Early environments and the ecology of inflammation

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Recent research has implicated inflammatory processes in the pathophysiology of a wide range of chronic degenerative diseases, although inflammation has long been recognized as a critical line of defense against infectious disease. However, current scientific understandings of the links between chronic low-grade inflammation and diseases of aging are based primarily on research in high-income nations with low levels of infectious disease and high levels of overweight/obesity. From a comparative and historical point of view, this epidemiological situation is relatively unique, and it may not capture the full range of ecological variation necessary to understand the processes that shape the development of inflammatory phenotypes. The human immune system is characterized by substantial developmental plasticity, and a comparative, developmental, ecological framework is proposed to cast light on the complex associations among early environments, regulation of inflammation, and disease. Recent studies in the Philippines and lowland Ecuador reveal low levels of chronic inflammation, despite higher burdens of infectious disease, and point to nutritional and microbial exposures in infancy as important determinants of inflammation in adulthood. By shaping the regulation of inflammation, early environments moderate responses to inflammatory stimuli later in life, with implications for the association between inflammation and chronic diseases. Attention to the eco-logics of inflammation may point to promising directions for future research, enriching our understanding of this important physiological system and informing approaches to the prevention and treatment of disease.

cardiovascular disease | developmental origins of health and disease | ecological immunology | evolutionary medicine

These days, inflammation is much maligned. Several studies have implicated inflammation in the etiology of a wide range of diseases of aging, including diseases of the cardiovascular, metabolic, musculoskeletal, nervous, and immune systems. Underscoring this point, on its cover in 2004, *Time* magazine labeled inflammation "The Secret Killer" (1). There is some irony in this label, because inflammation comprises a critical line of defense against infection, and without this protection, even minor injuries or infections can become potentially life-threatening.

This paper attempts to reconcile these views by considering both the costs and the benefits of inflammation from the perspective of comparative human biology. Although typically studied under controlled, circumscribed environmental conditions, the human immune system shows considerable developmental plasticity and functional variation across individuals and populations. Inflammation is no exception, and attention to the eco-logics of inflammation—principles related to developmental plasticity and ecological contingency that inform its organization and function—may advance scientific understandings of the regulation of inflammation and its impact on human disease.

Contrasting Approaches to the Study of Inflammation and Disease

C-reactive protein (CRP) is a prototypical acute-phase protein and commonly measured biomarker of inflammation (2). The recent advent of highly sensitive laboratory assays for CRP has led to the discovery that chronic low-grade inflammation—levels of inflammation previously thought to be inconsequential—may contribute to the pathophysiology of a wide range of diseases of aging, including cardiovascular disease (CVD) (3), type 2 diabetes (4), metabolic syndrome (3), and late-life disability (5) as well as all-cause mortality (6). As a result, CRP is increasingly measured in clinical and epidemiological settings, and recent consensus guidelines recommend CRP > 3 mg/L as the cutoff point to identify individuals at high risk for cardiovascular disease (7). These guidelines, however, are based on data from European and European-American populations, where approximately one-third of adults have CRP > 3 mg/L. The use of these guidelines for other demographic groups is not well-established.

This conceptualization of inflammation as a chronic phenomenon contributing to diseases of aging is relatively new. For nearly 2,000 y, since Celsus first articulated calor, rubor, tumor, and dolor as the four cardinal signs of inflammation (8), inflammation has been understood as a critical component of innate immune defenses against infection and injury. Acute activation of inflammatory processes after pathogen exposure is rapid—within hours—whereas more specific adaptive immune processes (mediated by T and B lymphocytes) take several days to come on line (9).

Biochemical mediators of inflammation like CRP play important roles in activating complement, promoting phagocytic activity, and opsonizing bacteria, fungi, and parasites (2). Trace amounts of CRP are normally detectable in circulation, and concentrations increase by several orders of magnitude as part of the acute-phase response to infection. Because the acute-phase response is stimulated by a wide range of pathogens, prior research has measured CRP as a nonspecific indicator of clinical or subclinical infection, with values above 5 or 10 mg/L commonly used to identify acute-phase activity (10, 11). This line of thinking has been in place since 1930, when CRP was first described as a pattern recognition molecule that reacted with C-polysaccharide of the cell wall of *Streptococcus pneumoniae* bacterium (12).

Thus, we have two perspectives on the complex associations among inflammation and disease (Fig. 1). The acute-phase approach emphasizes short-term elevations in inflammatory mediators like CRP as adaptive responses to pathogenic challenge that are necessary to protect us from infectious disease. In contrast, the chronic low-grade inflammation perspective assumes that individual differences in CRP levels are stable over time and that elevated concentrations of CRP—above 3 mg/L but below levels thought to be attributable to acute infectious events—contribute to the development of diseases of aging like CVD. These perspectives are typically applied in distinct epidemiological universes. A focus on acute-phase responses has predominated in lower-income nations to investigate inflammatory responses to endemic infectious diseases, whereas the conceptualization of inflammation as a chronic process that contributes to diseases of aging has

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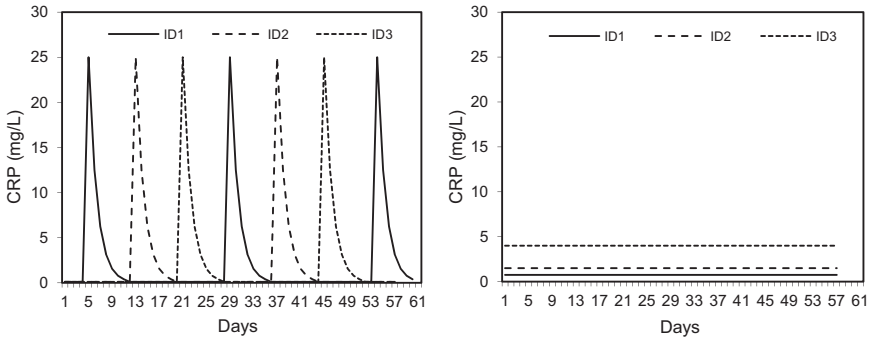

Fig. 1. Hypothetical pattern of CRP production over 8 wk for three individuals according to the acute-phase (*Left*) and chronic low-grade (*Right*) approaches to the study of inflammation and disease.

emerged in affluent industrialized settings, where life expectancies are relatively high and burdens of infectious disease are lower.

A more comprehensive understanding of inflammation may be gained by bridging these perspectives. Although the acute-phase and chronic low-grade approaches both focus on inflammation as a critical physiological process with links to disease, they have proceeded as parallel lines of research pursued by distinct teams of investigators in different epidemiological settings with divergent conceptual and empirical goals. Both lines of research have proven productive, but a more convergent approach may cast new light on the range of variation in key inflammatory processes and reveal the origins and implications of this variation.

Ecological Variation and Developmental Plasticity in the Human Immune System

Inflammation is one part of a larger network of immune defenses, the primary function of which is to provide protection from the ubiquitous bacteria, viruses, and parasites that share our world. The immune system is also centrally involved in cellular renewal and repair, and thus, it plays critical roles in wound healing and protection against cancer. Not unlike the nervous system (13), central aspects of the immune system are relatively undifferentiated early in development, with functional organization and complexity emerging over time through a process of engagement with expectable inputs from the environment. Both systems use developmental processes that learn about the external world, represent this information internally, and calibrate somatic investments in ways that optimize functionality within the constraints of a given environment (14, 15).

Ecological contingency in immune development is seen most clearly in clonal selection, where the process of immune development and maturation depends on interaction with antigens from the environment to adapt an individual's specific lymphocyte repertoire to the local disease ecology (9). However, the context-dependent nature of immune development extends well beyond clonal selection (15). For example, higher burdens of infectious disease in infancy increase the strength of the antibody response to typhoid vaccination in adolescence (16), suggesting a higher overall level of investment in specific immune defenses in high pathogen environments. In addition, low levels of infectious exposure in infancy have been associated with increases in Th2 cytokine production and total IgE concentration (17–19), a pattern of immune development that promotes allergic, atopic, and autoimmune diseases later in life. Research on the hygiene hypothesis has shown repeatedly that microbial exposures in infancy shape the development of immune regulatory networks in ways that are important for limiting immunopathological processes (20, 21), with recent findings pointing to potentially important roles for the human gut microbiota (22).

Prenatal and early postnatal nutritional environments also have lasting effects on human immunity. For example, infants born small for gestational age—indicating a relatively impoverished prenatal nutritional environment—are less likely to respond to vaccination in adolescence, have higher total IgE, and produce lower concentrations of thymopoietin, a thymic hormone important for cell-mediated immunity (16, 18, 23). In addition, slow rates of growth in infancy—likely indicative of inadequate postnatal nutrition—are associated with reduced vaccine responsiveness and thymopoietin production in adolescence (16, 23). These findings build on early research with animal models, showing that undernourished rats give birth to offspring with immune deficiencies that last into adulthood, although the offspring had unrestricted access to food (24, 25).

Psychosocial factors are also an important part of the ecology of human immune function (26, 27). The impact of stress on multiple aspects of immunity is well-established, and it has been investigated primarily in adulthood. The few studies conducted with children and adolescents indicate significant adverse impacts as well (28–30), whereas experimental research with nonhuman primates suggests that maternal stress during pregnancy and maternal separation in infancy have substantial effects on offspring immune function that persist beyond infancy (31, 32). Recently, neglect or abuse in early childhood has been associated with reduced cell-mediated immunity and increased inflammation in adolescence and young adulthood (33, 34). Similarly, low socioeconomic status early in life predicts elevated CRP among adults (35) as well as increased proinflammatory and decreased antiinflammatory gene expression (36).

In sum, emerging evidence shows considerable variation and plasticity in human immune development and function, and it points to aspects of the nutritional, microbial, and psychosocial ecology in infancy and early childhood as important determinants of an individual's immunophenotype. However, current research in biomedical immunology focuses primarily on the cellular and molecular mechanisms coordinating immune defenses using animal models and clinic-based patient populations, and it rarely applies longitudinal, life-course research designs. In contrast, an ecological, developmental approach recognizes that the immune system—like other physiological systems—develops and functions in whole organisms that are integral parts of their surrounding environments (14, 37). To the extent that ecological factors are relevant to inflammatory phenotypes, research on the regulation of inflammation may benefit from such an approach.

Early Environments and the Eco-Logics of Inflammation

In terms of human history, people living in contemporary industrialized environments enjoy unprecedented access to calorie-dense foods, low demands for physical exertion and energy expenditure, and regimens of sanitation and hygiene that have reduced—by orders of magnitude—the frequency and diversity of microbial

exposures (38, 39). In particular, saprophytic mycobacteria, lactobacilli, and many helminthes common in rotting vegetable matter, soil, and untreated water represent disappearing classes of microorganisms that have been part of the human and mammalian environment for millennia and are generally treated as harmless by their hosts (40). Of course, there is substantial heterogeneity in nutritional and microbial environments within contemporary industrialized nations, much of it structured by socioeconomic and geographic factors. However, this heterogeneity is relatively circumscribed compared with the qualitative shifts that have, on average, led to substantial caloric surpluses and reductions in contact with microorganisms.

Because the human immune system evolved in environments with marginal nutritional status and substantially higher levels of microbial exposure, it is reasonable to ask whether overnourished, underinfected industrialized populations capture the full range of variation that is necessary to understand the determinants of inflammatory phenotypes (14, 41, 42). In light of the key role of inflammation in antipathogen defenses and the importance of early environments in shaping the development and function of the human immune system, comparative research across different ecological settings is needed to generate insights into the complex associations among early environments, regulation of inflammation, and disease.

This logic has motivated us to conduct a series of studies in environments with higher levels of infectious disease, including the Philippines and lowland Ecuador. The Philippines is a lower middle-income nation with relatively low but rising rates of overweight/obesity, CVD, and metabolic syndrome (43, 44), and we have drawn on data from the ongoing Cebu Longitudinal Health and Nutrition Survey (CLHNS) to investigate the predictors of inflammation in this environment. Infectious disease continues to account for more than 30% of all mortality in the region, and respiratory infections rank beside ischemic heart disease as the top causes of death (45). Despite an ongoing legacy of infectious disease, one-quarter to one-third of Filipino adults are now overweight or obese (43, 44).

The Ecuadorian Amazon is home to the Shuar, an indigenous group living in small villages across scattered clusters of households that pursues a subsistence strategy based on horticulture, hunting, and fishing (46). Electricity and running water are not available, and the Shuar have very limited access to Western medicines or healthcare. Acute respiratory infection, gastrointestinal illness, and vector-borne disease are the primary sources of morbidity, with rates of mortality caused by infectious disease that are more than five times higher than the United States and Canada (47, 48). In contrast, the cardiovascular and metabolic risk profiles of Shuar adults are relatively favorable compared with adults in industrialized nations (49).

Among young adults in the Philippines (20–22 y), median CRP is exceptionally low at 0.2 mg/L compared with 0.9 mg/L for age-matched adults in the United States (50). Plasma samples were analyzed in a clinical facility in the United States using a gold-standard high-sensitivity CRP assay; therefore, differences in laboratory protocols are not likely to account for this discrepancy. Similarly, older women in the Philippines (35–69 y) have higher median CRP at 0.9 mg/L, but this concentration is still substantially lower than 2.02 mg/L, the median CRP for older American women (51). Additionally, in lowland Ecuador, median CRP for adults ages 18–50 y is 0.5 mg/L, despite a prevalence of infectious disease that is even higher than the Philippines (52).

Why do populations with higher burdens of infectious disease seem to have lower baseline levels of CRP? Given that inflammation is an important component of innate immune defenses, this association represents something of a paradox. In the Philippines and Ecuador, adults are relatively thin compared with US adults, and because visceral adipose tissue is an important source of proinflammatory cytokines like IL-6 (53), lower levels of body fatness could account for lower inflammation. This does not seem to be the case. In our Cebu cohort, median waist circumference for women is 66.5 cm compared with 85.0 cm for young adult women in the United States. However, when we restrict our analysis to women with waist circumferences between 70 and 80 cm—a range of values with substantial overlap across the populations—median CRP for women in Cebu is only 0.3 mg/L compared with 0.7 mg/L for US women (50). We found similar differences in the association between skin-fold thickness and CRP in men across the two populations (skin-fold thickness was the only adiposity variable significantly associated with CRP among men in Cebu). As such, low CRP in the Philippines cannot be explained away by the lower levels of overweight/obesity relative to populations like in the United States. Rather, these results suggest that the relationship between body fat and inflammation may differ across populations.

Similarly, genetic differences are another potential source of variation in CRP within and between populations (54), but they cannot account for lower concentrations of CRP in the Philippines. We recently reported that the frequency and pattern of associations between several SNPs and CRP in young and older adults in the Philippines are consistent with prior research in populations of European ancestry (55, 56). The proportion of explained variance in CRP attributable to direct genetic influences was small (4.8–5.6%), with evidence that the level of microbial exposure in the household environment moderated the effects of some of these genes. These results suggest that similar genetic influences operate across populations, their influences on inflammation are environmentally contingent, and differences in genetic background are not likely to be primary determinants of low CRP in the Philippines.

Rather, converging lines of evidence point to the potential importance of early environments in shaping inflammatory phenotypes, with implications for population differences in patterns of CRP production in adulthood. Based on prior research showing the importance of nutritional and microbial exposures to immune development in particular, one might hypothesize that these factors

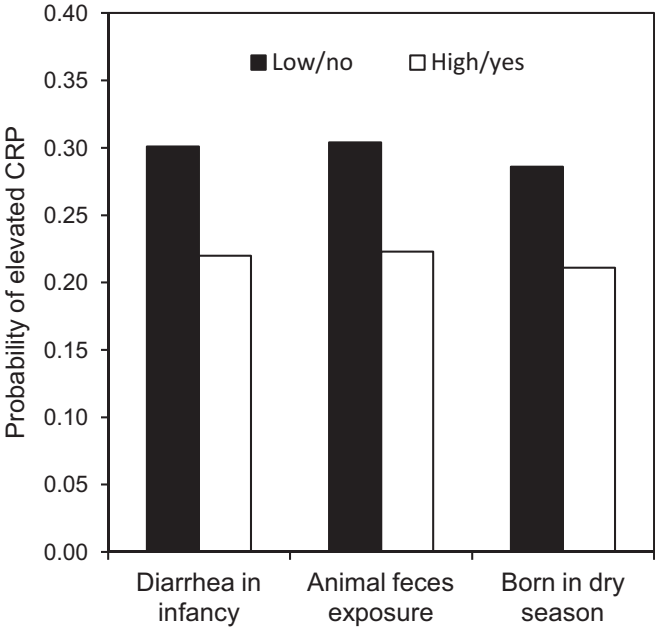

Fig. 2. Association between microbial exposures in infancy and probability of elevated CRP in young adulthood in the Philippines. Results are based on predicted probabilities from the fully adjusted logistic regression models reported in ref. 57. Low and high values for predictors were set as follows: diarrhea (zero to three or more episodes), animal feces exposure (zero to three or more intervals), and born in dry season (no or yes). Original values were retained for other variables in the model.

are significant predictors of inflammation in adulthood. We find support for this hypothesis within the Philippines, where birth weight is negatively associated with CRP in young adulthood (57), similar to results from other cohorts outside the Philippines (58, 59). However, birth weight is not likely to account for population differences in average CRP concentration between the Philippines and the United States. Because average birth weights in our sample were almost 400 g lower than average birth weights in the United States in 1983 (60), CRP concentrations should be, with all other factors being equal, higher in the Philippines than in the United States.

When the CLHNS began collecting data in the early 1980s, Filipino families in Cebu lived in a wide range of settlements, including rural towns and remote outlying areas as well as dense urban areas with affluent neighborhoods and poorly constructed squatter camps (61). Approximately one-half of the homes in the study had electricity, more than three-quarters of families collected water from an open source, less than one-half of families used a flush toilet, and more than one-half of families had animals (e.g., dogs, chickens, goats, or pigs) roaming under, around, or in the house. The level and intensity of exposure to infectious microbes were relatively high, and episodes of diarrhea were frequent when the cohort was in infancy (62, 63). There was also significant variation in exposure within the sample, because participants were drawn from households across settlement types and the full range of socioeconomic conditions in Cebu. Furthermore, because there is substantial seasonal variation in rainfall that is associated with pathogen transmission and infectious morbidity in Cebu (62, 63), month of birth contributes to additional variation in infectious exposures in infancy. These factors make CLHNS an ideal dataset with which to test the hypothesis that infectious exposures in infancy may have lasting effects on the regulation of inflammation in adulthood.

Support for this hypothesis comes from three distinct measures of infectious exposure in infancy (Fig. 2). Higher levels of animal feces in the home, more frequent episodes of diarrhea, and birth during the dry season each predicted lower CRP as a young adult (57). The magnitude of these associations was substantial. Moving from the highest to the lowest levels of diarrhea morbidity and exposure to animal feces, the probability of elevated CRP increased by a factor 1.4, whereas individuals born in the dry season were one-third less likely to have elevated CRP as a young adult. Births in the dry season were followed by a higher frequency of infectious disease in the first 12 mo than births during other parts of the year, indicating higher levels of microbial exposure in early infancy.

Negative associations between microbial exposures in infancy and inflammation in adulthood are broadly consistent with the hygiene or old friends hypothesis, in which low levels of microbial exposure early in life bias immune development and regulatory processes in ways that increase the likelihood of inflammatory conditions such as allergy, asthma, and autoimmune disease later in life (64–66). Frequent but transient encounters with microbes in the local environment may be important in this process, and/or local environments may influence the structures of resident microbial communities in the human gut and on mucosal and skin surfaces that have lasting effects on immune development (22, 67). The cellular mechanisms underlying these processes are not clear, but they likely involve regulatory T cells and the balance of pro- and antiinflammatory cytokine production and related intracellular signaling pathways (40, 65). Epigenetic modifications to genes involved in these processes represent a viable molecular mechanism through which microbial exposures in infancy may have a durable impact on inflammatory phenotypes (68, 69), particularly because prior research has documented substantial between-individual variation in the methylation status of genes involved in inflammation (70). The developmental and environmental factors contributing to this variation have yet to be explored.

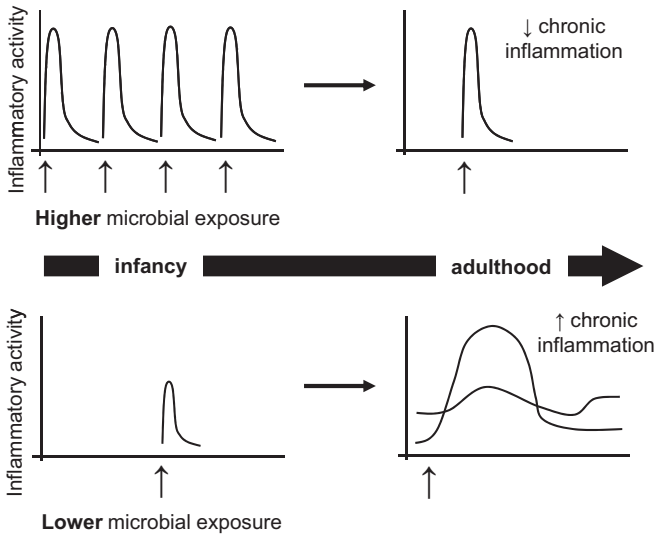

Fig. 3. Conceptual model of the association between microbial exposure in infancy and regulation of inflammation in adulthood. The arrow from infancy through adulthood represents developmental time. *Upper* applies to environments with higher levels of microbial exposures; *Lower* describes low-infection, highly hygienic environments.

Conceptually, one might hypothesize that microbial exposures play important roles in the establishment of effective regulatory networks during sensitive periods of immune development in infancy. Less hygienic environments increase the frequency and diversity of microbial inputs, which result in more frequent bouts of acute inflammation (Fig. 3). Repeated activation and deactivation of inflammation promotes the development of more competent regulatory pathways, which can effectively turn inflammation on when it is needed and off when it is not needed. To the extent that these pathways become established and carried forward, inflammatory stressors in adulthood are handled in a similar manner. Inflammatory responses ramp up quickly, and antiinflammatory processes keep the responses under control.

Conversely, more hygienic environments minimize the frequency and intensity of microbial exposures in infancy, limiting opportunities for the activation and deactivation of inflammatory pathways during critical periods of immune development. The result is a more proinflammatory phenotype. When inflammatory stressors are encountered in adulthood, proinflammatory pathways are readily activated, but effective counterbalancing antiinflammatory regulatory networks are not in place to prevent overblown, lingering, or chronic levels of activity.

It seems reasonable to conclude that a tightly regulated inflammatory system would confer substantial advantages over a less responsive system. Infectious threats to self are confronted quickly and effectively with a robust response, but collateral damage to self is minimized by actively down-regulating responses after resolution. Like many other experience-based neural and physiological systems (13, 71, 72), active engagement with the environment during critical stages of development is necessary to achieve this functional state. In the case of immune/inflammatory systems, microbial exposures seem to be important, expectable inputs that have been a normal part of the human environment for millennia. Natural selection could not anticipate the highly sanitized, low-infectious disease environments currently inhabited by humans in affluent industrialized settings, and a poorly educated immune system may be the result.

Support for an Eco-Logical Model of Inflammation

Is there an eco-logic to inflammation? Do principles related to developmental plasticity, ecological contingency, and experience-

based biology help resolve the paradox of low baseline CRP concentrations in high infectious disease environments? Might our understanding of how inflammation is regulated and how inflammation provides protection against some diseases but contributes to others be advanced by a comparative, developmental perspective that foregrounds ecological factors as drivers of functional variation?

Our findings from the Philippines point to early environmental factors as critical determinants of the dynamics of inflammation in adulthood, and circumstantial evidence for the importance of early microbial environments in shaping inflammatory phenotypes also comes from rising rates of allergic and autoimmune diseases over the past three decades, particularly among lower-income nations, where rates of these diseases tend to increase after economic development (40, 42). One might also interpret the divergent patterns of association between body fat and CRP discussed above in this light. If effective antiinflammatory networks are in place in environments like the Philippines, then perhaps they provide a counterbalancing influence when proinflammatory pathways are activated by excess body fat.

However, more research on the levels and regulatory dynamics of inflammation across ecological and epidemiological settings is needed. To that end, we have conducted three additional studies in the Philippines and Ecuador that highlight variability in key inflammatory processes and provide additional support for the hypothesis that early environments shape the regulation of inflammation in adulthood.

Vaccine Responsiveness in Adolescence Predicts CRP in Young Adulthood. In 1998–1999, when members of the Cebu cohort were 14–15 y old, we administered a typhoid vaccine to a subset of study participants to investigate the long-term effects of early environments on immune function. We measured the antibody response to vaccination as a functional marker of immunocompetence, and we found that prenatal undernutrition and low infectious morbidity in infancy were both associated with reduced responses to vaccination (16).

Parallels between this study and our more recent analysis of the early-life predictors of CRP suggest that microbial and nutritional exposures may initiate a more fundamental shift in the development and regulation of immunity. We explored this possibility by investigating whether antibody response to vaccination in adolescence was associated with CRP measured 7 y later in young adulthood. The results were striking: median CRP was more than four times higher in 2005 among individuals who did not respond to the vaccine in 1998–1999 (73). For nonresponders, median CRP was 0.8 mg/L compared with 0.2 and 0.1 mg/L for mild and robust responders, respectively.

These results suggest that the same set of early-life nutritional and microbial exposures that promote the development of more robust antibody-mediated immune defenses also influence the pathways involved in the regulation of inflammation, resulting in lower levels of chronic low-grade inflammation in adulthood. An alternative possibility is that early environments have a direct effect on adaptive immune defenses only, with secondary consequences for inflammation, or that the negative association between vaccine responsiveness and CRP production represents a tradeoff in the allocation of resources to different subsystems of immune defenses during development (14).

Regardless of the particular pathways involved, these results underscore the role that environments in infancy play in shaping multiple aspects of an individual's immunophenotype, and they point to the importance of microbial exposures in promoting more robust specific immune defenses as well as lower levels of chronic inflammation. Conversely, nutritional deprivation during sensitive periods in infancy may impede these processes, aside from the level of microbial exposure.

No Evidence for Chronic Low-Grade Inflammation in Lowland Ecuador. The hypothesis that chronic inflammation contributes to diseases of aging depends on a model of inflammation in which individuals reliably differ in their level of inflammatory activity. Prior research on the biovariability of CRP has largely validated this assumption, with some individuals showing consistently higher CRP levels than others across multiple time points (74, 75). This pattern is apparent in the United States, but is a similar pattern evident in environments with higher levels of infectious disease? Are inflammatory pathways constantly activated because of a lifetime of exposure to infectious microbes, or have these exposures led to the development of more tightly controlled inflammatory responses?

We sought to answer these questions by documenting the pattern of CRP variability in lowland Ecuador (52). We collected blood samples from 52 adults over four weekly intervals, and during this time, almost two-thirds of the participants reported at least one episode of infectious disease. Several individuals had CRP > 3 mg/L at one time point, indicating high risk for CVD based on current consensus guidelines (7). However, no individual had CRP > 3 mg/L across two or more sampling intervals, and all but one individual produced CRP values < 1.5 mg/L during the course of the study. This pattern provides a striking contrast to prior analyses in the United States, where a subset of individuals has been shown to reliably produce clusters of high CRP values (74, 75).

These findings underscore the critical importance of multiple CRP measures across time in determining the prevalence of chronic inflammation, particularly in environments with high levels of acute inflammation caused by infectious exposures. A study in this environment measuring CRP at only one time point would be justified in concluding that several individuals had high-risk levels of inflammation, but it would have failed to observe that these same individuals would be categorized as low risk the next week.

The implications for study design are clear, but these results also provide compelling evidence for a distinct pattern of regulation that challenges some assumptions of the chronic low-grade inflammation perspective. Most importantly, we found no evidence for stable between-individual differences in chronic inflammation: Individuals who produced high CRP at one observation also produced exceptionally low values of CRP at other observations. This is a remarkable finding. Of the 52 adults in our study, prior research would lead us to predict that 17 individuals (approximately one-third) would have CRP > 3 mg/L across all observations (7). How can it be that not a single individual had CRP > 3 mg/L across even two or more time points?

IL-6 and perhaps other proinflammatory cytokines are likely involved in up-regulating CRP in response to acute challenges in lowland Ecuador. However, the results bring into relief what seems to be an efficient set of antiinflammatory pathways that turn these responses off and reduce CRP concentrations to very low baseline levels—levels not commonly observed in the United States. We speculate that this distinct pattern of CRP variability traces back to environmental exposures early in life during sensitive periods of immune development. In particular, infectious exposures during these periods may promote the development of regulatory networks—involving antiinflammatory cytokines and/or intracellular signaling pathways—that can effectively down-regulate inflammation to very low levels of activity.

Inflammatory Cytokine Concentrations Differ Across Populations. Consistent with the finding that concentrations of CRP are low in the Philippines, we have reported low concentrations of the proinflammatory cytokine IL-6 compared with prior research (76). The median concentration of 1.0 pg/mL in our sample is among the lowest on record for studies of healthy adults. Conversely and perhaps more importantly, we found exceptionally high concentrations of IL-10: the median concentration of 7.56 pg/mL is more than two times higher than the average baseline value from other studies of healthy adults. This antiinflammatory cytokine suppresses IL-6 production as

well as other proinflammatory pathways (77), and lower concentrations of IL-10 have been associated with increased risk for chronic diseases (4, 78). This pattern of results provides additional evidence for meaningful variation in key aspects of inflammation across populations, and it suggests that the balance of pro- to antiinflammatory signaling may differ in the Philippines, perhaps explaining the exceptionally low concentrations of CRP (50, 57).

Unanswered Questions and Directions for Future Research

If the main thesis of this paper is true, that environmental exposures early in development influence the dynamics of inflammation in adulthood, then the implications for scientific and clinical understandings of the links among environments, inflammation, and disease may be substantial. This section poses three questions for future research that may represent particularly productive applications of an eco-logical model of inflammation.

Do Early Environments Moderate the Effect of Inflammatory Stressors in Adulthood? In the absence of inflammatory stimuli in adulthood, individual differences in regulatory dynamics may have little consequence. However, in the presence of activation, significant differences in patterns or levels of response may emerge. Individual differences in inflammatory phenotype may, therefore, be the key outcome of early environmental exposures, with the level of inflammation and its consequences for health emerging in interaction with inflammatory stimuli in adulthood. Analogous interactions have been reported for other physiological systems, pointing to a more generalized impact of environments early in development in calibrating set points for later responsiveness and function (71).

If early environments moderate the impact of current environments on inflammation, then additional explanatory power may be achieved by explicitly modeling these interactions. For example, perceived psychosocial stressors and depressive symptoms have been positively associated with CRP in the United States (79, 80). Might the effect of stressors on inflammation be modified by prenatal nutritional environments or the intensity of microbial exposure in infancy? Interaction terms or stratified analyses could be applied to test these hypotheses, and based on our results from the Philippines and Ecuador, one might expect that the association between psychosocial stressors and chronic inflammation would be strongest for individuals with lower birth weights or lower levels of microbial exposure in infancy. Recent studies indicating that childhood adversity modifies inflammatory responses to stressors later in life suggest that this life-course approach may be a particularly productive direction for future research (81–83).

Is Inflammation Associated with CVD in High-Infectious Disease Environments? The hypothesis that chronic inflammation contributes to CVD as well as other diseases of aging is not without its skeptics (84, 85), but it has generated considerable empirical support (3–5). However, the vast majority of this support comes from research conducted in affluent settings, where rates of infectious diseases are low and levels of overweight and obesity are high. To the extent that environments like lowland Ecuador and the Philippines represent an infectious disease ecology that was more common globally in the past than today, chronic inflammation might be labeled a disease of affluence, a problem that is unusual by historical standards and has only emerged recently in post-epidemiologic transition populations like the United States. Furthermore, if microbial exposures represent normative ecological inputs that guide the development of several immune processes, including the regulation of inflammation, then it is reasonable to hypothesize that rising rates of CVD and diabetes globally are not just a product of the nutrition transition, but also caused, in part, by regimens of hygiene and changes in lifestyle that have reduced the intensity and diversity of microbial exposures to levels not experienced previously in the history of the human species. The work by Raison et al. (86)—drawing on the cytokine theory of depression—has proposed a similar framework for explaining recent increases in major depressive disorder in high-income nations.

It remains to be seen if a pattern of frequent but acute activation of inflammation—similar to the pattern that we documented in Ecuador—is associated with elevated CVD risk. However, given that acute spikes in CRP were followed by very low levels of CRP, it seems possible that the regulatory dynamics of this inflammatory phenotype are distinct and do not contribute to the initiation or progression of CVD. Consistent with this interpretation, a recent study in rural lowland Bolivia failed to detect a significant cross-sectional association between CRP and atherosclerosis, despite high concentrations of CRP (87). It will be important for future research in international settings to collect multiple measures of CRP (as well as other inflammatory mediators) across time to differentiate acute from chronic inflammation, and to determine whether inflammation contributes to diseases of aging only when it transitions to a more chronic state. These studies should also reveal the ecological and lifestyle factors that bring on this transition in inflammatory phenotype.

Is Inflammation During Gestation a Mechanism Involved in the Intergenerational Transmission of Health? Inflammatory processes are a normative part of human reproduction, playing important roles in ovulation, implantation, gestation, and parturition. For example, CRP is elevated slightly among healthy pregnant women, but dysregulated inflammatory states contribute to preterm delivery and fetal growth restriction (88, 89). The regulation of inflammation during gestation is, therefore, an important determinant of preterm delivery and birth weight, which in turn, has implications for physiological function and health of offspring that last into adulthood. Indeed, current research on the developmental origins of health and disease focuses on the prenatal environment as a critical determinant of cardiovascular and metabolic disease risk in adulthood, and any factor influencing maternal physiology—and by extension, the earliest environment of the next generation—has the potential to have effects that reach into that next generation (90). Inflammation represents a plausible biological mechanism contributing to this cycle, but the factors that influence the regulation of inflammation during pregnancy are not known.

We and others have shown that individuals who were born small have elevated inflammation as adults (33, 57–59). If early environments shape inflammation in adulthood, one might hypothesize that the prenatal environment experienced by a woman will be an important determinant of how she regulates inflammation when she becomes pregnant. Similarly, microbial exposures in infancy and psychosocial stressors in childhood may shape the inflammatory milieu during gestation, with potential effects on the developing fetus. Together, these lines of research motivate additional investigation into inflammation as a potential mechanism for linking environments and health across generations.

Conclusion

Is inflammation a silent killer? Perhaps. However, it is worth asking when in human history and where around the world inflammation has become implicated in the pathophysiology of chronic degenerative diseases. A comparative human biological approach reveals substantial variation in the level and dynamics of inflammation within and across populations, and it points to ecological factors during development as key contributors to this variation. It also reminds us that inflammation plays a central role in innate defenses against infectious disease, even as current research tends to focus on chronic inflammation and diseases of aging. Hopefully, consideration of the eco-logics of inflammation will point to promising directions for future research that advances our understanding of this important physiological system and translates into novel approaches to the prevention and treatment of disease.

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