters. Lymphocytes activated by antigens in the mother's gastrointestinal tract enter circulation and migrate to mucosal and secretory tissues, including the mammary glands, where they differentiate into antibody-producing plasma cells (Hanson and Brandtzaeg, 1989; Keller, 1992). Secretory antibodies against a range of viral, bacterial, and microbial enteropathogens are released into breast milk and consumed by the infant, where they reduce infectious morbidity and mortality (Hoshower, 1994; Nayak et al., 1987; Pickering and Ruiz-Palacios, 1986).

Through transplacental IgG and sIgA in breast milk, the mother shares her immunologic experience with the infant, and confers a degree of specific immunity that cannot be quickly attained by the infant's inexperienced immune defenses. Maternally derived antibodies recognize pathogens and bolster infant immune defenses, but the infant's own immune system also encounters these pathogens. These encounters activate the infant immune system and initiate the somatic evolutionary processes that drive the acquisition of specific immunity. While the risk associated with pathogenic exposure is attenuated by passive immunity, the infant's immune system begins to "learn" about the local disease ecology, and acquires specific immune defenses that will endure beyond the period when passive immunity is no longer operative. In a sense, since the development of specific immunity is a time-dependent Darwinian process, passive immunity can be conceptualized as a transient Lamarckian process of inheritance of acquired characteristics, whereby the mother shares her knowledge of the local disease ecology to provide a period of buffered pathogen exposure while the infant builds its own repertoire of defenses through a Darwinian process of somatic evolution (McDade and Worthman, 1999).

Given the obvious survival benefits of breast milk, it is reasonable to ask why exclusive breastfeeding does not continue beyond infancy. It appears as though there is an upper limit on maternal milk production, and by approximately 6 months of age, supplemental foods become necessary to meet the expanding protein, calorie, and micronutrient needs of the rapidly growing infant (Jenkins and Heywood, 1985; Jenkins et al., 1984; Institute of Medicine, 1991). This poses a considerable dilemma for the mother and infant: continue to exclusively breastfeed, with its demonstrable immunological benefits, but at a potential cost to infant growth; or begin to consume supplemental foods to maximize growth potential, but at the risk of increased pathogen exposure (Waterlow, 1981). In addition, breastfeeding has substantial energetic, nutritional, reproductive, and productivity costs for mothers, and successful supplementation requires nutritionally adequate breast-milk substitutes. Breastfeeding entails considerable costs and benefits for both infant and mother, who should titrate these trade-offs in relation to their local physical and social ecology to determine the intensity and duration of breastfeeding (McDade and Worthman, 1998). Conflict between infant and maternal needs with respect to breastfeeding is a reality, although the intensity of this conflict is also a product of the local ecology (McDade, 2001; Trivers, 1974).

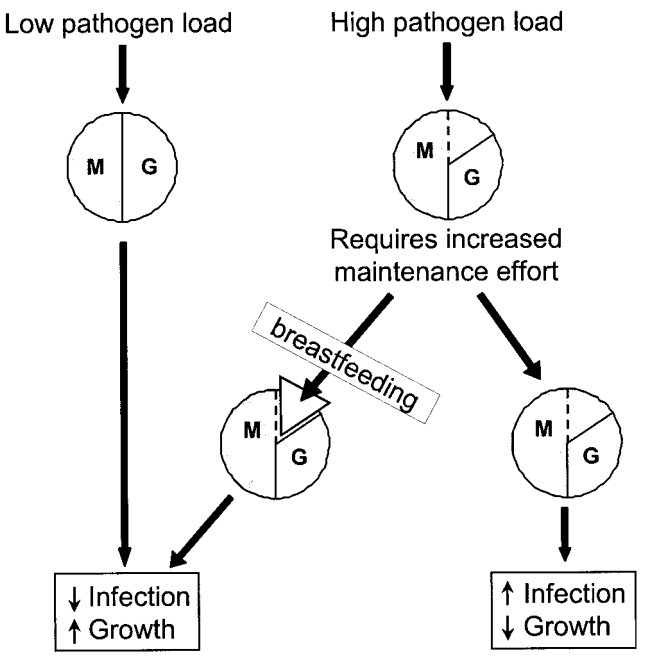

Fig. 7. Life-history model for relationships among pathogen exposure, breastfeeding, infection, and growth in infancy. High-pathogen environments increase maintenance (M) demands, potentially at a cost to growth (G). Nutritional and immunological benefits of breastfeeding cover some of these demands, and improve child health.

With the antipathogen benefits of breast milk and high infectious disease vulnerability in infancy, the intensity of pathogen exposure is likely to be a key factor in defining the life history trade-offs associated with breastfeeding (Fig. 7). In high-pathogen environments, demands for investment in immune defenses are elevated, and assuming a fixed amount of energy, this investment must come at a cost to growth. However, breastfeeding minimizes this cost by limiting the severity of pathogen exposure, and bolstering the infant's own immune defenses. In a sense, breastfeeding can be conceptualized as a ma-

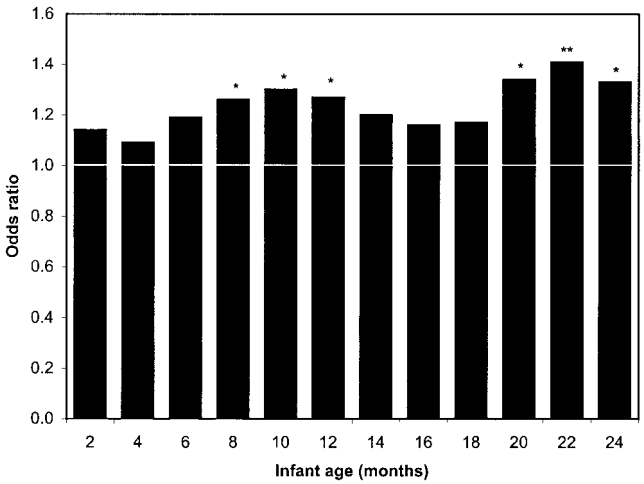

Fig. 8. Odds ratios for likelihood that infants in high-pathogen vs. low-pathogen environments are continuing to receive breastmilk at a given age. Odds ratios are adjusted for maternal education and household income. High-pathogen environments are associated with increased likelihood of prolonged breastfeeding. Data from Cebu Longitudinal Health and Nutrition Study[1](*$P < 0.05$, **$P < 0.01$).

ternal contribution to reducing the infant's own maintenance effort.

Data from the Philippines provide an opportunity to test the life-history model presented in Figure 7. The correlates of breastfeeding have been the subject of intense investigation in this population (Adair and Popkin, 1992; Adair et al., 1993; Popkin et al., 1990; Zohoori et al., 1993), but the potential role of pathogen exposure has not been considered. The following analyses should be regarded as exploratory, pending a more comprehensive evaluation. An index of household pathogenicity was constructed from the following variables: inadequate waste disposal, presence of domestic animals under the house, unsanitary food preparation area, and degree of crowding. In relatively unhygienic households, mothers exclusively breastfed their infants for an average of 62.7 days (SD = 42.3, N = 979), compared to 53.0 days (SD = 34.9, N = 1,036) in more hygienic households. If maternal education and household income are included as covariates, the adjusted durations of exclusive breastfeeding are 60.1 and 55.9 days, respectively. Although this difference is small (4.2 days), it is statistically significant ($P = 0.018$).

Similarly, even after the onset of supplementation, infants in high-pathogen environments were more likely to continue to receive significant amounts of breastmilk (Fig. 8). Rates of infectious morbidity in the first year of life are also consistent with the model: the lowest rates of morbidity (assessed at bimonthly intervals) were evident in prolonged exclusive breastfeeders in hygienic households (5.2 episodes), and the highest rates were found in short breastfeeders in unhygienic households (5.7 episodes). Prolonged exclusive breastfeeding in these households was associated with a reduced rate of 5.3 episodes, underscoring the protective nature of breastfeeding in high-pathogen environments.

Breastfeeding provides critical nutritional and immunological support during a high-risk period early in infancy characterized by rapid growth and high vulnerability to infectious disease. However, the implications of life-history trade-offs with respect to breastfeeding depend largely upon the local disease ecology.

Issue 3. Develop immune defenses that are adapted to the local disease ecology. The immune system has evolved to "expect" antigenic input as a major force driving its development, and infancy provides the first opportunity for the neonate to gauge the intensity and diversity of pathogen exposure. Given the high rates of infectious disease and severity of selection at this stage, this should be a particularly critical period of immunological development. In assaying the pathogenic environment, immune defenses can be tailored in such a way that they optimize protection against the specific pathogens that are most likely to be encountered during the course of an individual's lifetime. Therefore, one might hypothesize that exposure to infectious agents in infancy will have long-term effects on immune development and function.

Two lines of evidence are consistent with this hypothesis. First, and most obviously, exposure to specific pathogens drives the selection and somatic evolution of specific T and B cell lines, providing the basis for a more rapid and effective response following subsequent exposure to the same pathogen. For example, in the Soongnern District, Thailand, and Denver, Colorado, significant differences in age-specific levels of anti-*G. lamblia* antibodies reflect differential degrees of exposure to this waterborne parasite. In particular, higher levels of anti-*G. lamblia* IgA and IgG in Thailand provide a measure of protection that is associated with asymptomatic infection. In contrast, reduced antibody concentrations in Denver reflect the reduced frequency and intensity of *G. lamblia* exposure, and contribute to an episodic pattern of symptomatic infection and illness (Janoff et al., 1990).

Second, broad patterns of antigenic exposure (in addition to specific pathogen encounters) can have lasting immunological impact. Two subsets of helper T lymphocytes have been identified (Th1 and Th2) that are differentiated primarily by their patterns of cytokine production (Dong and Flavell, 2001; Paul, 1998). Both subsets play complementary roles in regulating specific immune activities, with Th1 involved in cell-mediated and inflammatory processes, and Th2 promoting humoral-mediated activities and antibody production. At birth, newborn T lymphocytes are biased toward the Th2 phenotype, with Th1 responses coming online with age (Jones et al., 2000).

Recently, a developmental trajectory in favor of the Th2 subset has been proposed as an explanation for rising rates of IgE-mediated atopic diseases such as allergy and asthma (Cookson and Moffatt, 1997; Rook and Stanford, 1998). This emerging epidemic has been concentrated primarily in relatively urban and affluent settings, and cannot be completely accounted for by increases in indoor or outdoor pollution, or dietary changes (Yazdanbakhsh et al., 2002). In 1989, a landmark study associating an increased number of older siblings with reduced risk of allergy suggested that the *absence* of infectious disease early in life may predispose children toward the development of atopic disease (Strachan, 1989). Since then, the "hygiene hypothesis" has received support from reports of negative associations between infectious morbidity early in life, and subsequent increases in Th2 cytokine production, IgE concentration, and symptoms of allergy and asthma later in life (Illi et al., 2001; Martinez et al., 1995; Matricardi et al., 2000; Shaheen et al., 1996; Shirakawa et al., 1997).

The notion that the frequency and intensity of pathogen exposure could have lasting organizational effects on the immune system is consistent with the developmental ecological framework proposed here. Immune function is a demand-driven system: it "expects" to receive appropriate input from the local environment. Evidence in support of the hygiene hypothesis indicates that this sensitivity to context goes beyond the antigen-specific process of clonal selection, and likely reflects a developmental responsiveness on the part of various components of immunity. In the Philippines, we found that infectious disease in the first year *increases* the likelihood that an individual will mount an adequate antibody response to typhoid vaccination in adolescence, controlling for a number of potentially confounding variables (McDade et al., 2001b). This finding is consistent with the life-history prediction that individuals in high-pathogen environments should invest more heavily in the development of antipathogen defenses. Early infancy is a critical period of immune development, and early pathogen exposure may serve as a predictor of future pathogen burden as well.

Conversely, and consistent with previous research, we found that the *absence* of infectious disease in the first year of life is associated with increased IgE production in adolescence (McDade et al., in press). Although the biomedical literature emphasizes the implications for rising rates of allergy and asthma, it remains to be seen if these are merely costs associated with a developmental trajectory that are outweighed by currently unrecognized benefits. Or perhaps this developmental trajectory is the pathological consequence of a mismatch between our current environment and that within which our immune systems evolved. Antigenic encounters drive the development of specific immunity, but what happens in the absence of meaningful input? Are antibacterial soaps, small family sizes, limited social encounters, and parents obsessed with cleanliness depriving infants of critical immunological stimulation?

In some sense, a bias toward Th2 cytokine production and elevated IgE may be the result of a *failure* to educate the immune system with specific antigenic encounters, thereby increasing the likelihood of inappropriate self-directed reactivity in the form of allergy and asthma (Rook and Stanford, 1998; Yazdanbakhsh et al., 2002). The nervous system may represent an analogous case: appropriate sensory input at critical periods is required for normal development, and the absence of input leads to lasting impairments in neurological function (Changeux, 1985). Future investigations of multiple aspects of immune ontogeny are necessary to evaluate the degree to which investment in one aspect of immunity is traded against another, and whether this represents an adaptation to the contingencies of an individual's developmental ecology.

Issue 4. Optimize trade-offs between competing demands for investment in immune function and growth. Resources are limited, and energy allocated to one function is not available for another. Increased levels of available energy will reduce the severity of these trade-offs, and on a population-level, may even lead to positive associations between growth and immune function due to the problem of phenotypic correlation. Nonetheless, affording the high levels of simultaneous investment in growth and immune development at this stage is likely to be a considerable challenge, particularly in resource-poor settings. Therefore, one might expect investment in immune function to be associated with impaired growth.

The negative effects of infection on child growth (particularly early in life when growth is most rapid) have been well-known for decades (Bogin, 1999; Martorell et al., 1975; Scrimshaw, 1981), and provide putative evidence in support of the hypothesis that investment in immune function comes at a cost to growth. However, the direct costs of immune processes are difficult to isolate, since illness often initiates other potentially growth-modulating processes, including loss of appetite, changes in diet, and impaired nutrient absorption. This issue will be addressed in more detail in the following discussion on childhood.

A recent study with bumblebees surmounted this obstacle by challenging their immune systems with lipopolysaccharides and microlatex beads (Moret and Schmid-Hempel, 2000). These artificial, nonreplicating "parasites" activate the immune system, but do not generate any pathogenic effect. Infected bees that were starved prior to infection were significantly more likely to die than nonstarved bees, demonstrating the direct energetic (and potential survival) cost of immune activation. Similar activation protocols with birds documented significant in-

creases in metabolic rate following mock infection (Martin et al., 2002; Ots et al., 2001).

Conversely, increased allocation of resources to growth should come at a cost to immune function. Through precise, daily measurement of infant length, linear growth has been reconceptualized as a saltatory process with periods of stasis punctuated by discrete growth episodes (Hermanussen, 1998; Lampl et al., 1992). Based on the allocation rule, one might expect an increased frequency of illness following a growth event, as this represents a significant short-term shift in resources toward growth, possibly at a cost to immunity. Preliminary evidence with 40 infants suggests that this is the case: both the occurrence and duration of illness are significantly predicted by time-constrained growth in body length (Lampl, 1996).

In addition to short-term trade-offs between immune activity and growth, a developmental perspective suggests that the rate of postnatal growth may be positively associated with immune function later in life. Energy above and beyond that required for maintenance is invested in productivity. At the age of sexual maturity, productivity shifts from growth to reproduction, and the rate of growth should be positively correlated with reproductive effort across species (Charnov, 1993). At the individual, developmental level, the rate of early growth may provide information on environmental quality that can be used to predict future resources, with reproductive investment adjusted accordingly (Ellison et al., 1993). Growth may serve a similar function with respect to setting the trajectory for long-term investment in immune function.

Note that this differs from the negative association between growth and immunity hypothesized above: in the short term, investment of resources in immunity limits the resources available for growth (and vice versa), resulting in a trade-off. But in the long run, early growth effort may be positively associated with later maintenance effort if growth is an indicator of current (and likely future) environmental quality.

Support for this hypothesis comes from the Philippines, where we found that growth in infancy is positively associated with immune function in adolescence, even after controlling for a range of potentially confounding factors. Infants who were one standard deviation above the mean in length gain during the first year of life produced 1.5 times as much thymopoietin in adolescence, indicating a higher level of hormone production in the thymus (McDade et al., 2001a). Similarly, infants above the median in weight gain during the first 6 months of life were 1.5 times more likely to mount an adequate antibody response to typhoid vaccination in adolescence (McDade et al., 2001b). While the short-term associations between poor environments, infant growth, and impaired immune function have been topics of intense public health interest (Gershwin et al., 2000; Suskind and Tontisirin, 2001), a life-history perspective suggests that infant growth may serve as an early assay of environmental quality, with implications for long-term investment in maintenance effort.

Childhood

Childhood is defined here as the period from age 2 years up to the initiation of gonadal steroid production presaging puberty. At this age, breast milk is no longer a significant nutritional or immunological resource, and the rate of growth has dropped precipitously from its peak early in infancy. Immunologically, passive immunity is no longer providing buffered exposure, and the child must rely on his or her own antipathogen defenses. While infectious disease mortality risk between ages 1–5 years is approximately one tenth what it was in the first year of life, it is still five times higher than between ages 5–15, indicating that early childhood continues to be a vulnerable period. T and B lymphocyte numbers, thymic cortical volume, and lymphocyte proliferative responsiveness decline steadily from their peak levels in infancy, but are all 1.5–2 times higher early in childhood than they will be in adulthood. Immunoglobulin concentrations continue their steady increase, as does the proportion of memory lymphocytes.

Investment in reproductive effort is negligible, and growth proceeds at a steady rate of 5–8 cm per year throughout childhood. This prolonged period of slow and steady growth with delayed reproductive maturation is a life-history pattern that is common to most primates, and is particularly exaggerated in humans (Bogin, 1999; Leigh, 2001).

Issue 1. Optimize trade-offs between concurrent, competing demands for investment in immune function and growth. As in infancy, resources invested in immune function are not available for growth, and significant trade-offs are expected given a fixed amount of available energy. Although the rate of growth is much lower than in infancy, a significant growth effort is maintained throughout childhood, and increased investment in immune function can still be expected to associate with impaired growth (assuming that resources are held constant).

Recent research employing direct measurement of immune activation provides support for this hypothesis. Blood concentrations of acute phase proteins such as alpha-1 antichymotrypsin (ACT) and C-reactive protein (CRP) increase in response to a wide range of viral, bacterial, and parasitic agents (Ballou and Kushner, 1992). As such, they can be measured as a nonspecific indicator of the degree of investment in antipathogen defenses. Panter-Brick et al. (2000) reported a negative association between ACT concentration and height-for-age z-scores (HAZ) in Nepali children.

Preliminary analyses of comparable data from Bolivia are consistent with this trade-off, but also sug-

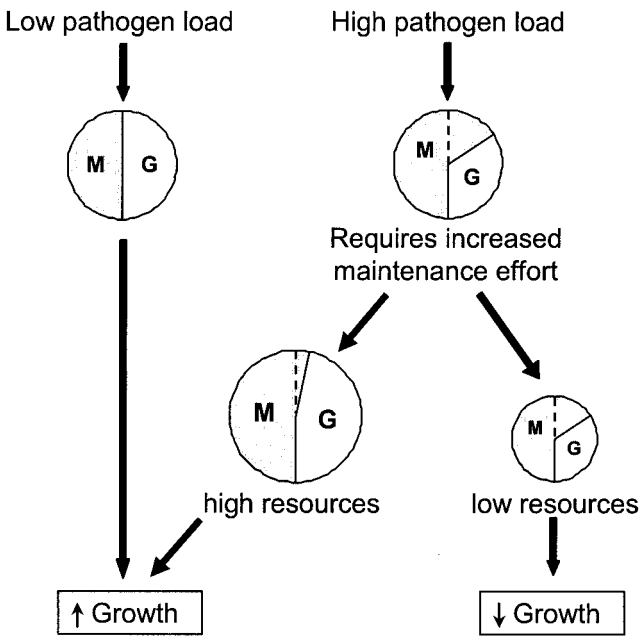

Fig. 9. Life-history model for relationships among pathogen exposure, maintenance (M) effort, and growth (G) in childhood. High-pathogen loads increase maintenance effort at a cost to growth, unless additional resources are available to cover these costs.

gest that individual differences in nutritional resources may moderate the costs of immune activation. For 2–4-year-old children (N = 93), elevated CRP was associated with a 0.30 z-score reduction in height-for-age, compared to children without elevated CRP (McDade et al., 2003). Although these data are cross-sectional, they are consistent with a trade-off between investment in immune function and growth.

However, the impact of increased immune activation was different for children with low or high energy reserves, as indicated by skinfold measurements that were below or above the median, respectively. For children with low skinfolds, elevated CRP was associated with a 0.74 z-score reduction in HAZ. With high skinfolds, elevated CRP was not associated with impaired growth (z-score difference = 0.11).

This pattern of associations is consistent with the causal model presented in Figure 9. High levels of pathogen exposure require an increase in maintenance effort, as indicated by increased immune activity. This effort imposes additional energetic demands, and for individuals with limited available resources, this effort will come at a cost to growth. However, this trade-off is less stringent for individuals with high resources: energy available in the body or in the environment (or the more efficient use of available energy) will increase an individual's ability to afford an increase in maintenance effort, thereby buffering the negative effects on growth. Longitudinal data will be necessary to validate this model, but it demonstrates the feasibility of controlling for phenotypic correlations to reveal a potential trade-off between growth and immunity.

Similar trade-offs may operate at the species level, where an association between increased investment in maintenance effort and slow growth rates might be expected. A juvenile period of slow growth is common to most primates, and is particularly extended in humans (Bogin, 1999; Leigh, 2001). Comparative analyses adjusting for differences in body size reveal an average primate growth constant of 0.4 (mammalian allometric growth law: $dw/dt = Aw^{0.7}$, where change in weight over time is a function of a growth constant, A, and weight, raised to the 0.7 power), and an even lower constant of 0.2 for hunter-gatherer children between ages 5–10 years (Charnov, 1993; Kaplan et al., 2000). This compares to a growth constant of 1.0 for most mammals, indicating an exceptionally low rate of human growth. This raises the obvious question as to why primates in general, and humans in particular, should grow so slowly when a prolonged juvenile period delays reproduction, and may increase risk of mortality prior to reaching reproductive age.

Adaptive explanations for this life-history pattern have focused primarily on slow growth as providing opportunities for enhanced brain development and learning (Kaplan et al., 2000; Leigh, 2001; Pagel and Harvey, 1993). Although productivity in the juvenile period is low and reproduction is delayed, increased knowledge and skill with respect to both the social and physical ecology pay dividends in terms of reduced mortality and increased reproductive success in adulthood. An alternative model conceptualizes juvenility as a period of "great ecological risk," since juveniles are more vulnerable to predation, and are less competent foragers compared with adults (Janson and van Schaik, 1993). Social living is a necessity to reduce risk of predation, but increased population density increases competition over limited food resources. Therefore, selection for slow growth reduces metabolic costs per unit time, and therefore reduces the juvenile risk of starvation.

To the extent that social living also increases pathogen exposure, elevated maintenance costs associated with investment in antipathogen defenses may represent an additional ecological risk factor for primates. Relatively fewer resources would therefore be available for growth, resulting in slower growth per unit time. An alternative causal process is also possible, where slow growth increases pathogen exposure over a prolonged juvenile period, necessitating increased immune investment. Either way, it may be hypothesized that low rates of growth are associated with increased maintenance effort (as indicated by investment in immune function) across species. A meaningful comparative measure of immune investment is an obvious challenge to testing this hypothesis, but analysis of spleen size (a potential indicator of immune investment) across species of primates reported larger spleens (adjusted for body size) in primates with slower life histories

(Nunn, 2002). However, spleen size and white blood cell counts are not significantly associated with primate sociality (Nunn et al., 2000). Comparative analyses with a wider range of species are necessary to evaluate further this hypothesis.

Issue 2. Acquire specific immunity that is adapted to the local disease ecology. The somatic evolutionary process of adapting specific immune defenses to pathogenic pressure continues through childhood. As children engage their environment and encounter a expanding range of antigens, they educate their immune system and drive the process of clonal selection. Antigenic "learning" is reflected in the steadily increasing proportion of lymphocytes bearing memory-cell markers, and the steadily declining proportion of naive lymphocytes (Fig. 6). However, the significance of this process goes beyond the generation of specific immunity, and reflects the emergence of a peripherally regulated system that helps make sense of the anomalous developmental trajectory of the thymus (McDade and Worthman, 1999).

While most organ systems do not reach their morphological or functional peak until adolescence and young adulthood, lymphatic tissue mass in infancy is twice its adult mass, with steady declines through childhood and adolescence. Given the importance of immune function throughout life, this pattern of early expansion and subsequent regression has puzzled developmentalists and immunologists. The thymus in particular (labeled the "master gland" of the immune system for its critical role in T-cell development and function; Cotman et al., 1987) was identified by a number of investigators as a potential target for intervention in the aging process (Fabris et al., 1988; Hadden et al., 1993). Others suggested that regression protects against autoimmune reactivity later in life (Aronson, 1991), and minimizes energetic costs associated with this relatively expensive tissue (George and Ritter, 1996).

Like the thymus itself, circulating T lymphocytes have receptors for glucocorticoids, sex steroids, growth hormone, and prolactin (Gala, 1991; Schuurs and Verheul, 1990; Shkhinek, 1985), and activated lymphocytes produce measurable quantities of substances similar if not identical to adrenocorticotropic hormone, thyroid-stimulating hormone, growth hormone, prolactin, gonadotropins, and beta-endorphin (Cotman et al., 1987; Fabris, 1992; Gala, 1991). In fact, peripheral lymphocytes have been referred to as a "minihypophis" for their ability to integrate information and manipulate the paracrine environment (Fabris, 1992). Given that immune defenses are in general localized to the site of infection, and that the "territory" subject to immune vigilance comprises the entire body, it makes sense for the system to be characterized by diffuse and peripheral regulation. A flexible, peripherally coordinated system allows sensitive responsiveness to a range of microenvironments.

In addition, clonal selection, somatic evolution, and the generation of immunological memory are processes that lead to the embodiment of information about nonself. This information is derived from the local antigenic environment, and is incorporated in a time-dependent learning process. From this perspective, it is not the size of the thymus or other immune tissues that is salient; instead, it is the information the system embodies in adapting the individual to the local disease ecology.

As such, the unusual developmental trajectory of the thymus can be understood as a necessary component of the development of a system defined by localized activity and peripheral regulation. The thymus releases a diverse population of lymphocytes into circulation, where antigenic encounters drive the selection and evolution of specific cell lines. Over time, a relatively self-sufficient T-lymphocyte population is generated that recirculates through blood, lymph, lymph nodes, and spleen, providing information in the form of differentiated cells across strategic sites throughout the body. As the thymus regresses in size, the amount of information embodied in circulating lymphocytes increases.

The rise in peripheral distribution and regulation can be modeled as an inverse function of the age-related regression of the thymus (Fig. 10). From this perspective, early thymic regression does not represent senescence or pathology in need of correction; nor should the thymus be considered a "master gland;" rather, regression is part of a necessary developmental trajectory. The fact that neonatal thymectomy leads to fatal wasting disease attests to the critical role of the thymus in proper immune function, but the degree of immune suppression following thymectomy is inversely proportional to age, indicating that the centrality of the thymus is age-dependent (Cardarelli, 1989).

Current data on thymic development are drawn from anatomical studies conducted exclusively among Western populations from low-pathogen environments. This raises the question as to whether this is a universal trajectory, or whether it is a product of the nutritional excess and low burden of infectious disease enjoyed by these populations. There are good reasons to expect thymic development to be responsive to the local ecology. The thymus receives input from all the major neuroendocrine axes, and in turn provides feedback that modulates neuroendocrine and thymic activity (Fabris et al., 1989; Grossman, 1994; Kelley et al., 1987). Growth, sexual maturation and reproduction, nutrition, and stress have all been shown to influence thymic activity, and therefore potentially shape its development. In addition, the thymus is energetically expensive, and investment in its activity is likely to be traded off against other critical life-history demands (George and Ritter, 1996). Even within Western populations, considerable variation in the age-related decline in thymic volume has been reported (Kendall et al., 1980).

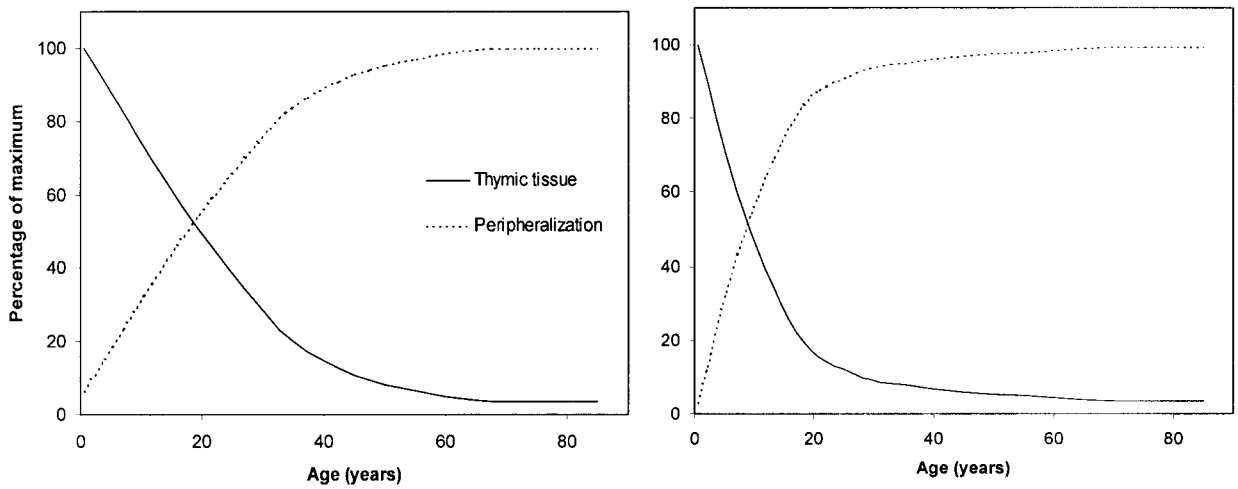

Fig. 10. Regression of thymic cortical tissue with age is complemented by increase in peripheral distribution and regulation of lymphocyte activity. Rate of these developmental changes may be responsive to divergent disease and/or nutritional pressures. **Left:** Trajectory of Western industrialized population. **Right:** Hypothetical trajectory in low-resource population.

If the thymus early in life is responsive to the context within which it develops, then one might expect different rates of regression and peripheralization in different ecological situations, particularly in situations of high vs. low pathogen exposure. Although it is difficult to speculate, given the paucity of data at this time, it is possible that intense pathogen pressure (in combination with the high resource costs of thymic activity) may be associated with accelerated peripheralization and earlier thymic regression (Fig. 10). This pattern would maximize protection against infectious disease, and minimize costs in what is likely to be an impoverished environment. Testing this hypothesis will be difficult, given the unlikelihood of obtaining anatomical specimens drawn from a range of diverse populations. However, thymic hormone levels in blood can serve as a proxy for thymic activity, and should provide insights into the ecological sensitivity of thymic development.

Adolescence

Upregulation of gonadal steroid production and the ensuing physiological and morphological events of puberty define this period of transition to reproductive maturity and the attainment of adult body size. With respect to immune function, the trends of childhood continue through adolescence, where declining T- and B-lymphocyte numbers, proliferative responsiveness, and thymic volume approach their adult levels. The proportion of naive lymphocytes continues to drop as clonal selection increases the proportion of memory lymphocytes following continued pathogen encounters. Reproductive effort (resulting in the development of primary and secondary sexual characteristics) is increased dramatically at this point. An increased investment in growth is also concentrated around the adolescent growth spurt. By age 15, infectious disease mortality risk increases by a factor of 2.5 from its nadir in late childhood, possibly reflecting the competing life-history demands of this period.

Issue 1. Optimize competing demands for investment in immune function, reproduction, and growth. From a life-history perspective, adulthood can be understood as the moment in development when investment in productivity shifts from growth to reproduction (Charnov, 1993). However, Figure 6 suggests that for humans (and possibly other primates with a preadult growth spurt), investments in growth and reproduction may not be mutually exclusive. Transient increases in growth effort associated with the pubertal growth spurt are superimposed upon burgeoning investment in reproductive function, increasing the energetic demands of this period. The costs to immunity may be attenuated a bit by the enhanced efficiency of immune defenses at this age (due to the generation of immunological memory), but this is likely a more vulnerable period than late childhood. In particular, one might hypothesize that the onset of puberty will be associated with reduced investment in immunity.

Evidence in support of a cost to immune function associated with puberty in humans is largely circumstantial. The sex difference in allergy risk switches from males to females at about age 15, implicating sex steroids as a causal factor (Wormald, 1977). Androgens and estrogens have both been shown to have generally immunosuppressive effects in humans, although these effects are far from simple and may in fact be more accurately characterized as immunomodulatory (Da Silva, 1999; Schuurs and Verheul, 1990). While testosterone is more consistently immunosuppressive, estrogen has been associated with suppressed cell-mediated immune processes, but also with enhanced B-lymphocyte activity and antibody production.

Recent data on CRP production in lowland Bolivia are suggestive of a reduced investment in specific

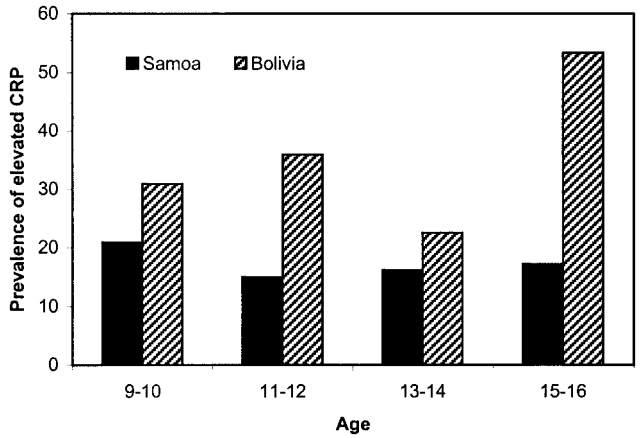

Fig. 11. Prevalence of elevated CRP (>1 mg/L) measured in whole blood spots by age in Samoa and Bolivia.

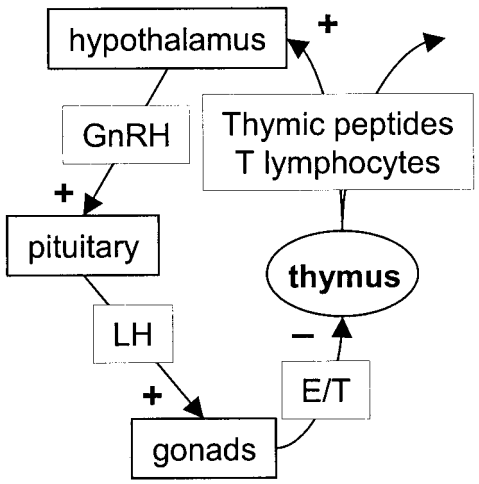

Fig. 12. Potential endocrine interactions between thymus and hypothalamic-pituitary-gonadal axis that may have implications for timing of puberty.

immunity at puberty (Fig. 11). The prevalence of elevated CRP (indicating a higher burden of infection) ranges from 23–31% between ages 9–14, but jumps to 53% in 15–16-year-olds (McDade et al., 2003). Comparably high rates of infection in this population are found only in infancy and early childhood, when immune defenses are naive. Of course, age is a poor proxy for the timing of puberty, and individual-level assessments of pubertal status will be necessary to confirm this potential association with infection. Furthermore, support for this trade-off relies on the interpretation that increased CRP is due to impaired pathogen control and reductions in immune vigilance, and not an increase in the degree of pathogen exposure.

For comparison, CRP data from Samoa are presented. Age-matched rates of infection are relatively low in this environment (characterized by nutritional abundance and better sanitation), and there is no increase in CRP in adolescence. This raises once again the issue of phenotypic correlation, and suggests that trade-offs associated with puberty may only be evident in high-pathogen, low-resource environments.

Recent findings from the Philippines provide more direct evidence for a trade-off between reproductive maturation and immune function in adolescence. All participants were 14 or 15 years old, with 44% in advanced stages of puberty at the time of the survey (as indicated by onset of menarche in girls, and advanced pubic hair growth in boys). These adolescents were 3.8 times *less* likely to produce an adequate antibody response to vaccination than adolescents in the early stages of puberty (McDade et al., 2001b). This association is independent of a range of potentially confounding factors, and suggests that puberty can exact a significant cost to immunity.

Conversely, aspects of immune ontogeny may play a key role in determining the timing of puberty. The onset of sexual maturation is a key life-history event, and for humans, this occurs sometime between ages 12–18 years (Eveleth and Tanner, 1990). This is an impressive degree of plasticity, leading to speculation that flexibility in the timing of puberty represents a facultative adaptation to the constraints and opportunities of the local social and physical ecology (Chisholm, 1993; Worthman, 1999). Undernutrition and a high burden of infectious disease are clearly involved in delaying the onset of puberty, although an elucidation of the underlying physiological mechanisms through which this occurs has remained elusive. Aspects of immune function may provide such a mechanism.

In murine models, sex steroids have been shown to have a clear antagonistic influence on the thymus: gonadectomy increases thymic weight and cortical volume, delays involution, and enhances in vitro proliferation of T lymphocytes in response to mitogen stimulation (Grossman, 1985; Windmill et al., 1993). Thymectomy of gonadectomized animals eliminates this enhanced proliferation, suggesting a direct inhibitory effect by the gonads on the thymus and thymic hormone production. Steroid receptors have been documented on thymic epithelial cells and T lymphocytes, and progesterone, estrogens, and several androgens have all been shown to cause thymic atrophy (Cardarelli, 1989; Windmill et al., 1993).

The associations between the thymus and gonadal activity are bidirectional: thymectomized animals have lower circulating levels of sex steroids, LH, FSH, and GnRH, indicating that thymic hormones may have direct neuroendocrine effects on HPG activation (Grossman, 1985). Indeed, thymosin has been shown to stimulate GnRH release from the hypothalamus, thereby activating the HPG axis and subsequently suppressing thymic activity, thus closing a negative feedback loop between the thymus and the HPG axis (Fig. 12). The strength of this association was demonstrated by the sex steroid-induced thymic atrophy that results from thymosin injection (Grossman, 1985).

If a coherent hypothalamus-pituitary-gonadal-thymus axis functions similarly in humans, then the thymus may be a critical life-history pacesetter, as well as an important mediator of trade-offs between maintenance and reproductive effort. This raises the intriguing, albeit speculative, possibility that the thymus may have a direct effect on the timing of puberty. From a life-history perspective, an adequate level of thymic function and immunocompetence (as indexed by thymic hormone production) may indicate that a prepubertal individual is ready to shift some of his or her maintenance resources into the costly processes of growth and reproductive maturation. If this is the case, then elevated levels of thymic hormones like thymosin might predict the onset of puberty.

The thymus is a central component of the neuro-immune-endocrine network (Grossman, 1994), and therefore a logical place to investigate physiological mediators of life-history trade-offs involving immunity. While thymic function is certainly not an exclusive determinant of pubertal timing, it may provide valuable information that is integrated with other measures of environmental quality and developmental status to optimize the onset of puberty. It may also be hypothesized that the role of the thymus will be more evident in boys than girls, as their reproductive careers are less constrained by time and they can therefore afford to be more sensitive to their environment (Stinson, 1985).

Adulthood

For this analysis, the attainment of reproductive maturity marks the end of adolescence and the beginning of adulthood. At this point, investment in growth is complete, and productivity consists of reproduction exclusively, with remaining resources available for maintenance activities. Declines in T- and B-lymphocyte numbers, lymphocyte proliferation, and thymic cortical volume have leveled off, immunoglobulin concentrations have reached their peak, and the establishment of a repertoire of memory cells has been completed. Later in adulthood, there are significant declines in functional aspects of immunity associated with senescence, although an in-depth analysis is beyond the scope of this review, particularly given the often contradictory pattern of findings (Goya and Bolognani, 1999; Miller, 1990). Instead, the trade-off between reproductive and maintenance effort is briefly discussed as a potentially interesting area for further research with adults.

Issue 1. Balance energetic demands of reproduction and maintenance. In humans, the energetic costs of reproduction differ dramatically by sex: for females, gestation and lactation are demanding in terms of both time and energy, whereas the male contribution can be as minimal as a single donation of sperm. However, somatic maintenance costs are much higher for men than women due to their larger overall body mass, and their higher proportion of skeletal muscle, which consumes 20% of basal metabolic expenditure (Bribiescas, 2001; Campbell et al., 2001). On top of these biological differences, culturally mediated, gender-specific patterns of reproduction, activity, resource access, and pathogen exposure will create considerable diversity in individual reproductive and maintenance costs across populations. These sex differences in reproductive and maintenance efforts are likely to have important implications for life-history trade-offs involving immune function in adulthood. A number of investigators have addressed this issue in fowl (Moller et al., 1999; Zuk and Johnsen, 2000; Zuk et al., 1995), although research with humans is currently lacking.

For females, direct evidence consistent with the hypothesis that increased reproductive effort is associated with reduced immune function comes in the form of strategic immunosuppression during gestation that prevents rejection of the fetus. Pregnancy slows neutrophil chemotactic activity, suppresses T-lymphocyte responsiveness, and lowers IgG levels as passive transfer to the fetus accelerates, and shifts T helper-cell activity to the Th2 phenotype (Blackburn and Loper, 1992; Iwatani and Watanabe, 1998; Jones et al., 1992). This leaves the mother more vulnerable to certain infectious agents, but attenuates autoimmune disease (Weetman, 1999). In addition, gestation and lactation have significant costs in terms of macro- and micronutrients, limiting their availability for maternal immune processes (Lunn, 1994; Prentice, 1994; Prentice and Prentice, 1988). In particular, progressive deterioration of maternal nutritional status from the cumulative demands of reproduction can lead to "maternal depletion," particularly when interbirth intervals are short and/or available nutritional resources are low (Merchant and Martorell, 1988; Merchant et al., 1990; Wood, 1994). Although the direct impact on immune function has not been considered, it can be assumed that low energy reserves impair maternal immunocompetence in these situations.

While the energetic costs of sperm production and delivery are miniscule in comparison with gestation and lactation, it has been suggested that muscle anabolism and maintenance are significant components of male reproductive effort (Bribiescas, 2001; Campbell et al., 2001). Since testosterone is central to musculoskeletal maintenance, and also has immunosuppressive properties, it may serve as a physiological mechanism mediating the trade-off between reproductive effort and immunity in males (the "immunosomatic metabolic diversion hypothesis;" Muehlenbein and Bribiescas, unpublished findings). Although this hypothesis has yet to be evaluated in humans, Campbell et al. (2001) found preliminary correlational support among Turkana men, who reported symptoms of chest infection likely linked to tuberculosis. Individual reports of infection were positively associated with testoster-

one concentration, consistent with the interpretation that increased reproductive effort was coming at a cost to investment in immune defenses.

Across mammalian species, the degree of sexual dimorphism in body size is predictive of the extent of sex bias in parasitic infection, suggesting that reduced investments in immune defenses are a cost of sexual selection (Moore and Wilson, 2002). This is consistent with the hypothesis that testosterone simultaneously increases investment in body size in males and limits investment in immunity. However, this cannot account for the finding that in species where females are larger than males, parasitic infection is biased toward females, and that independent of sexual dimorphism, mammals with larger body sizes tend to have a higher burden of parasitism. As such, body size itself, or differences in resource allocation associated with body size, may be sufficient to explain variation in parasite vulnerability.

Additional research with humans will be necessary to clarify whether testosterone is directly immunosuppressive, or whether it is an indicator of preferential allocation of resources to male secondary sex characteristics at the expense of immunity. The latter possibility would accommodate a similar role for estrogen in females. If sex steroids are indeed physiological mediators of the trade-off between reproductive effort and immunity, then it is almost certain that their effects emerge in interaction with other immunomodulatory endocrine signals (e.g., glucocorticoids, or leptin).

Given the costs of reproduction, one might also hypothesize that increased lifetime reproductive effort will be associated with accelerated immunosenescence and early aging. The trade-off between current and future reproduction is central to life-history theory. Reproduction must entail a survival or fertility cost; otherwise, selection would favor maximal fertility at every age (Hill and Hurtado, 1996). Costs of reproduction have been documented in a wide range of species (Lessells, 1991), but the physiological mechanisms through which these costs are mediated have not been elaborated (Sheldon and Verhulst, 1996). Immune function is a likely candidate. Similarly, the disposable soma theory of aging suggests that among iteroparous species, selection will always trade survival for early fecundity, and that investment in maintenance effort will always be less than that required to prevent aging (Kirkwood and Rose, 1991).

This logic could provide an ultimate explanation for the immune dysregulation associated with aging in human populations, although it remains to be seen whether increased reproductive effort early in life will accelerate immunological aging later in life. However, circumstantial evidence comes from a historical analysis of demographic data from Germany: controlling for the duration of marriage, a woman's lifespan was negatively related to the number of children to whom she gave birth (Lycett et al., 2000). However, this apparent cost of reproduction was significant only among poor landless women, once again demonstrating the importance of controlling for phenotypic correlations. It is also interesting to note that Hawkes et al. (1997) have suggested that reproductive costs for human females are reduced, compared with other nonhuman primates, by significant provisioning of grandchildren by grandmothers. An increased investment in somatic effort is therefore possible, leading to the evolution of the unusually long human lifespan. An increased investment in immunity may be a physiological mediator of this process.

CONCLUSIONS

An ontogenetic, ecological perspective on human immunity reveals that this complicated antipathogen defense system is largely a product of the environment within which it develops, and that there is substantial population variation in immune development and function that is not considered by current biomedical approaches. Life-history theory provides a predictive framework for investigating this variation by highlighting the challenges and trade-offs that define each life stage, and that may shape immune development and function in important ways. Although this analysis raises as many questions as it answers, it casts new light on what promises to be a fruitful area of research.

Antipathogen defenses are a critical component of maintenance effort, and additional research on immunity in relation to competing life-history demands may provide a physiological basis for many life-history trade-offs, and provide insights into human life-history variation. In their groundbreaking work among the Ache, Hill and Hurtado (1996) found only limited evidence for expected trade-offs between reproductive effort and other life-history traits. They cited unmeasured kin effects, individual differences in resource availability, or individual differences in the ability to use available resources as potentially confounding factors. Individual variation in maintenance effort is another possibility. Resources can be dedicated to growth, reproduction, or maintenance, and the allocation rule predicts negative correlations among investments in these areas. However, even with a fixed amount of energy, it is possible to see a positive correlation between investments in growth and reproduction if they are accompanied by a proportional reduction in maintenance effort. Just as phenotypic correlations need to be addressed in investigating life-history trade-offs within populations, a complete analysis requires attention to maintenance as well as the more intensively considered allocations to growth and reproduction. Measures of immune function may be useful in this regard.

Challenges in the assessment of immunity at the population level are a serious (although not insurmountable) obstacle to future research. The existence of multiple interacting subsystems of defense,

the high degree of compartmentalized activity, and the absence of central regulation mean that no single measure can provide a global assessment of immunocompetence. Furthermore, low values for one measure do not necessarily indicate reduced overall investment in immunity, as other components of activity may be independently upregulated. Careful thought needs to be given to the significance of each measure, and whether it is an indicator of immune protection or immune activation. In addition, although this paper has focused on the life-history trade-offs that are likely to shape immune function, it should be emphasized that these trade-offs cannot be removed from the social, cultural, and political-economic contexts within which they emerge. Sociobehavioral factors play as large a role in defining the developmental ecology of immune function as do pathogens themselves, both by patterning probabilities of exposure, and by influencing an individual's nutritional status and burden of psychosocial stress.

Research in human ecological immunology is just getting underway, but a comparative, adaptationist, life-history framework has the potential to contribute greatly to current knowledge of human immune development and function. The now well-established area of reproductive ecology (building on biomedical research in endocrinology) has repeatedly demonstrated how such a framework can lead to insights at conceptual and physiological levels (Campbell and Wood, 1994; Ellison, 2001; Konner and Worthman, 1980; Vitzthum, 1994; Wood, 1994). The time has come for similar efforts in field-based, population-level research in immunology. Hopefully the analysis presented here will serve as a catalyst for further exploration in this direction.

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