Chapter 2

Psychoneuroimmunology: The Experiential Dimension

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Abstract

Accumulating evidence has made clear that experience—the knowledge an individual acquires during a lifetime of sensing and acting—is of fundamental biological relevance. Experience makes an impact on all adaptive systems, including the endocrine, immune, and nerve systems, and is of the essence, not only for the unfolding of an organisms' healthy status, but also for the development of malfunctional traits. Nevertheless, experience is often excluded from empirical approaches. A variety of complex interactions that influence life histories are thereby neglected. Such ignorance is especially detrimental for psychoneuroimmunology, the science that seeks to understand how the exquisite and dynamic interplay between mind, body, and environment relates to behavioral characteristics. The article reviews claims for incorporating experience as a member of good explanatory standing in biology and medicine, and more specifically, claims that experiential knowledge is required to enable meaningful and relevant explanations and predictions in the psychoneuroimmunological realm.

Key words: Experience, Microbiome, Umwelt, Development, Evolution, Function, Psychoneuroimmunology, Immune

1. Introduction

Ideas that the nervous, immune, and endocrine systems work in close concert with each other as well as with external inputs were not in high vogue prior to the 1980s. Scientists were still preoccupied with elaborations of the internal workings of the three adaptive systems, and rarely made cross-over connections. That such an integrative effort would be rewarding was, however, highlighted in a 1981 landmark publication entitled Psychoneuroimmunology (1). The book, edited by Robert Ader, consisted of a collection of reviews on emerging work, and made a fascinating but also a challenging reading.

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In the book's foreword, Robert A. Good (2) outlined a research agenda for the integrative efforts that should follow:

> The question that remains is how these three major networks—the nervous system, the endocrine system, and the immunologic system—interact and, how, by understanding these interactions in precise quantitative terms, we can learn to predict and control them (2, p. xix).

In the immediate follow-up article, *Psychosocial factors in infectious disease,* S. Michael Plaut and Stanford B. Friedman (3) additionally stated that psychoneuroimmunology needs to understand how various psychosocial factors of the experiencing subject can modify external challenges. They thus elaborated further on an often observed phenomenon—that not all individuals infected with a certain infectious agent come down with disease—and emphasized that there must be "something more" involved in pathogenesis than just a battle between the infectious agent and the immune system. They made references to results from human studies which demonstrated that the meaning a person attaches to a phenomenon makes an impact on disease outcome, and so claimed that:

> The relevant question is not whether a given disease is caused by a pathogenic agent or by psychological factors, but rather to what extent the disease can be related to each of a number of factors in the history, makeup, and environment of the organism (3, p. 7).

By this claim they highlighted a shift in research focus—not only should scientists investigate why individuals are *susceptible* to illness, they should as well investigate why individuals are *resistant* to disease. The "received view," that infectious agents and psychological stressors are sufficient causes of disease, should therefore be replaced with a more comprehensive and interdisciplinary understanding of causation.

The challenge posed by Plaut and Friedman—that the human organism's life history needs to be included in the explanatory framework—is demanding. For not only did the two researchers claim that the life history should be approached from a scientific viewpoint, it should in addition be approached from the individual's perspective—from the meaning the susceptible person and his adaptive systems attach to precipitating situations. These are hard tasks indeed—for they ask of science more than science is allowed to deliver, the reason being that science in its "craving for generality" actually takes a "contemptuous attitude towards the particular case" (4, p. 18).

This idea can be explicated by way of a dilemma from scientific publishing. On the one hand, editors are reluctant to communicate case reports because cases are subject to a variety of uncontrolled and uncontrollable influences, and so generalization of the individual outcome is a precarious undertaking. On the other hand, editors endorse group-based investigations, because such studies are amenable to strict control and thus generalization. However, as publishers well know—results from group-based investigations lack an important virtue of the case. Individual characteristics and contextual parameters are seldom irrelevant for the outcome, and by treating these as confounders, group-based studies thereby neglect the experiential dimension and thus lose touch with the very individuals they represent.

Even a science that acknowledges the experiential dimension and thus attempts to incorporate experiential parameters in the form of major life events—e.g., divorce, death of a spouse, or serious disease—often fails the task. As highlighted in a critical review, individuals rarely apply the same meaning to a life event (5). Different subjects interpret events differently, and this differential interpretation is a determinant of how individuals respond psychoendocrinologically. The "objective" characteristics of an event, which are foundational in group-based investigations, are thus not objective in a strict sense—they are rather interpreted in an idiosyncratic manner by each different participator.

Knowledge of group characteristics is highly relevant but nevertheless insufficient for understanding the individual, and it thus appears that science needs a theory of the organism that also allows for the emergence of "private" responses. This does not, however, imply that science should become subjective and so comply with the slogan "anything goes." Science's ultimate task is to give objective accounts of nature, also of individual experience. To stay true to its ideal, science should therefore give well grounded *accounts of subjective experience*. *Subjective accounts of experience*, although important for individual behavior, are nevertheless, at least for the time being, outside the scientific realm.

In the following I will provide an exploration of the challenge posed by Plaut and Friedman. In so doing I will invoke the age old dilemma between the one and the many, and investigate how this applies to the objective perspective taken by an external observer and to the subjective perspective of a participant. The importance of the subject's environment, exemplified by the microbial communities of our intestines, will also be highlighted, as will the role of subjective interpretations of environmental stimuli over the life cycle. These deliberations will hopefully reveal the complexity of the experiential challenges facing psychoneuroimmunology.

2. The Meaning of Perception

A good starter for objective appropriation of subjective experiences can be found in the Estonian zoologist Jakob von Uexküll's (1864–1944) elaborations on the individual organism's dealing with nature. When confronted with contemporary views of the organism, Uexküll noted a discrepancy between what he believed was the animal's world—an active organism that interacts with its surroundings in a meaningful manner, and the scientific conceptualization of it—an animal that mechanically adapts its behavior to a given environment. To rectify this incongruity, he set out to build a new biology in which the animal's perspective was retained (6). And in so doing, he came to emphasize the importance of perception. As he saw it, the animal's perceptual perspective is not something gained by passively receiving inputs in the shape of information; rather, it involves an active interpretation of signals rendered meaningful by the animal's previous experiences.

Upon portraying animals as developmental structures with communicative capabilities, Uexküll also came to notify that environmental stimuli are of unequal importance for different kinds of animals. He thus elaborated a distinction between the animal's environment, i.e., its physical surroundings, and the animal's Umwelt—the meaning-carrying structure that contains a "sign or symbol that members of the same species can understand, but that those of another species cannot comprehend" (7, p. 77). Hence, even though animals of different species may share the same environment, their differing Umwelts make them experience the same environment differently.

By emphasizing the animal's perspective, Uexküll reached a surprising insight—environmental signals are already meaningful as they reach the animal. To see how this may come about, one has to think of the couplings between organisms and their surroundings as emerging from activity played out during two distinct temporalities—one during the evolutionary history of the species, when perceptual abilities are being shaped, and the other during the developmental history of the individual, when the same perceptual capabilities are being structured in relation to external inputs.

Perception of the Umwelt thus consists of a phylogenetic component, which allows for a fairly stereotyped pattern of behavior, and an ontogenetic component that serves to diversify and tailor each organism's behavior to the actual environment (Fig. 1) (8).

Although Uexküll initially received many followers, including the ethologist Konrad Lorentz and the philosopher on human experience Martin Heidegger, his work had vitalistic undertones and was therefore regarded unscientific. His emphasis on the qualitative aspects of animal perception and behavior were therefore soon replaced by more quantitative and mathematically oriented theories, and investigations related to the organism's perceptual couplings to the environment were thereby relayed to the background. However, much of this changed in the 1970s when Uexküll's ideas were revitalized by the emerging field of biosemiotics (9), and not the least by neurophysiologists and immunologists who began to reorient their investigations along similar integrative lines. To achieve the most from universalizing investigations, while at the same time avoiding loss of the individual, it would thus be

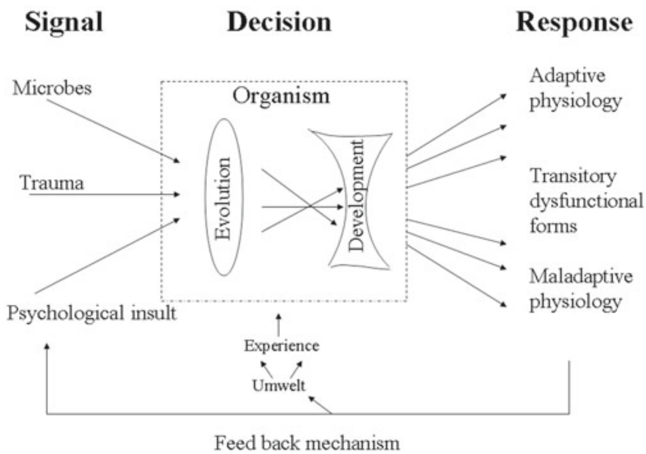

Fig. 1. Each individual is the result of the lineage's adaptive processes during evolutionary time and adaptive processes during developmental time. These two adaptive processes are integrated in every organism. The concave lens depicts the evolutionary resources of the organism, and includes its genetic make-up. The convex lens, in contrast, depicts the developmentally shaped resources of the organism, including the epigenetic make-up and the wirings of the central nervous system, the immune system, and the endocrine system. The Umwelt makes up the context in which the experiences make their impact. Dependent upon how these systems integrate within the organism, the response may turn out as functional or dysfunctional. And, since the organism's responses are in many ways instructive of latter responses, the responses are depicted to feed back to alter both the Umwelt and latter responses to the same or dissimilar challenges.

fruitful to integrate psychoneuroimmunology with the biosemiotic view of the world. But as humans differ from other animals in several respects, the Uexküllian path needs to be adapted to the specific human trajectory and situation.

3. The Human Umwelt

Compared to other mammals and primates, humans differ in several respects. Human life stories are distinguished by having an exceptionally long life span, an extended period of juvenile dependence, and support of reproduction by older postreproductive females as well as by males (10). In contrast to other animals, with the exception of primates, humans also possess specific brain structures that enable them to experience and interpret internal physiological processes (11). When such processes, which may be pain, motion, nausea, thirst or hunger, reach consciousness, they create a subjective experience of own body. Variations in this structure may thus be part of the explanation for the great variation of experience of a given bodily state by different humans (12).

Human beings are also distinguished by having unique psychological characteristics—a capacity for self-reflection, for designing sophisticated symbolic structures, for attaching metaphorical concepts to experiences and for building models and categories with the aid of the imagination. There is thus a creative element in man's dealing with his world—our brains create "a fantasy that coincides with reality" (13, p. 111). And exceptionally—when this reality seems unfit, humans additionally have the capacity to alter the same reality in radical ways during a process termed niche construction (14). Man's Umwelt is thus not only ecological, but also cultural—all the way (15). And as culture is an important part of man's Umwelt, it should not come unexpected that artifacts of culture may act as a selective force, thus feeding back on human beings in a form strong enough to even alter the genome (16). In the same vein, alterations in perception and thought processes feedback on the brain, thus altering neurophysiological and neurochemical activities involved in perception, action, and emotional control (17)—thus *mind matters* in a literal sense.

Man's experiences are not entirely determined by the way the world is—man is himself active in acquisition, selection, interpretation, and organization of the information. And as culture is shaped as a cooperative effort along the generations, the human organism is always and without exception a lived body in which history and biography are woven together with interpersonal meaning as well as individual purpose. While humans create and convey meaning in coexistence with other humans, every person nevertheless interprets experience within his own horizon which only partly coincides with "all the others," even within the same cultural circle or society. Such interpretation does not disappear in reality, even when scientific methodology excludes these elements from the study—and thereby from science (18).

By disregarding experience, science also disregards the effects of culture on human action. Since the meaning of a situation has strong cultural bindings—something regarded as an upsetting event in one culture may go quite unnoticed in another—there are reasons to anticipate a major contribution of culture to variation in psychoneuroimmunological development and function. The habit of including a relatively homogenous group of participants from Western, Educated, Industrialized, Rich, and Democratic (WEIRD) societies in psychoneuroimmunological studies thus effectively precludes the chance of understanding variation across human populations (19). There are even reasons to believe that these WEIRD individuals are amongst the least representative members one could use to generalize across human populations.

4. Restructuring the Explanatory Gap

Human beings come into the world with naturally selected coping mechanisms. And since these mechanisms have evolutionary preconditions, it is a task for science to ask whether or not such preconditions interfere with man's perception of the Umwelt in a true manner.

There are two reasons why this question is important—first, a science that aims to understand humans has to know how humans experience the world and second, a science that aims to understand the world must have an idea of science's own foundations for knowledge acquisition. Exactly such preconditions and preconceptions have been given critical attention by researchers in the phenomenological tradition (20) and their investigations are thus in many ways supplementary to the Uexküllian tradition.

The phenomenological tradition has made huge efforts to understand the human experiential dimension and thus make it accessible to investigation. As the phenomenologist sees it, any biological individual accesses the Umwelt through a *first-person* perspective. For humans, this is the world as they know it, imbued with meaning and emotions. Any human being has access to a wide range of historically situated knowledge that helps him to respond to external challenges in a meaningful way. The knowledge of each generation is different, and knowledge also differs in different parts of the world. Such knowledge is therefore spatiotemporally restricted.

But human beings can also access knowledge that is true irrespective of time and place. To obtain such valued knowledge, man has to "bracket" his first-person perspective on the world. He has to take a God-like perspective, be the spectator who takes a view from nowhere. The *third-person* perspective, which is the foundational view of science, is not easily achieved. To reach the goal of true knowledge, scientists have to act as disinterested, emotionless, and neutral observers, and so have to undergo a long and arduous training to achieve control over their inborn perceptual capabilities. This is a complicated task, as they have to erase some of their developmentally learned presuppositions.

The degree to which the third-person perspective can be achieved varies widely between the sciences. While mathematicians and logicians can be trained to master their subject in a true "disinterested" manner, it is more questionable whether biologists, social scientists, and humanists can achieve the same degree of perfection. And for a simple reason—biological entities, including human beings, are historically situated; they have a history that matters as to what and who they are. That biological entities, including the nervous, immune, and endocrine systems, have a history, does not, however, imply that they elude investigation by a science with universalizing ambitions. But it does imply that science should make more precise which aspects of the historical entities it can reach firm conclusions about and which it cannot.

Although an arduous task, especially since science constantly develops new concepts and exploratory technologies that push the line of demarcation between knowledge and ignorance, it does appear evident, at least for the time being, that science cannot reach the innermost experiences of an individual. Science can for example explore the general effects of major life events, but how each individual experiences a divorce or the loss of a beloved one is a private matter. It thus appears necessary to make an analytic distinction between a *public* first-person perspective, which is amenable for scientific investigations, and a *private* first-person perspective which is not. The private perspective is a specific characteristic of each individual, be it a human being or a perceptual system. And as such, it has no characteristics that can be generalized—it is thus located beyond the realms of science. The public first-person perspective is, on the other hand, accessible from the outside. It includes perceptual traits that are specific for a given species, and is as such co-extensional with the animal's Umwelt.

While the public first-person aspect can be made explicit by means of genetic, environmental, and developmental investigations, the private first-person aspect is an experiential dimension and as such not accessible for scientific investigation. Such experience does not lend itself easily to standardized interpretation; it is always an experience of something for someone, in a unique context. There is thus a gap between what science can explain and what it cannot—and the gap goes straight through the individual, between the private and public aspects of the first-person. Nonetheless, exactly where the line of accessibility should be drawn is a matter on which science should have a saying. The explanatory gap should be made more precise, but prospects for its closing are for the time being dim.

5. Relations: All the Way

Some of the most surprising knowledge coming out of the genomics research programs has been novel insights into man's relations with the environment as well as to himself. Not only have the sequencing efforts yielded rich empirical crops, they have in addition highlighted the importance of different analytic perspectives. The latter is perhaps made most apparent by recent efforts to understand relations between hosts and their microbes.

Ever since the microbiological revolution in the late eighteen hundreds, led by Louis Pasteur and Robert Koch, microbes have been conceptualized as external enemies against which man had to fight a war. Although the perspective has been extremely rewarding in terms of lives saved by vaccines and antibiotics, the war metaphor has been seriously misleading as an aid to understand man's microbial Umwelt. Only about 100 microbial species regularly infect human beings and cause disease, while millions of others either ignore us or they cooperate with us in an evolutionary selected manner, thus making their absence—not their presence—the real problem.

Several new observations derived from investigations of the human genome as well as from the microbial communities that colonize our mucous membranes and skin have made evident that it is no longer possible to conceptualize microbes as simply "external." They are internal and cooperative as well. The sequencing of the human genome made clear that our chromosomes are teemed with microbially derived elements. The genome consists of 45% transposons—DNA sequences that are able to copy and move within chromosomes—of which approximately 8% are retrovirus-like (21). Some of these retroviral integrations have been of great importance for vertebrate physiological development. Although most transposons that accumulate in the genome have no known function, they contribute a large potential substrate for the evolution and development of regulatory networks (22, 23).

The genome also contains bacterially derived DNA, some of which regulates the interaction between the eukaryotic cells and their bacterially derived mitochondrial symbionts. The mitochondria, which have evolved to become an integral part of the host's cells, have transferred some of their genes to the cell's nucleus. And in so doing, they lost the ability to reproduce freely. This loss has, however, been matched by a comparative gain in survival capacity—mitochondria, by their very location, have become shielded off from immune destruction. The importance of keeping the interaction between the eukaryotic cell and its mitochondria tightly regulated is dramatically spelled out during debilitating physical trauma in which mitochondria relocate or become destroyed. This leads to a breakdown of the conditions for cooperation between the host cell and the symbiont, and the host may thus develop a dangerous systemic inflammatory response. The response includes fever, low blood pressure and increased heart rate (24), and is thus analogous to the inflammatory process observed as a result of contaminating bacteria during sepsis.

Another surprising observation that came out of the sequencing of the human genome was the relative paucity of genes. Based on complexity estimates, man was thought to have about 100,000 genes prior to the sequencing. But only about 25,000 genes were detected. Man was as complex as before, so how could the complexity be accounted for by so few genes? One answer has to do with the way the DNA is used for making proteins and regulatory factors, and it has turned out that this process is far more efficient than first thought (25). But this is not the whole story; additional data have since revealed that humans also have access to a plethora of genes not coded for in the genome. And these genes, which are located within bacteria and viruses on the skin and the mucous membranes, by far outnumber the genes in the cellular nucleus. Estimates have indicated that an adult human being is composed of 10^{13} eukaryotic and 10^{14} prokaryotic cells, and human beings can thus be described as super-organisms consisting of 90% prokaryotic and 10% eukaryotic cells. Since every bacterium may be infected with as many as 100 bacteriophages, thus giving an estimate of ten billion viruses in each gram of human feces, there is definitely a plethora of genes availably within the human niche (26, 27).

The community of intestinal microbes, termed the microbiota, which establishes itself shortly after birth, reaches adult levels in early childhood. Although influenced by changes in diet and life events, the microbiota appears to be relatively resilient to alterations caused by stressful life events and antibiotic treatments. Its non-random organization depends on both host genetics and environmental exposure of microbes (28–30), but relatively little is known about the rules of its assembly or how the human body controls microbiota composition (31). Neither is much known about what constitutes a healthy microbiome—the collection of genes in these organisms—nor on how this in turn influences human health. Nevertheless, evidence increasingly converge on the hypothesis that gut microbes may shape the host metabolic and immune systems and thus influence the development of obesity, diabetes, and other inflammatory diseases (32, 33).

It is by now well established that the microbiota regulates the developing immune system (34), and that it likely played a critical role in the evolution of the adaptive immune system (35). There is also accumulating evidence demonstrating that the gut microbiota can modulate brain development and thus behavior. For example, a recent study revealed that mice raised in germ-free conditions have significantly increased motor activity and decreased anxiety as compared to mice with normally colonized intestines (36). Furthermore, when re-colonized with microbes, the developmental deficits in the germ-free pups normalized while re-colonization of adult germ-free mice did not, thus suggesting that there is a developmental window during which the microbiota is critical to brain development.

The mechanisms by which the gut microbiota effectuate changes in synaptic connections, which provide the essential substrate for functional brain networks that underlie perception, cognition, and action, are still not known. But since the microbiota has an effect on immune cells, it seems likely that some of the effects are mediated by signals from these cells. This interpretation is supported by evidence showing that the immune system is capable of modulating brain function both during development and adulthood (37). In addition, the vagus nerve, which plays an important role in the transmission of immune information from gut to brain as well as from brain to gut (38, 39), apparently also plays an important role during development of the microbiota–brain communication.

Given the bidirectional flow of regulatory signals between the microbiota and the brain, it should come as little surprise that psychological stress leads to altered intestinal barrier function (40) and host–microbiota interactions (41). Increasing values of psychological stress also negatively affects the immune system (42), as demonstrated by reduced antibody responses to vaccines (43). There thus appears to be a close connection between the hypothalamic–pituitary–adrenal (HPA)-axis, the autonomic nervous system, the gut, the kidneys, and the immune system, and this connection is mediated via cortisol, neuronal transmitters, cytokines, and hormones (44).

The long-time observation—that infectious disease is too complex to be analyzed exclusively in terms of mechanistic interactions between the immune system and the pathogen—has thus received rich empirical support. Adaptive systems are relational all the way, and to understand a given interaction, we have to understand a whole lot more than the target system. To define immunocompetence singularly in terms of internal molecular and cellular properties of the immune system is, accordingly, misconceived. This way of understanding immunocompetence provides a one-sided and thus insufficient understanding. Immunocompetence should rather be understood as a relational property that transcends the boundaries of the organism. To understand immunocompetence is thus to understand how the individual's immune system relates to the other adaptive systems as well as to the organism's Umwelt. Accordingly, organisms may be immunocompetent despite harboring deficient immune resources. And conversely, immunocompetence may be reduced despite the presence of a well-functioning immune system. It all comes down to how the relations develop.

6. The "Early Origins" Scheme

The relevance of external inputs, in the form of infection or stress, is in many ways dependent upon the internal wirings of the experiencing organism's adaptive systems. And since these wirings are laid down during the developmental process, it follows that development is of tremendous importance for the organism's adaptability. The now obvious idea that development is an integral part of evolutionary biology was, nevertheless, largely ignored by evolutionary biologists from about 1900 to about 1980 (45). The separation of the fields was so extensive that when Mayr (46) in an influential paper discussed cause and effect in biology, he still distinguished between evolutionary and developmental biology as of two separate explanatory fields that differed in methods, explanatory projects, and concepts.

During the making of the "modern synthesis" of evolution in the 1930s, in which Darwin's theory of natural selection was blended with the rediscovered Mendelian genetics, evolution was portrayed as an interplay between mutation and selection, with the former providing a supply of variation and the latter acting as a fitness-based sieve (45). In the case of unicellular organisms, this representation is fairly accurate. But in the case of multicellular organisms, where genes serve as modulators of biochemical and physiological parameters that in turn influence the growth of embryonic tissues, the effects of mutation on fitness are not directly accessible for selection. Since selection works on phenotypes and their functional characteristics, since development is a major determinant on the multicellular organism's phenotype, and since some ontogenetic trajectories are better for reproducing and survival than their competitors, development is important for the pathway taken by natural selection.

Development impinges on evolution because it ties the organism up in a system of references to other living and non-living entities in-between fertilization and death. Hence, organismal life is not simply conforming to a predetermined trajectory but follows a variable path upon which developmental decisions are influential. Genes, the "master modulators" of the modern synthesis, are thus acting more as context sensitive difference makers than as determining factors; genes make regulatory factors, signaling molecules, enzymes, and receptors that interact with each other in highly regulated networks, and these are all strongly modulated by epigenetic processes, including histone modification and DNA-methylation (47). Thus, identical twins with the same genetic make-up may turn out quite different owing to epigenetic processes and developmental plasticity (48).

Epigenetic and developmental processes have been evolutionary selected because they adapt organisms to the environment. But, as has been increasingly recognized, they have maladaptive potential as well. This may occur if environmental signals, for instance such that were required for the establishment of proper DNA transcription or stable patterns of interaction between cells of the adaptive systems, change in salient ways. The so-called hygiene hypothesis, the best-reasoned theory for the epidemic-like recent increase in allergy and autoimmunity, utilizes this explanatory framework. According to the hypothesis, humans of today experience an absence of stimuli from microbes which are important for the functional development of the immune system. This creates an input-deficiency syndrome, thus leading to malfunctional development of the regulatory cells of the immune system (49, 50). Although little is known about why one kind of inflammatory disease develops instead of another, or why it develops in one individual but not in another, compelling evidence indicate that the malfunctioning develops as a consequence of perturbations to the long co-evolutionary relationships between intestinal microbes and their vertebrate hosts (51).

Not only does the hygiene hypothesis tell a story of how the microbial Umwelt affects the maturing immune system, it additionally tells the story of how human beings affect their microbial Umwelt. Man, being an expert niche constructor (14), is capable of changing his environment at an astonishing rate—for better and worse. On the better side, epidemiological data from European countries have taught us that human life expectancy was about 25 years until the mid eighteenth century (52). Up to that time the leading cause of death was infectious diseases in childhood, and so the increasing life expectancy primarily reflected progress in the control of infectious disease; in the mid-nineteenth century by means of hygiene, in the late-nineteenth century by vaccines, and by antibiotics in the mid-twentieth century. The adaptations were thus of cultural type rather than adjustments of immunity by natural selection.

The downside is that the constructed niche gives rise to a mismatch between man's biologically derived response patterns and environmental challenges. The westernization of society has, for example, made food available in large quantities. And along with better housing and health conditions, the struggle for daily survival has almost vanished. But this change has by no means ended life's struggles—man has instead become increasingly susceptible to developmental aberrations and precipitation of various diseases, including coronary heart disease, diabetes, hypertension, as well as cognitive and psychological impairment (53, 54).

7. The Paradox of Deterioration

As of today, individuals in low and middle income countries in Africa have a life expectancy of 49 years, while people in high income European countries may expect to live until they reach the age of 80 years (55). It is still the young that die in Africa—46% of all deaths in Africa are children aged under 15 years, whereas only 20% are 60 years or older. In contrast, only 1% of deaths in high income countries are in children less than 15 years, whereas 84% are aged 60 years and over. This uneven distribution of death is matched by a similar uneven distribution of causes—while infectious disease is still the major cause of death in Africa, people in Western societies die from cardiovascular disease and cancer.

Owing to the remarkable postponement of death that has occurred during the last 100 years, folk increasingly develop degenerative diseases of the adaptive systems, including diabetes, Alzheimer's disease, and immunodeficiency—death rates for people over 65 years of age compared to people aged 25–44 are, for example, 43-fold for cancer and 89-fold for pneumonia and influenza (56). Aging people thus struggle with a loss of integrity, in many ways a truly astonishing phenomenon since it suggests that the adaptive systems, which produce and maintain themselves during development, are unable to perform the seemingly much simpler task of maintaining what is already formed. This paradox of deterioration is a real challenge for scientists that aim to predict and control the psychoneuroimmunological systems. Unfortunately, the paradox' solution provides little theoretical support for the achievement of therapeutic control.

As summarized by Mayr (46), there are two principled kinds of cause in biology—proximate causes that give explanations in terms of developmental and physiological mechanisms, and ultimate causes which provide explanations in terms of evolutionary mechanisms. The two are connected by evolutionary time—the ultimate causes shape the proximate causes. And since natural selection is a progressive force, one would expect evolution to shape developmental systems to near optimal functioning. But, as elaborated by Williams (57), natural selection works on genes that enhance reproduction, not longevity. And the genes responsible for aging may thus be kept in the gene pool by selection on their beneficial effects to the young that possess them and not owing to their detrimental effects in senescence. This phenomenon, termed antagonistic pleiotropy, explains why the selective pressure on machinery responsible for maintenance of genomic and cellular integrity in aging tissues has been insignificant (58).

Since infectious disease has been a major threat to the survival of young children and thus to their reproductive potential, natural selection should be expected to shape the immune system so as to increase its efficiency during the early years of life. And as evidenced by observational data, production of inflammatory mediators by the innate immune system complies well with the antagonistic pleiotropic framework. The importance of a highly active innate immune system has been corroborated by comparative data between African and European populations. The data strongly suggest that individuals of African ancestry have a more active inflammatory response, perhaps owing to a greater burden of infectious disease (59). Furthermore, emerging evidence indicates that pro-inflammatory genotypes are associated with a higher incidence of inflammatory disease in later life, including atherosclerosis, diabetes, and cancer (60). The selection for a strong pro-inflammatory immune response, which is necessary to resist otherwise fatal infections in early life, is thus—as predicted by Williams' hypothesis—a double edge sword; the overproduction of inflammatory molecules may cause inflammatory diseases and even death later in life. Natural selection thus gives rise to mechanisms that both create and destroy the organism.

Surprising data from the last couple of years have even shown that this overproduction may be enhanced by various cultural "practices." Early experiences, which can affect adult health either by cumulative damage over time or by adversities that take place during sensitive periods (61), can take dramatic and often unexpected courses. Experience of maltreatment in childhood is, for example, a strong predictor of adult inflammation (62), and, more specifically, increases the risk for autoimmune disease (63). To control such malfunctions psychoneuroimmunologists thus have to treat culture no less than biology.

Also the adaptive immune system follows the logic laid down by Williams, but in a modified form. Newborn children come with immature adaptive immune systems and thus have to rely on maternally derived IgG and IgA for their first 6 months of life. However, this immunodeficiency of the young does not contradict Williams' prediction. Adaptive systems are designed by natural selection to mature over the life course and so their seeming failure in early life is part of their developmental program. The same goes for their deteriorating function with age, as evidenced by increasing tendencies to autoimmunity and immunodeficiencies, and as predicted by the antagonistic pleiotropy framework. For the adaptive immune system this malfunctioning is partly owing to a reconfiguration of T cell immunity, manifesting as the accumulation of senescent and dysfunctional cells (64), and a shift in subpopulation frequency as well as expressed repertoire of antibodies and T cell receptors (65).

8. Summing Up

Compelling evidence has demonstrated that early environments are important determinants of nervous, endocrine, and immune functions over the life course. As adaptive systems seem inherently disposed to degeneration, and since the prospects of controlling such evolutionary selected disintegration seem dim, a major aim of psychoneuroimmunological investigations should be to lay out early conditions that serve to increase the integrative processes and, of no less importance, to delay the disintegrative processes. Such investigations should acknowledge the importance of the experiential dimension, and should take a life cycle perspective in which the organism's timely unfolding is correlated to salient environmental contingencies. To develop, the organism needs to extract resources from the environment, and variation in the organism's local ecology will thus in large part determine the levels of available resources and thus the developmental course.

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