

The Ecologies of Human Immune Function

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immunology, growth and development, human biology, infectious disease

Abstract

Immune function is notoriously complex, and current biomedical research elaborates this complexity by focusing on the cellular and molecular mechanisms that characterize immune defenses. However, the human immune system is a product of natural selection that develops and functions in whole organisms that are integral parts of their surrounding environments. A population-level, cross-cultural, adaptationist perspective is therefore a necessary complement to the micro levels of analysis currently favored by biomedical immunology. Prior field-based research on human immunity is reviewed to demonstrate the relevance of cultural ecological factors, with an emphasis on the ecologies of nutrition, infectious disease, reproduction, and psychosocial stress. Common themes and anthropological contributions are identified in an attempt to promote future research in human ecological immunology that integrates theory and method for a more contextualized understanding of this important physiological system.

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mune and atopic diseases. The majority of this work relies on selectively bred strains of laboratory animals or on humans carefully selected from specific clinical populations. The contributions to disease prevention and treatment, as well as to basic biology, are difficult to overstate.

However, current biomedical approaches tell only part of the story. Human physiological systems are products of natural selection, developing and functioning in whole organisms that, in turn, develop and function in relation to surrounding physical and social environments (Oyama 1985, Williams & Nesse 1991). Studies relying on animal models, or on humans drawn from clinics in relatively affluent Western settings, do not adequately represent the diverse cultural and environmental circumstances around the world that contribute to human variation. Biological anthropology in particular has demonstrated the importance of this diversity in shaping human biology, development, and health across a wide range of human populations (Little & Haas 1989, Stinson et al. 2000).

For these reasons, there is emerging scholarly interest in field-based research on human immune function and its relevance to adaptation, ecology, and life history (Lochmiller & Deerenberg 2000, McDade 2003b, Sheldon & Verhulst 1996). Much of this work is reviewed here, along with findings from international health, behavioral ecology, and biomedical immunology that demonstrate the relevance of cultural and ecological factors to the development and function of the human immune system. Genetics also plays an important role (Tishkoff & Williams 2002, Weiss 1993) but is not covered in this review. Rather, the direct contributions of nutritional, pathogenic, reproductive, and psychosocial factors to human immune function are discussed in an attempt to lay the groundwork for an integrated human ecological immunology that incorporates theory and method for a more contextualized understanding of this important physiological system.

INTRODUCTION

Immunology has recently gained the attention of anthropology for at least three reasons. First, infectious disease has been, and continues to be, a major global health burden, particularly in many populations of anthropological interest (Inhorn & Brown 1990). Second, the immune system is an excellent model for exploring developmental processes, phenotypic plasticity, life history trade-offs, and adaptation—all central concepts for biological anthropology. Finally, the metaphors commonly used to characterize immune function reference biological as well as broader social processes and may reflect, as well as reinforce, contemporary cultural models and social divisions (Martin 1990, Wilce 2003). This third point—alluding to the critical perspective of cultural and linguistic anthropology—is beyond the scope of this review.

Biomedical immunology dominates current immunological research and focuses almost exclusively on the proximate cellular and molecular mechanisms that function to protect us from infectious and neoplastic diseases and that malfunction to cause autoim-

Ecological immunology: an adaptationist approach to investigating the costs and benefits of investment in immune activity and the potential role of pathogens in shaping life history variation

INTRODUCTION TO HUMAN IMMUNE FUNCTION

A detailed discussion of the immune system is well beyond the scope of this review; instead key terms, concepts, and components are highlighted and the reader is referred to introductory and advanced texts for more details (Goldsby et al. 2000, Paul 2003). The primary function of the immune system is to provide protection from the myriad bacteria, viruses, and parasites that share our world. The tension between host and pathogen is not unique to humans, and all vertebrates—from cartilaginous fish to mammals—share homologous elements of immunity (Du Pasquier 1992, Marchalonis & Schluter 1994). The immune system is also centrally involved in cellular renewal and repair and thus plays a critical role in wound healing and protection against cancer.

The immune system is composed of multiple interdependent and complementary subsystems that establish a relatively seamless network of antipathogen defenses (**Table 1**). Components of innate immunity include anatomical barriers such as skin and mucosal membranes; antimicrobial soluble proteins in blood, saliva, and tears; phagocytic cells that

scavenge extracellular macromolecules; and the inflammatory response (involving acute-phase proteins and the recruitment of phagocytic cells to the site of injury or infection).

Cell-mediated and humoral-mediated immune processes define specific immunity, which, unlike innate immunity, can recognize and target specific antigens. T and B lymphocytes are the central mediators of specific immunity and contain receptors that recognize antigens with exquisite precision, to the point that a single amino acid substitution may prevent binding by a given T or B lymphocyte receptor. Other characteristics 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 distinguish self from nonself.

T lymphocytes perform a range of regulatory, activational, and effector functions that are critical to eliminating intracellular pathogens and managing specific immune processes. Subsets of T lymphocytes are identified by the expression of membrane glycoproteins, in particular CD4 (identifying helper T cells) and CD8 (associated with cytotoxic/suppressor T cells). Helper T lymphocytes have also been further differentiated

Innate immunity: also called natural immunity, these defenses are phylogenetically older than specific immune defenses, do not depend on prior antigen exposure, and represent the body's first line of defense against infection and injury

Specific immunity: the defining features (also called acquired or adaptive immunity) include specificity, diversity (wide range of antigen-binding specificities), memory, and self/nonself discrimination

Antigen: a substance that elicits a specific immune response; most pathogens (i.e., bacteria, viruses, parasites) are composed of multiple distinct antigens

Table 1 Major components of the immune system and methods used in their measurement

Component	Measures
Lymphoid organs	
Thymus, spleen, bone marrow, lymph nodes	Organ size/histology; patterns of cell circulation; production of thymic peptides, cytokines
Nonspecific defenses	
Complement	Assays for complement and acute-phase protein concentrations; phagocytic cell counts; functional measures of cellular chemotaxis, lytic ability
Acute phase response	
Phagocytosis	
Cell-mediated immunity	
T lymphocytes: Helper (Th1, Th2) Suppressor/cytotoxic Naïve/memory	Number, percentages of T lymphocyte subpopulations; in vitro measurement of lymphocyte proliferation and/or cytokine production in response to mitogens; delayed-type hypersensitivity; assay for antibody titers to latent herpesviruses
Humoral-mediated immunity	
B lymphocytes Immunoglobulins (IgA, IgM, IgG, IgE, and IgD)	Number, percentage of B lymphocytes; in vitro measurement of lymphocyte proliferation; assay for Ig concentrations; assay for specific antibody titers following vaccination

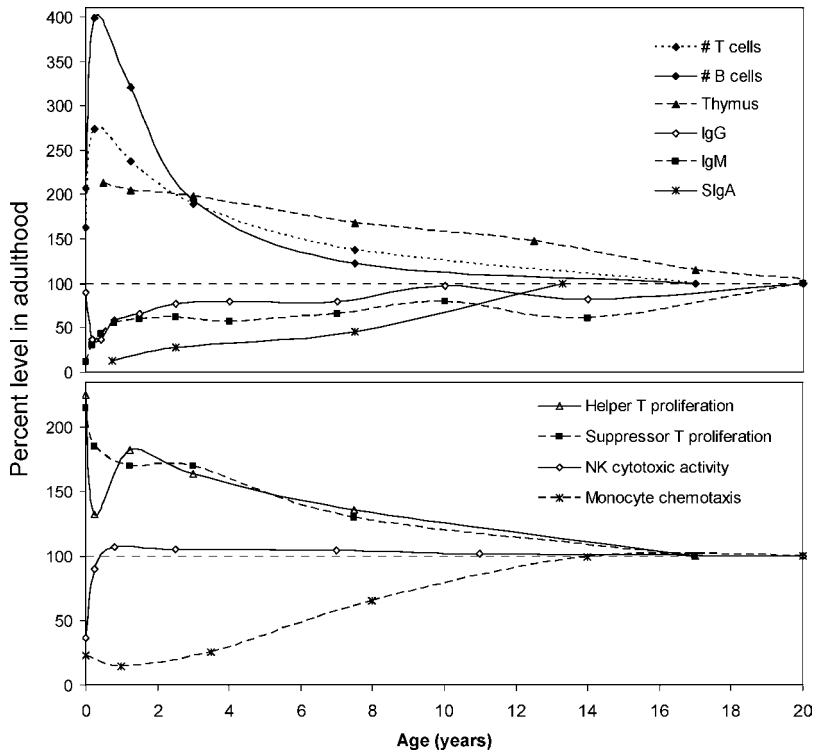


Figure 1

Development of enumerative (*top*) and functional (*bottom*) aspects of human immune function with age (McDade 2003b).

sIgA: secretory IgA

recently into Th1 and Th2 subtypes that regulate distinct patterns of immune activity.

B lymphocytes and the antibodies they produce are definitive components of humoral-mediated immunity and are involved primarily in protection against extracellular pathogens. Antibodies belong to one of five immunoglobulin isotypes (IgG, IgA, IgM, IgE, or IgD), each of which possesses unique structural and functional properties. IgG is the predominant immunoglobulin in circulation, whereas secretory IgA (sIgA) is abundant in external secretions, including mucus, saliva, breastmilk, and tears. IgM is produced when a new antigen is first encountered and accounts for less than 10% of the total serum immunoglobulin concentration. IgE is a potent mediator of allergic reactions and is involved in antihelminthic defenses. IgD is present in serum in very low concentrations, and its function is not well understood.

Figure 1 presents age-related changes in major aspects of immunity from infancy to young adulthood. Immediately apparent are the elevated numbers of T and B lymphocytes and the relatively high volume of thymic cortical tissue (in which T lymphocytes mature prior to their release into circulation). Lymphocyte activity is also upregulated early in life, whereas remaining immune factors demonstrate the more familiar developmental trend of incremental increase with age.

Prior work has interpreted the unusual developmental trajectory of human immune function within an adaptationist, life-history framework (McDade 2003b, McDade & Worthman 1999). From this perspective, increased activity in multiple parameters of specific immunity early in life can be understood as a response to the fundamental evolutionary advantage enjoyed by pathogens relative to their long-lived human hosts. Pathogens are present in high numbers, they have short

intergenerational intervals, and they produce large numbers of offspring with increased opportunities for mutation (Zinkernagel et al. 1985). Humans can never match the pace of pathogen evolution; rather, the process through which specific immune defenses are established incorporates evolutionary processes to counter this advantage.

In particular, lymphocytes circulate in high numbers, reproduce quickly following activation, and display a tremendously diverse range of antigen-binding receptors. Even though the human genome contains fewer than 30,000 genes, the judicious incorporation of stochastic processes during receptor development (random rearrangement of mini-gene segments, imprecise joining of nucleotide sequences, random combinations of heavy and light peptide chains, and somatic mutation during replication) produces far more than 100 million different antigen-binding specificities (Paul 2003).

Once this diverse pool of lymphocytes is established—each lymphocyte with its own unique antigen-binding receptor—the maturation of specific immune defenses is a relatively straightforward Darwinian process termed clonal selection: Antigens select lymphocytes with matching receptors; these lymphocytes activate, replicate, and pass on their receptor genes to daughter cells; and these cell lines become disproportionately represented in subsequent generations of the lymphocyte population. In essence, pathogens drive a developmental process that closely resembles natural selection, leading to somatic evolution of the lymphocyte repertoire. A major implication of this design is that the development of immunity is context dependent: The system is designed to incorporate information from the surrounding disease ecology, and the intensity and diversity of antigen encounters—especially early in life—can have a lasting impact (McDade & Worthman 1999).

Excessive or self-directed immune responses can do more harm than good, and immune processes are therefore regulated at multiple levels. Many aspects of immunity are

self-limiting in that antigens activate an array of innate and specific defenses, and once the antigen is cleared these defenses downregulate. In addition, the immune system receives input from the nervous and endocrine systems through innervation of lymphoid organs and through receptors for major endocrine axes expressed on lymphocytes as well as lymphoid tissues (**Figure 2**). Information from the immune system feeds back to the nervous and endocrine systems, forming an integrated neuro-immune-endocrine network that is central to the development and regulation of immune function (Ader et al. 2001, Besedovsky & del Rey 1996). These reciprocal connections provide a number of physiological pathways through which ecological factors may influence human immunity.

Thus, there are conceptual, developmental, and physiological reasons to anticipate a major contribution of culture and ecology to variation in immune development and function across populations. Unfortunately, very few investigators have addressed this issue,

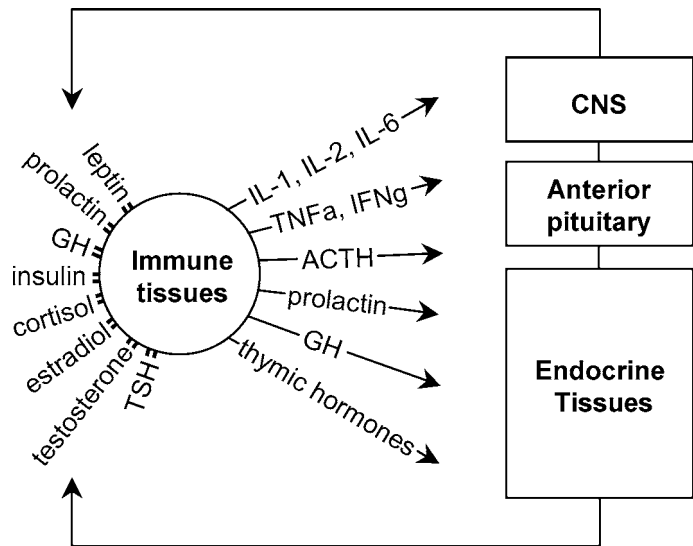


Figure 2

Immune function is an integral part of nervous- and endocrine-system activity. Immune tissues express receptors for major neuro-endocrine products and release a wide range of substances that modulate immune, nervous, and endocrine system processes at multiple levels (Besedovsky & del Rey 1996).

although a handful of field-based studies in diverse populations are suggestive. For example, reference values for lymphocyte development have been established in Western populations (Denny et al. 1990), but healthy, well-nourished children in West Africa (Lisse et al. 1997), as well as healthy adolescents in highland Papua New Guinea (Witt & Alpers 1991), demonstrate developmental patterns that differ significantly from these “norms.” Investigators have also documented wide population variation in age-related patterns of immunoglobulin production (Lau et al. 1992, Rowe 1972), as well as the production of nonspecific defenses such as C-reactive protein (McDade 2003b). Such variation underscores the importance of an ecological approach to complement and contextualize the cellular and molecular emphasis of biomedical immunology.

Measuring Immune Function

The complexity of immune function poses a serious challenge to measurement, particularly in field-based settings with limited laboratory facilities. Current research uses a range of enumerative and functional measures (Table 1), but these protocols typically require large volumes of blood collected through venipuncture and prompt access to laboratory facilities for the processing and analysis of samples. These procedures have served as major impediments to field-based, population-level research on human immune function and are a primary reason why the vast majority of current work is based in laboratory or clinical settings, with relatively homogeneous, opportunistic samples. With considerable effort (and expense), rudimentary laboratory facilities can be established in remote areas that allow for limited sample processing and analysis (Powell et al. 2001), but this is not likely to facilitate anthropological work in a wide range of cultural settings. Rather, a growing number of minimally invasive methods are now available that are amenable to the constraints of field-based research.

Salivary measures such as sIgA assess mucosal defenses protecting the gastrointestinal tract, a major entry point for pathogens (Mestecky 1993, Nishanian et al. 1998). Immune factors in blood provide more comprehensive information on systemic immune activity, and a number of methods have been developed using small quantities of whole blood collected from a simple finger stick. For example, a single drop of blood collected on filter paper can be assayed for acute-phase proteins and antibodies against the Epstein-Barr virus (EBV) (an indirect measure of cell-mediated immunity) (McDade et al. 2000a, 2004a; Panter-Brick et al. 2004). In addition, whole blood smears on glass slides allow the quantification of white blood cell fractions and lymphocyte subsets (Lisse et al. 1990). Last, delayed-type hypersensitivity—involving the intradermal application of test antigens to the forearm—has been successfully used in a number of sites as a semiquantitative measure of cell-mediated immunocompetence (Shell-Duncan & Wood 1997). Additional methodological development is needed, particularly given the complexity of immune function and the fact that no single measure can provide a comprehensive indicator of immunocompetence.

ECOLOGIES OF HUMAN IMMUNE FUNCTION

By focusing on the proximate mechanisms underlying the development and function of the immune system, biomedical immunology has established a solid mechanistic foundation upon which an ecological perspective can be built. Expanding the level of analysis to include the individual in context allows us to ask new questions. What constitutes “normal” immune function, and do immune parameters vary across populations? Which cultural and ecological factors contribute to this variation, and through which mechanisms? What is the contribution to differential patterns of disease, or variation in life histories? Because physiological systems are products

of natural selection, can an adaptationist perspective help explain, rather than just describe, the impact of ecology on immune development and function?

In protecting the body against infectious and neoplastic diseases, the immune system is central to survival, and thus evolution. However, immune function is costly, both in terms of the resources it consumes and in its effect on well-being when immune processes are misdirected. Other critical physiological and developmental systems also require resources, and natural selection can be expected to favor the optimal allocation of resources across these systems in ways that maximize fitness. In contrast to biomedical or epidemiological approaches, an adaptationist, ecological perspective recognizes that there are costs, as well as obvious benefits, associated with immune activity, and that trade-offs are therefore inevitable (Lochmiller & Deerenberg 2000, Sheldon & Verhulst 1996).

These trade-offs may be genetically encoded, or they may be developmentally mediated as a result of facultative adaptation to environmental circumstances during an individual's lifetime. The latter process is generally invoked to explain biological variation across human populations, where limited phenotypic plasticity allows individuals to respond adaptively to a range of ecological conditions (Hill & Hurtado 1996, Stearns & Koella 1986). Conceptually, trade-offs may occur between major life history functions (e.g., investing resources in maintaining the soma versus investing in reproduction or growth), between physiological systems (e.g., investing in immune tissues at the expense of the musculoskeletal system), and/or between subsystems within one system (e.g., biasing immune function toward Th1- versus Th2-mediated processes). Key ecological factors will determine the intensity of these trade-offs and will make investment in certain physiological systems (or subsystems) more critical than others.

The following sections review evidence demonstrating the impact of nutritional,

pathogenic, reproductive, and psychosocial factors on human immune development and function. This organization mirrors the state of current research that highlights the importance of these ecological domains, but tends to investigate their effects in isolation. But from an anthropological perspective, each of these domains falls under the rubric of culture. For humans, culture and ecology are inseparable: We actively construct our environments, and culturally mediated behaviors structure our interactions with these environments. In reviewing prior research in the pages that follow, common themes and anthropological contributions are identified in an attempt to plot a course for future research in human ecological immunology.

Nutritional Ecology

History documents a close relationship between inadequate nutrition and epidemics of pestilence and communicable disease (Chandra 1992). Today, international health research consistently associates malnutrition with immunosuppression and infectious disease risk in low-resource settings (Gershwin et al. 2000, Lunn 1991). For these reasons, nutritional inadequacy has been the most intensively investigated ecological factor linked to human immunity. A large body of research has documented the effects of macro- and micronutrient deficiencies on immune structure and function, and recent attention has been focused on the costs of immune function and their implications for child growth, as well as the long-term immunological consequences of undernutrition early in life.

Cell-mediated immunity is particularly sensitive to deficiencies in macronutrition: Thymic volume declines dramatically, T lymphocytes circulate in reduced numbers, proliferative responsiveness is attenuated, and delayed-type hypersensitivity is suppressed (Table 2). In contrast, humoral-mediated immunity is relatively buffered: B lymphocyte numbers remain within the normal range (except with severe undernutrition), and

Table 2 Summary of the effects of protein-energy malnutrition on parameters of human immunity

Immune component	Effect
Lymphoid organs	
Thymus	↓
Spleen	↓
Lymph nodes	↓
Nonspecific defenses	
Acute phase response	↓
Phagocytosis	↓
Complement levels/activity	↓
Cell-mediated immunity	
# T lymphocytes	↓
Lymphocyte proliferation/cytokine production	↓
Delayed-type hypersensitivity	↓
Thymic hormones	↓
Humoral-mediated immunity	
# B lymphocytes	↔ or ↓
Immunoglobulin concentrations	↔ or ↑
sIgA	↓
Vaccine responsiveness	↓

immunoglobulin concentrations are in many cases elevated, possibly reflecting higher levels of pathogen exposure in malnourished individuals (Lunn 1991). Cases of kwashiorkor or marasmus have been associated with major reductions in serum albumin production but normal or slightly elevated immunoglobulin production, suggesting preferential allocation of protein resources to immune function under these circumstances (Cohen & Hansen 1962, El-Gholmy et al. 1970). The acute-phase response is also impaired, although even severely malnourished children can mount a response to infection (Morlese et al. 1998).

Micronutrient deficiencies rarely arise independently of some degree of protein-energy deficiency, but they are also independent modulators of immune function. Deficiencies in vitamins A, C, E, and B complex, as well as trace elements iron, zinc, selenium, and copper, impair cell-mediated immunity, antibody production, and a wide range of non-specific immune processes (Chandra 1997, Gershwin et al. 2000). In addition, recent work has suggested that oxidative stress resulting from micronutrient deficiency may ac-

tually promote the evolution of more virulent viral strains within the undernourished host (Beck 2000).

Among the micronutrients, iron has received considerable attention, both because iron deficiency is common globally and because it has been linked to a wide range of adverse developmental outcomes, including impaired immunity (Stoltzfus 2001). Although reductions in cell-mediated and nonspecific immune processes may result from iron deficiency (Bhaskaram 1988), mild anemia has also been associated with increased resistance to infectious disease (Murray et al. 1980) and may represent an adaptive, nonspecific immune response to infection (Weinberg 1984). Iron is an essential nutrient for many microbes, and iron-binding proteins (e.g., transferrin, lactoferrin) sequester circulating iron during infection and limit its availability to pathogens. This raises the question as to whether diets that limit iron intake may represent a nutritional adaptation to infectious disease risk in high pathogen environments (Kent et al. 1994, Murray et al. 1980).

The close association between immunocompetence and dietary factors—particularly macronutritional adequacy—underscores the high resource costs of immune activity. Infection motivates major shifts in the body's metabolic priorities; severe infections increase resting metabolic rates by 25%–55% and consume 15%–30% of body weight (Lochmiller & Deerenberg 2000). Responses to less severe, as well as subclinical, infections also require energetic and protein resources to fuel immune cell replication and function, as well as the production of antibodies, cytokines, and acute-phase proteins. In addition, the thymus is a relatively large organ that contains an enormous number of maturing T lymphocytes, nearly a quarter of which are created each day. More than 95% of these T lymphocytes are destroyed before being released from the thymus owing to stringent selection criteria that reduce the chances of self-reactivity (George & Ritter 1996). The costs of these immune processes are substantial,

particularly for those on the margins of nutritional adequacy. Given these costs, an adaptationist, ecological perspective recognizes that there may be situations—particularly in low-resource settings—where it is necessary to downregulate investment in immunity to free up resources for other purposes.

Such trade-offs may provide insight into the complex associations among nutrition, infectious disease, and child health. The synergistic effects of malnutrition and infection on child growth and child survival are well known (Pelletier et al. 1995, Scrimshaw 2003), but few studies have considered immune function as a potential mediator. This is particularly important given that infection and malnutrition may contribute to growth faltering and increase mortality risk through multiple pathways: (a) Undernutrition may reduce the effectiveness of immune defenses and therefore increase the frequency and/or severity of infection; (b) more frequent infections (either due to higher levels of pathogen exposure or compromised immunity) require a higher level of energetic investment in immune activation, consuming resources that would otherwise be available for growth; (c) pathogens (and associated immune responses) can cause long-term damage to intestinal mucosa, which impairs nutrient absorption beyond the point of recovery (Lunn 2000); (d) cytokines associated with fighting infection may lead to loss of appetite, reducing energy intake when demands are high (Hart 1990, Martorell et al. 1980); and (e) symptoms of infectious disease may motivate culture-specific caregiving behavior, often replacing normal foods with watery substitutes lacking in nutrient and caloric density (Mata 1992).

Recent research in biological anthropology has begun to investigate these issues. In a highland population in Papua New Guinea with extreme burdens of infectious and nutritional stress, measures of child growth have been associated with white blood cell fractions, including numbers of circulating leukocytes, lymphocytes, and neutrophils (Ulijaszek 1998). Among nomadic Turkana

children in northern Kenya, low weight-for-height has been related to increased rates of acute respiratory infection (Shell-Duncan & Wood 1997). However, suppressed cell-mediated immune function (measured by delayed-type hypersensitivity) was a stronger predictor of infectious morbidity, indicating that immunity may be the proximate variable mediating the nutrition-morbidity relationship in this population.

Taking a slightly different approach, recent field studies in Nepal and Bolivia have investigated the direct contribution of immune activation to impaired growth. 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, making them potentially useful nonspecific indicators of the degree of investment in antipathogen defenses (Calvin et al. 1988). A major advantage of this approach is that it can detect subclinical infectious processes that may not manifest as observable symptoms (and would therefore not be reported) but that may nonetheless involve the activation of energetically costly antipathogen defenses (Rousham et al. 1998). Accordingly, among 10- to 14-year-olds in Nepal, elevated concentrations of ACT have been associated with growth faltering (Panter-Brick et al. 2000). Boys residing in rural villages—who had the highest concentrations of ACT—had the lowest level of self-reported morbidity, further underscoring the value of direct measurement of immune activation in relation to growth outcomes.

Preliminary analysis of data from ongoing research with a horticulturalist population in lowland Bolivia reports similar associations between immune activation (as measured by CRP) and growth faltering but also suggests that individual differences in nutritional resources may moderate the costs of immune activation. Height was measured at baseline and again three months later, with height gain interpreted as investment in growth effort during this period. Skinfold measures of body fat stores at baseline were used as

ACT: alpha-1 antichymotrypsin
CRP: C-reactive protein

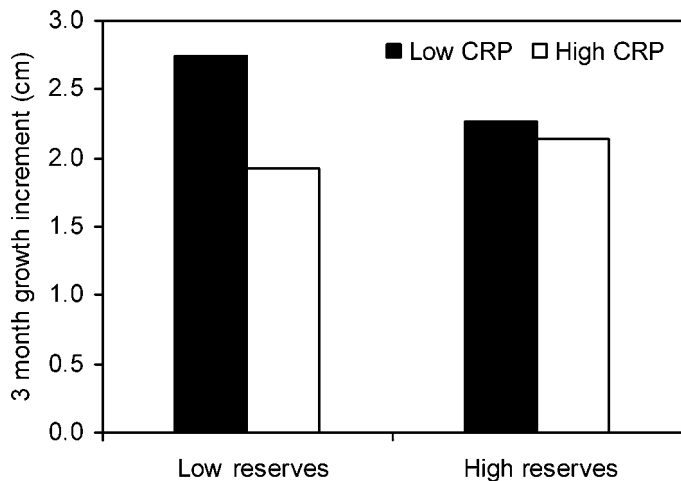


Figure 3

Growth costs of immune activation in lowland Bolivia. Elevated concentrations of CRP at baseline are associated with reduced height gain in the subsequent 3 months in 2–4-year-old children ($N = 122$) who have low body fat reserves (as indicated by skinfold measurements) (McDade 2005).

indicators of energetic reserves that could be drawn on to fuel immune function. Young children with elevated CRP at baseline grew less than did children with low CRP, and this difference was most pronounced among children with low energetic reserves at baseline (Figure 3). These results demonstrate a potential cost of immune activation and suggest that environments characterized by low nutritional resources may increase the severity of trade-offs between immunity and growth (McDade 2005).

Although the short-term effects of undernutrition on the immune system are well-established, recent research suggests that nutritional factors early in life may condition long-term investment in immune function. For instance, early studies showed that undernourished rats gave birth to offspring with immune deficiencies that last into adulthood, even though the offspring had unrestricted access to food. Furthermore, these immune deficits carried over into the next generation of offspring, demonstrating a long-term, intergenerational effect of maternal undernutrition (Beach et al. 1982, Chandra 1975).

Similar processes appear to be at work in humans. Infants in an expanding urban area of the Philippines born small-for-gestational age—indicating a relatively impoverished prenatal nutritional environment—are less likely to respond to vaccination in adolescence, and produce lower concentrations of thymopoietin, a thymic hormone important for cell-mediated immunity (McDade et al. 2001a,b). In addition, slow rates of growth in infancy—likely indicative of inadequate post-natal nutrition—are associated with reduced vaccine responsiveness and thymopoietin production in adolescence. In this population, the relationships among early undernutrition and adolescent immunocompetence are independent of a wide range of potentially confounding variables and suggest that nutritional factors early in life may have organizational effects on important immune processes.

In a mechanistic sense, because gestation and early infancy are critical periods of immunological development, early nutritional insults may therefore have a disproportional impact on immunity later in life (Moore 1998). A complementary, and by no means contradictory, adaptationist explanation suggests that environments early in life may be reliable predictors of future resource availability and that individuals may set long-term investment in immune defenses accordingly. Given the relatively high resource costs of immune function, limiting one's allocation to immunity may serve to ensure sufficient resources for other critical purposes (McDade 2005).

In sum, nutritional factors have direct implications for immune development and function, as well as indirect effects by determining the severity of trade-offs associated with investment in immunity versus other life history functions. The quantity and quality of local food resources are therefore likely to contribute to variation in immune function, along with other cultural factors such as subsistence strategy, food preferences and taboos, gender- and age-specific patterns of food distribution, and patterns of supplemental feeding in infancy.

Ecology of Infectious Disease

Because protection against microbial invasion is the primary function of the immune system, one might anticipate significant developmental sensitivity to the ecology of infectious disease. Furthermore, as noted above, immunity is a demand-driven system that “expects” antigenic input to guide its development and function. This occurs on two levels: through specific antigenic encounters that determine an individual’s memory lymphocyte repertoire, and through broad patterns of pathogen encounter that have more generalized effects on specific immune subsystems.

The first and most obvious way in which the local disease ecology shapes immune development and function follows logically from the mechanics of clonal selection. Specific antigens bind only those T and B lymphocytes with matching receptors. These lymphocytes become active, replicate, and differentiate into effector as well as long-lived memory cells that mobilize stronger and more rapid responses upon antigen re-exposure (Paul 2003). Different patterns of antigen exposure lead to the selection and proliferation of different lymphocyte clones, establishing different repertoires of specific immune defenses. Through this antigen-driven process of clonal selection, the immune system literally embodies knowledge about the local disease ecology in its repertoire of memory T and B lymphocytes. Different ecologies will therefore produce different immune repertoires.

In addition to specific pathogen encounters, broad patterns of exposure can have lasting developmental implications. For example, in the Philippines, a higher burden of infectious disease in the first year of life more than doubles the likelihood of responding adequately to typhoid vaccination in adolescence, controlling for a number of potentially confounding variables (McDade et al. 2001a). Similar associations between early infection and later immunocompetence have been reported in other populations as well (Rook & Stanford 1998), although inconsis-

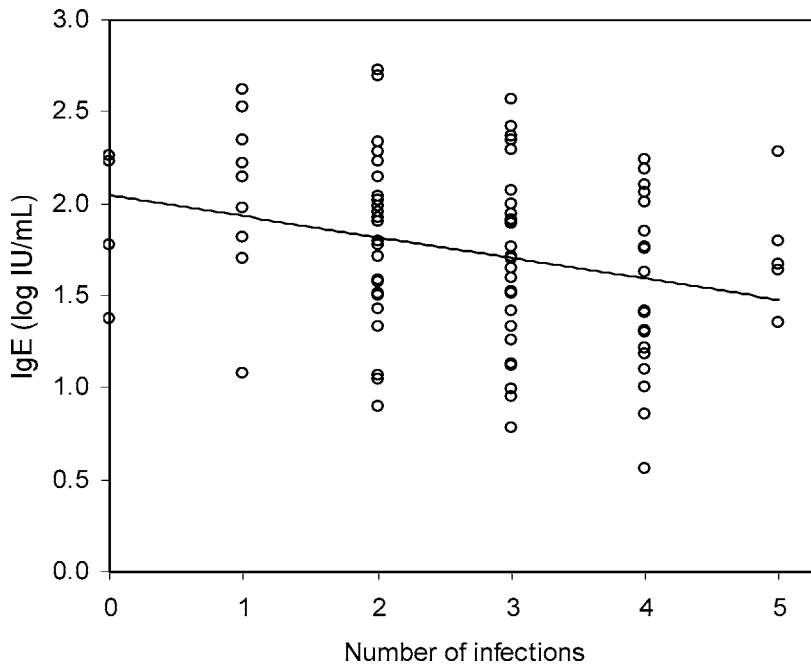
tent findings are also present (Shaheen et al. 1996). Just as early nutritional environments may influence long-term investment in immunity, early pathogen exposure may serve as a predictor of future ecological pathogenicity. Investments in immune function may be set accordingly; individuals in high pathogen environments may devote more resources to the development of antipathogen defenses.

In addition, the frequency and intensity of pathogen exposure may have lasting organizational effects on subsystems of defense. For example, two subsets of helper T lymphocytes play complementary roles in regulating specific immune activities, with Th1 cells contributing to cell-mediated and inflammatory processes and Th2 cells promoting humoral-mediated activities and antibody production (Dong & Flavell 2001, Paul 2003). T lymphocytes are biased toward the Th2 phenotype at birth, and developing a proper balance between Th1 and Th2 responses is critical for maximizing effectiveness against a wide range of potential pathogens and for minimizing the risk of immunopathology. Exposure to infectious disease early in life plays a critical role in entraining an effective regulatory T cell network (Yazdanbakhsh et al. 2002).

The absence of such input may be responsible for rising rates of IgE-mediated atopic diseases such as allergy and asthma in populations where recent improvements in sanitation and vaccination have significantly reduced pathogen exposure (Cookson & Moffatt 1997, Rook & Stanford 1998). Support for this “hygiene hypothesis” comes from a number of studies reporting that infectious morbidity early in life is associated with increases in Th2 cytokine production, IgE concentration, and symptoms of allergy and asthma later in life (Matricardi et al. 2000, McDade et al. 2004b, Shirakawa et al. 1997) (**Figure 4**). In contrast, populations characterized by chronic helminthic infection also produce high concentrations of Th2 cytokines and IgE but do not suffer from allergy or asthma (Hurtado et al. 1997, Yazdanbakhsh et al. 2002). In these cases, chronic pathogen

Figure 4

Relationship between infectious morbidity in the first 6 months of life and total IgE concentration at age 14–15 years in the Philippines. Results are adjusted for sex, pathogen exposure in the first year of life, birth weight-for-gestational age, weight gain in the first 6 months, and current household income (McDade et al. 2004).



exposure promotes the development of a strong anti-inflammatory regulatory network that allows Th2-mediated processes to fight helminthic infection without invoking the immunopathological side effects that such processes may elicit in populations with low levels of pathogen exposure (Yazdanbakhsh et al. 2002).

Thus, the ecology of infectious disease may shape physiological trade-offs within the immune system itself and contribute to the development of antipathogen defenses that are adapted to the local disease ecology. This plasticity may explain the divergent effects of early pathogen exposure on adolescent immune function in the Philippines: High rates of infectious disease in infancy are associated with stronger vaccine responses in adolescence but lower concentrations of total IgE. Early pathogen exposure may have organizational effects by selectively upregulating investment in certain aspects of immunity, while downregulating others. Whether this is an adaptive process that mobilizes more effective defenses that are tailored to the local disease ecology remains to be seen.

Rising rates of allergy and asthma may represent a breakdown in this process. Just as the nervous system relies on appropriate sensory input during critical periods of development (Changeux 1997), the immune system may expect antigen encounters to guide the development of regulatory networks, inform investment in subsystems of defense, and establish a mature lymphocyte repertoire. Indeed, Fessler & Abrams (2004) have argued that the propensity of infants to mouth objects during the first two to three years of life—despite considerable risk of choking and toxin exposure—may be motivated by the need to sample the pathogenic environment.

However, cultural models that construct germs as threats to be avoided at all costs, that promote the use of antibacterial soaps and other “sanitizing” products, and that encourage parents to believe that infections are not a normal part of child development may limit pathogen exposure early in life. Demographic trends toward small nuclear families living in relatively isolated residential units may contribute further. The cultural ecology of pathogen exposure may therefore result in

a poorly educated immune system that is more likely to engage in inadequately regulated or self-reactive activities, with implications for allergy and asthma later in life.

Reproductive Ecology

Reproductive ecology is a thriving area of anthropological research that has transformed current understandings of human reproduction on multiple levels (Ellison 2001, Konner & Worthman 1980, Vitzthum 1994, Wood 1994), but links with immunity have yet to be elaborated. Recent work relying primarily on bird models has emphasized the costs of reproduction, and similar issues may affect immune function in humans as well.

In particular, a number of studies have evaluated whether secondary sexual traits in male birds (e.g., size of combs, tail feathers) are honest signals of their ability to resist parasitic infection that serve as cues for sexual selection (Moller et al. 1999, Zuk et al. 1995). The extent to which androgens—testosterone in particular—mediate these associations has been the subject of recent debate, and a number of investigators have emphasized the more general point that immune activity and reproductive effort must compete for limited energetic resources (Buttgereit et al. 2000, Lochmiller & Deerenberg 2000, Sheldon & Verhulst 1996). For example, experimental lengthening of ornamental tail feathers in male barn swallows decreases immune responsiveness to immunization (Saino & Moller 1996). And across mammals, species with a higher degree of sexual dimorphism in body size have a more pronounced sex bias in parasitic infection, suggesting that sexual selection for increased body size comes at a cost to investment in immune defenses (Moore & Wilson 2002).

Analogous processes linking sexual dimorphism, reproductive effort, and immunity may be operating in humans, although empirical tests are currently lacking. The costs of reproduction for humans differ dramatically by sex: For females, gestation and lactation are

demanding in terms of both time and energy, whereas cost for males can be as minimal as a single contribution of sperm. However, the development and maintenance of male secondary sexual characteristics can be conceptualized as investment in reproductive effort, and males pay relatively higher costs than do females in this area owing to their larger overall body mass and higher proportion of skeletal muscle (Bribiescas 2001, Campbell et al. 2001).

The immunological consequences of differential allocations to reproductive effort within males have not been directly evaluated, although recent findings from the Turkana are suggestive. Men reporting symptoms of chest infection (likely the result of tuberculosis) had higher concentrations of testosterone, consistent with the interpretation that reproductive effort may come at a cost to investment in immune defenses (Campbell et al. 2001). Contrary evidence comes from a large study of aggression and immune function in American men, in which enumerative measures of immunity were positively associated with testosterone (Granger et al. 2000). However, these associations were weak and can be explained largely by the positive association between testosterone and risky health behaviors.

Alterations in immune function associated with puberty correspond to rising concentrations of sex steroids and may provide evidence in support of a trade-off between reproductive effort and immunity. However, the causal role of sex steroids is not clear: Although their effects are generally immunosuppressive (particularly testosterone), these effects are far from simple and may be better described as immunomodulatory (Da Silva 1999, Schuur & Verheul 1990).

The immunological costs of reproduction for females are more direct: Pregnancy initiates a number of changes, including reduced T lymphocyte proliferation, shifts in helper T activity toward the Th2 phenotype, slowed neutrophil chemotaxis, and reduced concentrations of IgG as a result of active transfer to

the fetus (Blackburn & Loper 1992, Iwatani & Watanabe 1998). This strategic pattern of immunosuppression prevents rejection of the fetus but increases vulnerability to certain infectious agents during pregnancy. Recent work has suggested that the mechanisms invoking this immunosuppression may function maladaptively outside of pregnancy to contribute to the etiology of HIV (Hoff 1999).

In addition to direct immune suppression, increased demands for macro- and micronutrients during gestation limit their availability for immune processes (Lunn 1994, Prentice & Prentice 1988). This can be particularly problematic when opportunities for compensatory increases in dietary intake are limited, and when the cumulative demands of multiple, closely spaced pregnancies can lead to progressive declines in maternal nutritional status (Merchant & Martorell 1988, Wood 1994). The immunological costs of reproduction may be particularly high for women in pronatalist settings that do not provide the social and/or nutritional resources necessary to support this effort.

Lactation is also an important link between reproduction and immune function because breastmilk provides effective protection against infectious disease. Infants are particularly vulnerable owing to the naïveté of their specific immune defenses, but the antigen-binding specificities of sIgA in breastmilk are the product of prior maternal antigenic encounters and therefore provide specific immune defenses that are tailored to the local disease ecology. Cultural practices that shape the intensity and diversity of maternal antigen exposure therefore have direct implications for infant immunity. In addition, a range of nonspecific defenses are present in breastmilk that inhibit pathogen colonization and growth in the infant gastrointestinal and respiratory tracts, and growth factors facilitate the maturation of mucosal tissues (Ogra & Fishaut 1990). Breastfeeding thus bolsters the infant's developing defenses and provides a period of buffered exposure during which pathogen encounters can educate

the infant's immune system while posing a reduced risk of infection (Fessler & Abrams 2004, McDade & Worthman 1999). Breastfeeding also has long-term effects on immune development, with implications for allergy later in life (Bjorksten & Kjellman 1990).

Although there are nutritional and emotional, as well as immunological, benefits to prolonged breastfeeding, mothers pay significant energetic, nutritional, and reproductive costs as well. Mothers and infants must balance these costs and benefits in relation to a range of social and cultural ecological factors that support, as well as constrain, breastfeeding behavior (McDade & Worthman 1998). With the antipathogen benefits of breastmilk and the high risk of infection in infancy, the intensity of pathogen exposure is likely to play an important role in defining this trade-off. This appears to be the case in an urban environment in the Philippines, where mothers living in less sanitary households exclusively breastfeed their infants for significantly longer than do mothers in more sanitary households where pathogen exposure is likely to be reduced (60.1 versus 55.9 days) (McDade 2003b). The nutritional resources of the mother are also likely to be an important factor since undernourished mothers are less able to pay the costs of prolonged breastfeeding, even in high pathogen environments.

Last, given the costs of reproduction and their relevance to immune function, increased reproductive effort over the life course may contribute to accelerated immunosenescence and early aging. For example, historical demographic data from Germany reveal that a woman's lifespan is negatively related to the number of children to whom she gave birth (Lycett et al. 2000). This association was significant only among poor landless women, which suggests that reproductive effort may exact a higher toll in ecological or cultural circumstances that limit resource access. Immune function may be an important mediator here, although it remains to be seen if increased reproductive effort early in

life can affect immunological aging later in life.

Social Ecology

Although aspects of the surrounding physical ecology are important to immune function, recent research has also demonstrated that social and cognitive processes leading to psychosocial stress have direct implications for multiple parameters of immunity. As noted earlier, the immune system interdigitates with the nervous and endocrine systems at multiple levels, providing the physiological infrastructure through which psychosocial experience can have direct immunomodulatory consequences (Ader et al. 2001, Besedovsky & del Rey 1996). The growing field of psychoneuroimmunology (PNI) has established this as an important area of research, and has challenged prevailing notions of brain/body dualism by elucidating the mechanisms through which psychosocial phenomena influence physiology (Ader et al. 2001, Glaser & Kiecolt-Glaser 1994).

Most PNI research uses experimental animal models or clinic-based research designs, but a number of studies have established that human immunity is sensitive to a wide range of naturalistic stressors (Table 3). In particu-

lar, social relationships are important sources of stress, as well as sources of support. For example, early work in this area has reported consistent impairments in immune function following the loss of a loved one (Irwin et al. 1987), whereas more recent research along this theme has demonstrated that problematic personal relationships adversely affect a range of immune parameters (Kiecolt-Glaser et al. 1994). Slowed wound healing, increased likelihood of infection, and impaired response to vaccination are all immune-mediated health outcomes that have been convincingly associated with psychosocial stress (Cohen et al. 1991, Glaser et al. 1992).

The impact of stress on immune function has been investigated primarily in adults, but the relatively few studies conducted with children and adolescents indicate significant adverse effects as well (Birmaher et al. 1994, Boyce et al. 1993). In addition, experimental research with nonhuman primates suggests that maternal stress during pregnancy and maternal separation in infancy have lasting effects on offspring immune function that persist into adulthood (Coe et al. 2002).

Chronic psychosocial stressors have been consistently associated with decreased numbers of T, B, and NK cells, suppressed lymphocyte proliferation and cytotoxic activity,

PNI: psychoneuroimmunology

Table 3 Previous research with healthy individuals documenting an association between naturalistic stressors and human immune function (Biondi 2001)

Stressor	Immune outcomes
Natural disasters	↓ lymphocyte proliferation; ↓ NK activity; ↓ # CD4+, CD8+
Loneliness/low social support	↓ lymphocyte proliferation; ↓ NK activity; ↓ # lymphocytes
Bereavement	↓ lymphocyte proliferation; ↓ NK activity
Separation/divorce	↑ herpesvirus antibody titers
Marital conflict	↓ lymphocyte proliferation; ↓ NK activity; ↑ herpesvirus antibody titers; ↑ # CD4+
Caring for disabled or demented relative	↓ lymphocyte proliferation; ↓ NK activity; ↓ vaccine response; ↑ herpesvirus antibody titers; ↑ # CD8+; ↓ # NK cells
Unemployment/economic crisis	↓ lymphocyte proliferation; ↓ IL-2, ↑ IL-4 production
Starting a new school	↓ lymphocyte proliferation; ↑ #, % CD4+
Academic stress	↓ NK activity; ↓ vaccine response; ↑ herpesvirus antibody titers; ↓ # CD4+

and lower levels of sIgA and IgM. Antibodies to latent herpesviruses are also consistently elevated under stress, indicating reduction in aspects of cell-mediated immune function (Biondi 2001, Herbert & Cohen 1993). A meta-analysis of this literature supports the following tentative conclusions regarding the impact of stress on human immune function: (a) Objective events have greater effects than do self-reports of stress; (b) long-term stressors have more consistent negative effects than do acute stressors, with little evidence that the immune system adapts to chronic stress; and (c) social and nonsocial stressors have different immunological consequences (Herbert & Cohen 1993).

One shortcoming of PNI is that the vast majority of studies draw from relatively homogenous, affluent Western populations. A recent review underscores this point, stating “[t]he typical experimental subject in psychoimmunology is a young, male, Caucasian, healthy, medical or psychology student, probably a light or nonsmoker, consuming little or no alcohol or coffee, with no history of allergy or recent infectious disease. . .” (Biondi 2001, p. 202). This scenario reflects in part methodological constraints associated with assessing immune function, but it also indicates that sociocultural factors shaping the experience of stress are not of central concern. Rather, stressors are conceptualized as the starting point for investigating the proximate physiological mechanisms linking behavior, neuroendocrine activity, immune function, and disease. The experience of stress is locally constructed and embedded within specific cultural contexts (Young 1980), and the relatively narrow focus of PNI misses an opportunity to consider cultural and ecological diversity in stressors and their impact on immunity.

Stress is a central concept in biological anthropology (Brown 1981, Dressler 1995, Goodman et al. 1988), but relatively few studies have considered its impact on immune function. Flinn & England have conducted a long-term, naturalistic investigation of childhood stress and physical health in Dominica

using multiple measures of salivary cortisol to gain insight into the physiological effects of a range of psychosocial stressors (Flinn & England 1995, 1997). Chronic stressors—in particular stressors related to family composition and stability—are associated with higher average cortisol, which is in turn associated with increased frequency of infection. Stress-induced alteration in immune function may be an important mediator of these associations: Recent analyses report that chronically stressed children have lower concentrations of sIgA and that salivary concentrations of neopterin and β 2-microglobulin (interpreted as measures of cell-mediated immune activity) are suppressed for at least two days following a stressful event (Flinn & England 2003).

In an explicit attempt to integrate PNI and biological anthropology, McDade and colleagues have investigated culture change, stress, and immune function among children and adolescents in Samoa. Immunity was assessed in 760 4- to 20-year-olds by measuring EBV antibodies in dried blood spot samples collected following a simple finger prick (McDade et al. 2000a). This indirect, functional measure of cell-mediated immune function is among the strongest and most consistent immunological correlates of chronic stress (Herbert & Cohen 1993), and its measurement in dried blood spots overcomes logistical obstacles associated with collecting and transporting serum or plasma.

Ecological comparisons indicated that children and adolescents in the capital city and surrounding areas had higher EBV antibody titers than did their peers in remote areas, independent of a range of potentially confounding factors (McDade et al. 2000b). Higher EBV antibody titers reflect poorer cell-mediated immune function and suggest an increased burden of psychosocial stress, possibly due to the emerging influence of Western lifestyles in more urban areas of Samoa. In addition, consistent with previous research on stress and immunity in U.S. populations, major life events were

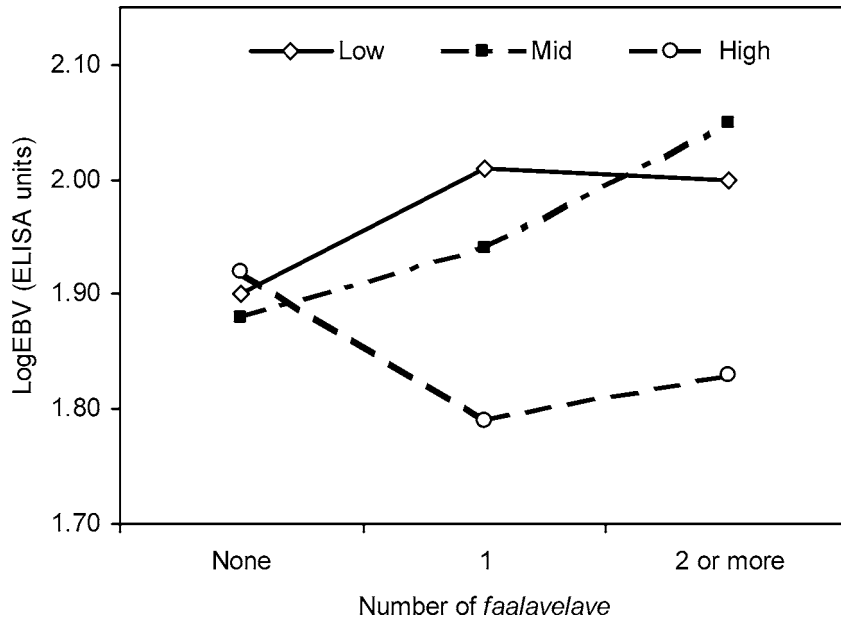


Figure 5

Interaction between the occurrence of *faalavelave* in the previous year and household socioeconomic status in predicting EBV antibody titers in 10–20-year-olds in Samoa. *Faalavelave* is a system of public, formalized gift exchange in Samoa, and the financial and social debts associated with *faalavelave* are a significant source of stress (McDade 2003a).

associated with increased EBV antibodies, although socioeconomic status was a moderator of this effect (**Figure 5**) (McDade 2003a). An additional series of analyses has explored more fine-grained, individual-level models of culture change and stress (McDade 2002, McDade & Worthman 2004). This work has been significant in demonstrating the feasibility of studying stress and immune function in non-Western, nonclinical settings and in underscoring the importance of cultural factors in defining the experience of stress.

It is not clear why, in an evolutionary sense, psychosocial stress should suppress immune defenses, particularly because stressful circumstances may be associated with greater risks of infection and/or injury. Psychoneuroimmunology has addressed this question in mechanistic terms, focusing largely on the dual role of cortisol as a central component of the physiological response to stress and as a potent immunosuppressive agent (Munck & Guyre 1991). Given the costs of immunity, suppressing immune activity under times of stress may serve the adaptive function of freeing up limited resources for more pressing metabolic demands (Maier et al. 1994,

Sapolsky 1994, Sheldon & Verhulst 1996). Alternatively, cortisol-mediated immunosuppression may reflect an important regulatory mechanism that prevents immune responses from getting out of control, thereby reducing the risk of self-reactivity and autoimmunity in times of stress (Raberg et al. 1998).

In sum, psychosocial factors have direct effects on multiple parameters of human immune function. Stress is an inevitable part of human experience, and current research in PNI has built a solid foundation upon which a more contextualized, cross-cultural approach can be constructed.

Political Ecology

Just as cultural factors are defining components of the ecologies of human immune function, regional as well as global political and economic processes inform the local cultural ecology. Broader political-economic structures—and individuals' positions within them—limit access to nutritional and economic resources, condition probabilities of pathogen exposure, motivate patterns of

reproductive behavior, and impose differential burdens of psychosocial stress.

There are substantial challenges associated with linking macro- and microlevel processes, and a political ecology of immune function has yet to be elaborated. A recent analysis takes a step in this direction by proposing that increased consumption of processed foods produced and distributed by the global food industry may modify immune reactivity and therefore contribute to rising rates of allergy and autoimmune disease (Cone & Martin 2003). In addition, although the epidemiologic triad of host, pathogen, and environment has guided public health approaches to infectious disease, critical medical anthropology has emphasized that economic, social, and political factors are the ultimate causes of disease (Farmer 1993, Turshen 1984). A political ecology of immune function can draw on these conceptual and analytic tools and contribute to the new biocultural synthesis that attempts to integrate political-economic factors into the study of human biology and adaptation (Goodman & Leatherman 1998).

TOWARD A HUMAN ECOLOGICAL IMMUNOLOGY

The ecologies of human immune function are multiple: Central aspects of immune development and function are responsive to a range of nutritional, pathogenic, reproductive, and social factors. However, research in each of these areas has proceeded in relative isolation. A fuller understanding of the contextual factors shaping human immunity requires a more comprehensive, multidimensional approach (Figure 6). Despite significant methodological and conceptual challenges, there are several advantages to such an approach.

First, an integrated perspective mirrors the overlapping nature of real-world environments. Although laboratory or clinic-based research can isolate specific variables of interest, psychosocial and ecological stressors are rarely discrete. For instance, undernutrition and infectious disease frequently go hand

in hand. Food insecurity may be a significant source of psychosocial stress, as well as a contributor to malnutrition. Reproductive behavior may be associated with patterns of pathogen exposure. Simultaneous consideration of these factors represents the reality of the environments in which we live and that shape human immune function.

Second, simultaneous consideration of multiple ecological factors is consistent with the fact that physiological systems integrate information across multiple sources. For example, as noted above, the hypothalamic-pituitary-adrenal axis, and its primary end product, cortisol, are important mediators of the association between psychosocial stress and immune function. However, cortisol also plays a critical metabolic role in mobilizing energetic resources, and concentrations increase with undernutrition (Sapolsky 1994). Furthermore, cortisol production is upregulated following infection (Munck & Guyre 1991). Testosterone and estradiol—primary products of the hypothalamic-pituitary-gonadal axis—may mediate trade-offs between investment in immune function and reproductive effort (Bribiescas 2001, Campbell et al. 2001), but their physiological activity is also affected by psychosocial stress, nutritional status, and infection (Ellison 2001, Sapolsky 1994). The point here is that multiple ecological factors affect immune function through shared mechanisms, and these mechanisms are in turn sensitive to a variety of ecological factors. Although the simultaneous consideration of the immunological impact of nutritional, pathogenic, psychosocial, and/or reproductive factors adds considerable complexity, it reflects the complexity of the underlying physiology that transduces ecological information into physiological action.

Third, an integrated approach encourages investigation of interactions across ecological domains. For example, the extent to which undernutrition exacerbates, or overwhelms, the impact of psychosocial stress on immune function is currently unknown. Current research in psychoneuroimmunology avoids

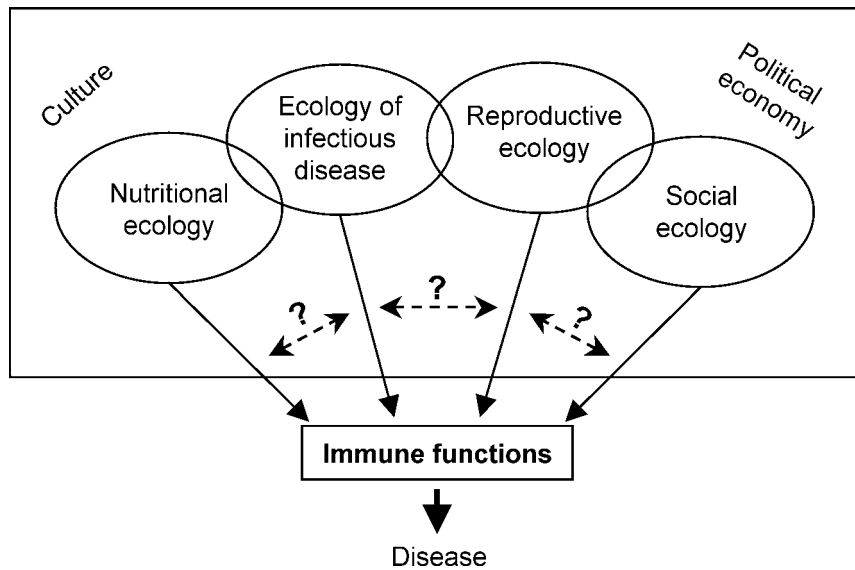


Figure 6

A conceptual model for human ecological immunology. Overlapping ecological factors are embedded in broader cultural and political-economic contexts and have direct effects on immune development and function. Interactive effects are also likely but have yet to be fully investigated.

this question by conceptualizing undernutrition as a nuisance factor that must be controlled for by focusing exclusively on healthy individuals. As with other physiological measures that are responsive to multiple exogenous factors (e.g., blood pressure), there is no a priori reason why population-level analyses cannot model the simultaneous effects of multiple physical as well as psychosocial stressors on human immune function. The nature of interaction across these domains then becomes an interesting empirical question. For example, does undernutrition obscure

the immunosuppressive effects of psychosocial stress, or are their joint effects additive or multiplicative?

A foregrounding of development will be important to an integrated ecological perspective since the immune system may be more or less sensitive to various ecological inputs at different life stages (Figure 7). Current research suggests that nutritional and pathogenic factors are particularly critical early in life, whereas reproductive trade-offs are not likely to emerge until adolescence. Psychosocial stress is important

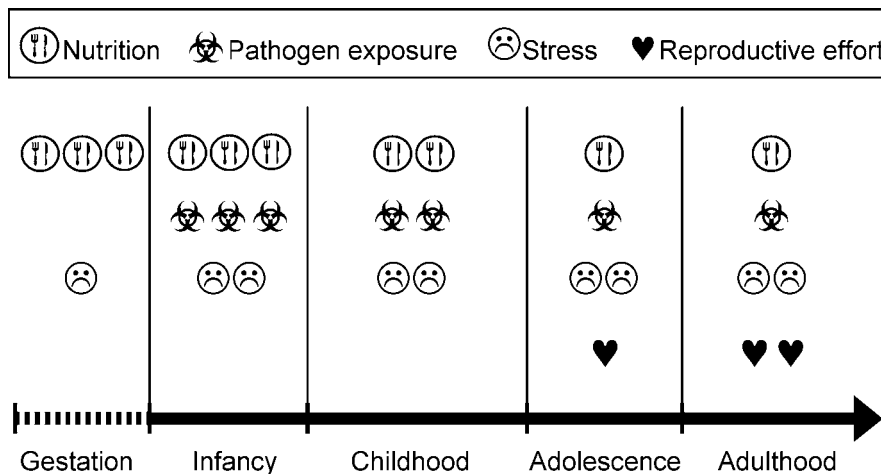


Figure 7

The relative impact of different ecological factors on immune function at multiple developmental stages.

Life history theory:

a branch of evolutionary theory that emphasizes the life cycle and that attempts to explain variation in reproductive and developmental strategies (and related traits), both within and across species

throughout life, although organizational effects may occur early in life. At this point, the relative strength of these effects must be regarded as speculative because they have yet to be evaluated simultaneously. In addition, different factors may be more or less relevant to specific subsystems of immune defense, and circumstances early in life may condition sensitivity to ecological stressors later in life. Regardless, as human ecological immunology moves forward it will be important to keep developmental issues in mind.

Last, human ecological immunology can proceed as a purely descriptive endeavor, or it can draw on theory to guide hypothesis testing and interpretation. Life history theory has provided such an adaptationist framework for a growing body of avian research (Moller et al. 1999, Sheldon & Verhulst 1996, Zuk et al. 1995), and human ecological immunology may profit from its application as well. With its emphasis on strategies for the optimal allocation of limited resources, life history theory can suggest testable hypotheses regarding trade-offs in investment in immunity at various life stages (McDade 2003b). It can also help identify the culturally mediated behaviors and settings most likely to set the parameters for these trade-offs. A grounding in life history theory provides a basis for anticipating and explaining—not just describing—the associations among cultural ecological factors and human immune function.

CONCLUSION

The human immune system—like other physiological systems—is a product of natural selection and is responsive to the contingencies of the surrounding nutritional, pathogenic, reproductive, and psychosocial environments in which it develops and functions. A population-level, cross-cultural, adaptationist approach is therefore a necessary complement to the cellular and molecular levels of analysis currently favored by biomedical immunology. Just as previous research in reproductive ecology has led to conceptual and physiolog-

ical insights into the dynamics of human reproduction (Ellison 2001), human ecological immunology promises to make similar contributions to our understanding of this multifaceted system of defense.

Research in human ecological immunology is in its earliest stages and will face considerable challenges as it progresses, not the least of which is the complexity of immune function and its assessment. This is, however, a surmountable obstacle because a number of robust field methods are currently available, and the range of options will increase with future technological innovations.

An important first step will be the application of these methods across a wide range of populations to investigate the degree of variation in major parameters of immunity. Such variation may challenge current definitions of “normal” immune function based on research in overnourished, underinfected Western populations and will provide a foundation for testing hypotheses regarding the relative contributions of multiple ecological factors. Conceptual and analytical tools borrowed from life history theory can be used to construct an adaptationist framework that will encourage the development of human ecological immunology as an explanatory, rather than merely descriptive, endeavor. Attention to cultural and political-economic processes will further increase explanatory power and acknowledge their fundamental contribution to human behavior, biology, and health.

Biological anthropology is in an excellent position to play a major role in this effort. Development, human variation, and adaptation are central concepts, with an emerging emphasis on the underlying physiological processes that link cultural and ecological contexts with developmental and health outcomes (Dressler 1995, Goodman & Leatherman 1998, Panter-Brick & Worthman 1999). In addition, a longstanding tradition of fieldwork has encouraged the application of innovative methods that are amenable to the constraints of population-level, community-based research in remote settings (Ellison

1988, Worthman & Stallings 1997). We currently possess the theoretical and methodological tools to develop human ecological

immunology as a thriving area of investigation that makes important contributions to anthropology, immunology, and beyond.

SUMMARY POINTS

1. The immune system is a product of natural selection, and a population-based, adaptationist, ecological perspective is a necessary complement to current biomedical perspectives that emphasize clinical and molecular levels of analysis.
2. There are trade-offs associated with investment in immunity, and a consideration of costs as well as benefits across a range of ecological settings may help explain patterns of variation in this complex physiological system.
3. Immune function is context-dependent: There are multiple mechanisms through which the immune system incorporates information from surrounding ecological factors to inform its development and function.
4. Nutritional resources, patterns of pathogen exposure, reproductive behavior, and psychosocial stress are all critical determinants of immune development and function, and together they comprise the cultural ecology of human immunity.
5. Current research considers these ecological factors in isolation, but an integrative, developmental approach is needed to promote human ecological immunology as an active area of research that can make important contributions to anthropology as well as immunology.

UNRESOLVED ISSUES/FUTURE DIRECTIONS

1. The complexity of the immune system is a significant obstacle to its measurement—particularly in field settings—and additional work is needed to validate methodological tools for assessing and interpreting parameters of immune function.
2. The measurement of immune parameters across a wider range of populations is needed to determine the degree of variation in these parameters, and to establish a foundation for formulating hypotheses regarding the relative contributions of ecological factors to explaining this variation.
3. Theoretical and conceptual tools—possibly borrowed from life history theory—will be necessary to develop human ecological immunology as an explanatory, rather than merely descriptive, endeavor.

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