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IMMUNITY IN NATURAL HISTORY

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Battle Within?

The worldview of an immunologist, it often seems, is that life is a microscopic war in a macroscopic world: "the battle within."[1] "Every minute of every day wars rage within our bodies. The combatants are too tiny to see." "Besieged by a vast array of invisible enemies, the human body enlists a remarkably complex corps of internal bodyguards to battle the invaders" [1, pp. 702, 706]. The body is a citadel surrounded by infiltrating invaders. Innumerable hostile bacteria, viruses, and parasites lurk everywhere; they float in the air, infest the water, pollute our food, cover every surface we touch. Even the body's own cells can turn traitors, such as cancer cells.

The imagery is vivid. But imagery needs philosophical analysis, especially imagery that colors worldviews, even more if this seems to have scientific sanction [2]. When scientists speak of ant wars, or selfish genes, or queen bees and their slaves, they borrow words from one domain of experience and transfer them to another. What about this "battle within"? Does it need to be set in a more comprehensive scientific, and philosophical, picture? What is the place of immunity in natural history?

Physicians are scientists, and if one sees the world as a physician of infectious diseases, the world is full of these tiny enemies. There is no doubt about the struggle for health versus disease: that is not metaphor but straight truth. Infectious diseases can reach epidemic proportions, killing as many people as does war. *Orthomyxovirus* the influenza virus, killed 20 million people in 1918, more than were killed in World War I [3, p. 620]. We forget how feared were the black death, smallpox, or diphtheria, polio, or cholera—before modern medicine won the battle against them. Malaria still affects 300 million persons worldwide, with a million deaths annually [4, p. 311]. Each person suffers from microbial and viral diseases; our bodies are constantly at work killing these killers.

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[1] From the Nobel Conference XXVIII, "Immunity: The Battle Within," at which this paper was presented.

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Still, the "battle within" might not be the whole truth, even from within immunology—and much less when the other sciences, such as evolutionary biology or ecology, are added. Another term used just as often in relation to immunology is "self": immunology has been called "the science of self-nonself discrimination" [3]. That concept also requires a closer look.

Self-Identity

Life involves organization, information, reproduction—impossible for an organism until there is an inside and an outside. The phenomenon of life is, almost by definition, a self separated from nonself, the setting of limits (de-fining, Latin *definio).* There must be some defining envelope. After that, an organism can take in nutrients from the environment and sequester them for its own uses. The boundary line demarcates the order contained and maintained within against entropy without, an order which, in prospect of the disorder of death, has to be reproduced.

An immediate biochemical implication is that an organism can have invaders: things inside that do not belong, nonself, other selves violating these limits. Life must control passage across the defining membrane. That is part of the bigger truth that life is constantly self-defense; there are all kinds of things and events outside that the somatic self must protect itself against: hot and cold, wet and dry, solar radiation, poisons, predators. Cells have to be repaired when damaged, and outsiders that get in have to be controlled or eliminated. Also, there can be insiders that no longer belong inside. So the body has to void or recycle dead cells, to program the death of cells no longer needed. Sometimes, insider cells get out of control (neoplasia),and, lest these become tumors, they must be stopped. Immunologists think of this as "killing"; they also think of this as ordering the self.

In a multicellular organism, such as a mammal, this becomes quite complex. Residing in a world with millions of species, making billions of kinds of organic molecules, the body has to produce a defense against almost any type of organic molecule except those of the self—ingesting it, digesting it, encysting it, eliminating it. The mammalian body has many millions of cells of quite diverse kinds. Immunity defends the self as a microscopic assignment, but it is part of complex macroscopic natural history.

The question of immunity is really that of identity in natural history. Immunity is implicit in life from the beginning and co-evolves with the sophistication of the self: "From the humble amoeba searching for food . . . to the mammal with its sophisticated humoral and cellular immune mechanisms . . . the process of 'self versus non-self recognition' shows a steady development, keeping pace with the increasing need of animals to maintain their integrity in a hostile environment. The decision at which point 'immunity' appeared is thus a purely semantic one" [5, p. 3]. Biology has to be arranged to keep organismic selves apart. The fight is for a terri-

tory within which the organism can operate a self. Without outer membranes, the organism is nothing. And since these have to be crossed, outsiders will get in and they have to be gotten out Living well is a matter of being semipermeable.

At the molecular level, the identification of others takes place as antigen recognition. The body is primed to attack strange cells. A T cell or B cell is programmed with a single question—whether there is some stranger that has crossed the body boundary. In that sense, xenophobia (or allophobia, for immunologists) is logically and empirically essential to individually. Opposing others on the wrong side of one's life-boundary keeps life from getting muddled. The body is systematically sweeping through itself raising a kaleidoscopic set of inquiries about nonself. With millions of lymphocytes each asking its own particular version of this question, the body is patrolling its privacy.

Diversity has to be protected. One organism cannot be different from another unless it posts a boundary that keeps the other out The skin, therefore, is a surface of identity. It is part of the larger picture of stabilizing an inner environment in which the vital process can continue. Self-identity means self-defense, self-stability, self-integrity. Since the skin has holes in it and can be breached, immunity has evolved to protect this identity within. That is immunity's role in natural history, and the battles within—the terms in which we started to think of immunity—have to be set in the context of selves preserving an identity as a fundamental feature of all life.

The Idiographic Self

In all advanced species, the self is a singularity. An everyday word for this is *unique,* but a more philosophical word is *idiographic,* which means that an organism writes *(graphs)* its own peculiar *(idios)* career through the world. There is no living thing on Earth that does not possess some defense reaction. Plants can defend themselves against pathogens and are protected against injury. They produce toxic substances in self-defense, reject genetically incompatible grafts, and can heal their wounds. Still, such self-defense does not always require idiographic selves. In some forms of life there are selves that are clones of each other. In some protozoans *(Difflugia),* individuals of the same species grown in the same medium are histocompatible. But this is not true past the earlier levels of evolutionary history. After that, there arise idiographic selves. Indeed, the degree of idiosyncrasy in nature is quite remarkable: any one person is immune to everybody else on Earth. Is that a biological self-identity gone bizarre? Or is it welcome biological diversity?

Biologically, it is not surprising that the body can distinguish self from nonself when fighting invaders. Perhaps it is not hard to recognize a very different self (a human molecule recognizing a bacterium). But the im-

mune system can recognize as not self a brother, a mother, a father, with whom half the genes are shared. (Identical twins are a special case; they were once one individual). This is surprising, for there is no particular cause to think one brother's cells would have been invaders of another brother's body during evolutionary history. No organ transplants had to be rejected in order for humans to survive.

This highly specific capacity to recognize nonself has probably developed as a capacity to detect cancerous cells, where detecting a little difference early can be important to survival. The self needs to be able to detect altered-self, for such cells too are dangerous. In fact, this is the second great threat to life. In youth, the threat is germs, invaders, infectious diseases. In the second half of life, the threat is self cells gone out of control, cancerous cells. The battle within is also against self gone awry, insiders turned others. We have to resist both the foreign and the abnormal. Also, organisms need to be able to repair wounded self. Such needs seem to have launched the evolution of this idiographic immunity. And once started, it elaborated dramatically.

The recognition of nonself is signaled by the molecules of the major histocompatibility complex (MHC). Class I molecules are placed on every nucleated cell in the body to identify the self. It is also important to discriminate which cells to kill, and this is done by T cells, using Class II molecules, which are placed on macrophages, B cells, and some T cells. T cells have to be activated by one's own body cells that have ingested antigens and then display them. A T-cell receptor recognizes a combination of the antigen along with one of the body's own "self" markers. It sees a "self-nonself" complex. That recognition of nonself, or altered self, triggers an effector reaction by which the offending microbes, viruses, or cells are killed.

Immunology has been unfolding how idiographic this process is. B cells and T cells are formed from genes on chromosome 6 in humans, the HLA locus. The B cells produce immunoglobulins (Ig), with variable regions at one end of the molecule, primed to recognize peculiar antigens on the surfaces of invading cells. One might think that there could be some all-purpose antibody, one that could kill any and all strangers, but this is not so because such an antibody would kill self cells as well. The suspicious strangers have to be picked out one by one, like singular faces in a large throng of people. To do this the variable region has to have a high degree of specificity. A particular IgG molecule, made by a particular B cell, can bind to an antigen with only a rather particular shape. Like the particularity of faces of persons in a crowd, really, no two are alike.

The process is idiographic in extreme. Asking how many kinds of antigens there can be is like asking how many kinds of faces can suspicious looking strangers have. The answer for antigens is in the range of 10^7 to 10^8. The body cannot encode genes for all these possibilities; that would use up most of the mammalian genome just for the immune system. So, in the case of

B cells, the body pieces together several DNA segments that are physically separated in the genome of an embryonic cell. This piecing has enormous combinatorial diversity. The body takes a relatively few genes and spins them round like turns of a kaleidoscope to generate a genetic recombination that will code for one of myriads of variations on the ends of IgG molecules. The body dips into the gene pool and rearranges various gene segments to get a high number of specificities out of a relatively small number of gene segments: So the body can make over 10^8 different kinds of immunoglobulin molecules, to match the possible kinds of antigens that it may encounter [4]. With T cells, by a similar combinatorial process. antigen receptors, rather than antibodies, are generated—receptors that work in combination with the MHC complex.

So the body not only makes molecules that display its own specific diversity, it has found a way to anticipate the myriad specificity that the world of bacteria, viruses, and parasites can bring against it. One can think of this as biodiversity at the molecular level, recalling that it is intimately related to biodiversity at the ecosystem level, because each of these antibody and receptor molecules is really a question about what sorts of bacteria, viruses, or parasites may be out there in the ecosystem the body inhabits. Each type of cell (B cell and T cell) is "wearing" receptors that are fine-tuned to some specific antigen. Some such antigens might be produced by microbes that have not evolved yet and perhaps never will. But many microbes and their specific antigens exit, while some new ones evolve; and if and when such an antigen shows up, the immune system is ready for it—usually.

Thus, the idiographic particularity in nature adds up to make extremely particular selves. There are about 5 billion other people on Earth. There are trillions of other organisms, insects, crustaceans, grasses, bacteria. And yet each person has labels—markers—on the surfaces of his or her cells that identify that self as one in these trillions. This is, one might say, outrageously idiographic. It also underscores the historical particularity of Earth's history, right down to the biomolecular level.

The Selfish Self?

Now an opposite worry arises: there seems to be a kind of overshoot. Nature is full of idiographic selves each clamoring to defend its own interest. Self is cast against self in ceaseless combat—the wars with which we started. One organism defeats another, or there are standoffs between adversaries. Geneticists and sociobiologists frequently use an especially vivid metaphor: "We are survival machines—robot vehicles blindly programmed to preserve the selfish molecules known as genes" [6, p. v; 7]. This couples with the immunologist's view of the world as a microscopic battleground, and so we seem to have several scientific perspectives converging. What philosophical analysis are we to give of these selfish selves, which are full

of selfish genes—protected, the immunologists might add, by selfish immunoglobulins, T cells, and B cells?

Even before one thinks as an immunologist, one might want to ask geneticists whether this reductionist approach does not fall into seeing the organism as nothing but an aggregation of genes and their outputs, each gene being individually "selfish," a kind of bottom-up approach. The more comprehensive picture could be a top-down approach, where the organism is a whole, a synthesis, and codes its ways of coping in the genes, which are analytic bit-units of that synthesis. We have to guard against anthropomorphism in such language. There are senses in which the genetic system is a cognitive system; but a single gene, strictly speaking, "knows" nothing about the big world in which the phenotypic organism copes. A gene only "knows" how to code a protein; everything else is going on "over its head." It does not have the slightest hint what a "predator" or a "mate" is. These bitsy "knowings" in ensemble are integrated into what the organism "knows," if we must use such cognitive language. No one gene "knows" enough to be selfish. On its own, a gene is only a tiny knowledge fragment.

A gene is what it is collectively, in a genome. The picture we need for a self is organismic, holistic, hierarchical. It is hard to see how any one gene is in any position to act selfishly, as though this could mean it has its "own" interests separably from the interests of other genes, or separately from the interests of the organism in which it is embedded. Continuing to think along these lines, it would make little sense to speak of a selfish immunoglobulin molecule, with its high degree of specificity. A T cell, producing the MHC complex, is a kind of reductio ad absurdum of selfish genes, since the body's genes are expressed only in reshuffling fragments that combine with other fragments. For any one lymphocyte, success really has to be collective. The guarding of the whole organismic self can be done only by assigning bits and pieces of the task to these immune cells.

Turning to skin-out biology, life is lived as a singular individual. The organism is on its own in its Earth habitat. Natural selection selects the better adapted fits, those coded for the best coping. Now the "selfish" behavior of an organismic self becomes more plausible. There is an identifiable self that can act in its own interests in an arena where other selves, of the same or other species, have interests that can be acted for or against. Immunity is part of that picture.

But at this level geneticists and sociobiologists, though they suppose there are selfish genes, insist that when we ask about one individual's genes we have to enlarge the scope of that individuality and go up to the family level of that individual by the same logic that goes down to the genetic level. From the gene's eye view, since a gene is an information bit, a gene is present in all cells where there are copies of it. A particular gene may be co-present in relatives, copies within kin in a different skin. Facing out, the individual self finds that it is sometimes facing in, finding its self, or

parts of it, in others. Expanding the concept of the self to include this "inclusive fitness" [8], the survival and reproduction of a relative is partly equivalent in evolutionary effect to an individual's own survival and reproduction. Assistance to a relative will be favored if the benefit to the relative, proportioned to the degree of relationship, exceeds the cost to the donor.

Here we have reached an odd sort of selfishness, one that affects how we must interpret immunity, because now the individual self is vitally related to, partially identical to, familial individuals to which it is at the same time immune. An individual's fitness is shared with kin—more and less, all those blood relations in whom there are partial copies of its genes, of whose genes its own genes are partial copies. It does not matter whether the descendants (gene copies) are its own immediately, as a result of a particular self's individual fitness, or in its family. If an individual fails to reproduce, it is just as well to have copies transmitted in cousins.

This clouds the seemingly clarity of having located an immunologically particular "self" that can be selfish. It is not just the organismic, somatic self protected so zealously by the immune system that counts: it is the reproductive, genetic self. If a surgeon makes a skin transplant, my immune system may reject my brother, but my genetic program still disposes me to aid that brother. In relatives, a self acts to preserve shared genes even if the self is not the one to perpetuate them. A complete worldview, even from a scientific perspective, needs to check idiographic immunity by inclusive fitness. The biological identity question has a kin selection answer as well as an immunoglobulin answer, a sociobiological as well as an immunological answer.

Further, the allegedly selfish self is checked by sexuality. The idiographic self cannot survive alone but has to mate; male and female alike must throw away half their genes. When the genes go through just that phase of the life cycle where the fully selfish gene, having been protected by immunity molecules, might wish to construct a faithful copy of itself, there is chop-up and reshuffle, as though to bar genetic and immunological fidelity as the only rule in the game. The system the self inhabits insists on variation. It is hard to be selfish, if one is a genome and must be split in half at every reproduction.

Sexually reproducing organisms cannot make identicals; offspring must be *others (alteri),* and in this sense sexual reproduction is by necessity "altruistic." It is not possible for an organism to make other-very-differents; it can only breed after its kind. So now immunity has to be relocated in a matrix of kinship and common heritage. An organism arrives in the world as a beneficiary of past variations, and it inhabits a natural system in which it can cope only if it can make variant copies of itself. So far as these are copies, the organismic history is inherited; so far as they are variants, history is generated anew. The organism is itself a product of history, but its particular self cannot continue long somatically: it dies. And it cannot replicate

itself except as it also generates otherness, copies with variance. Sexuality is a key to this variance. At the same time that it creates, it breaks up unique biological identity.

From the perspective of immunity, the female mammal does have to tolerate another—the fetus in her womb, only half her own. At conception, she gets inoculated, so to speak, by a genetically unrelated male with several million sperm cells, highly motile, with alien antigens, each programmed to fuse with an ovum she has produced. That will produce a zygote, her cell yoked with another, an alien genetic set. A skin graft from mate or offspring would be rejected, but should she be immune to a mate's sperm she could not conceive. The zygote is a kind of allograft; but if she were immune to the zygote, she would abort. Embedded in her womb, she must carry this parasitic, half-alien fetus through pregnancy. In addition to nutrients, she may even convey her own immunity to it. In that sense, biologically speaking, sexuality is the opposite of immunity. Yet both are vital developments in evolutionary natural history.

From this perspective the 50-50 split made at each reproduction in the haploid meiosis in diploid animals is a misperception: there is no more than a fraction of a percent difference between reproducing mammals, as any sexually reproducing animal has almost all of his or her genes in common with all other members of the species, even though a particular act of reproduction sorts those genes uniquely. Those genes of the female that seemed alien to the male mate a moment ago are mostly her genes after all; or, the other way round, his genes are hers. In the human case, both mates have hemoglobin in their veins and opposable thumbs on their hands, as do all "alien" humans around the globe. There are only four blood types as far as transfusion is concerned. All 5 billion humans have copies of genes mostly like the copies any one person shares with them, and the differences between persons, when we compete about these, all turn on a trifling fractional percent and a different turn of the genetic kaleidoscope.

The other side of the picture of the idiographic self, protected by an immune system, is that each such self is really a cluster of bits and pieces inherited from all over everywhere, copies of which are still present in relatives with which such a self may live side-by-side in family relationships, but copies of which are also scattered all over the species. We are composites. A self's genes are not so much heterogeneous, as is its particular combinatorial package. Even the immune system, though the genetic reshuffling makes idiographic molecules incessantly, works the same way in all members of *Homo sapiens.* Most of an individual's genes are not unique to a particular self at all, nor even to its family; on the contrary, they are common to conspecifics. Those in-common genes, so far as they affect behavior as well as determine structure, will be pushing a self to cooperate with any and all fellow species members. Or perhaps they will be neutral to behavior

that differentiates between members of any species, since they are co-present in all.

In one sense each human is singular, and that is the viewpoint of the immune system. But it is just as true that the relationships between humans lie on a spectrum of kinship and commonality; humans have shared genes, shared humanity. Indeed, many aspects of life at the molecular level reveal the unity of life, human and nonhuman. The difference in the protein coding sequences of DNA for structural genes in chimpanzees and humans is quite small: "The average human protein is more than 99 percent identical in amino acid sequence to its chimpanzee homolog" [9]. Differences between the two species lie largely in regulatory genes [10]. Further afield, the genetic code is essentially the same for all organisms. The 20 amino acids are common to all. When we place immunity in the fuller picture of sexual reproduction, of a species line in which the individual stands, and of speciation in natural history, biological identity mingles with biological solidarity.

Immunity and Ecology

We must next place the self, with its immunity, in an ecology. The skin is the surface of exchange with the environment, and what is outside is as vital as what is inside. The incoming molecules include air and nutrients, user-friendly molecules, if also some user-hostile molecules. The world outside is resource and community that supports life. Interdependence and dependence are as true as battle and attack. If an organism were really immune to everything coming in—if the immune system isolated the self from the world, like a bubble baby surrounded by impermeable plexiglass—the self would be dead in a few minutes. The immune system regulates this exchange with the world, as much as fights invaders. The environment is over against the organismic self, but the environment is not something that, from an ecological perspective, the self is against or that is against the self.

From the perspective of immunity, "foreign" means any molecule not coded for by the organism's DNA. Everything in the environment is foreign. But from the perspective of ecology, the organism inhabits a niche; the environment is its domicile, its "home" (the root of ecology, Greek: *oikos).* The organismic integrity, protected by immunity, has to fit into an ecosystemic integrity. An organism without a habitat is soon extinct. The immune system is zealously defending the self, but all the while the ecosystem in which this self lives is the fundamental unit of development and survival. There are no immune organisms, period; there are only immune organisms-in-ecosystems. The skin boundaries are privacy zones inside a home, like rooms inside a house, more than like cease-fire zones in a war. The outside is not foreign, but home.

Why are there microbes? A historical answer is that such organisms are simple, relatively speaking, and evolved first. But why do they continue? An ecological answer is that every ecosystem is a trophic pyramid, with microbes a functioning part of such pyramids, as are plants and lower animals. These kinds serve continuing roles. All the undertones of the pyramid remain occupied. We cannot interpret molecular life without understanding ecosystemic life, and vice versa. Ecosystemic life, as found on Earth, requires microbes, and most of them occupy their places in ecosystems without any particular disturbance: doing their own thing, fitting in as members of ecosystems, filling niches in the general life-support system. They are not disease organisms at all.

Nor are all these incoming others hostile. "Perfectly healthy young adult mouths contain germs *by the billion"* [11, p. xiii]. Each person has about 80 species of bacteria inside his mouth. In fact, there are bacteria throughout the human digestive systems: for example. "The total number of bacteria excreted in feces by an adult each day ranges under normal conditions from 10^{11}-10^{14}—from 100 billion to 100 trillion" [11, p. 31]. There are far more other organisms in and on a person than there are other persons on Earth.

From an ecological perspective—complementing an immunological one—most of the relations between organisms are networks of interdependence and tolerance. This includes eating each other and being eaten. It also includes standoff relations, which can sometimes become adversary relations. These relations can be pathological; and when they are, we need the world view of immunology. But the bigger truth is ecological: that every organism is connected to and dependent on many others. Joining this holistic biological picture with a philosophical perspective, we have to find a place for both idiographic self-defense and community dependency in tandem. Ecology is the full truth, of which immunity is a subordinate half-truth. Immunity is necessary for highly particularized life, but only if we can locate such immunity in an ecology do we have conditions sufficient for life.

Immunity in Evolutionary History

We are now able to place immunity in natural history. There is self-defense in the context of natural selection. Sometimes that means sharp fangs, or fleet feet, or caring for offspring, events in the macroscopic world. But selection also involves events at the microscopic level: the capacity to digest cellulose better, or to regulate body temperatures, or to store fats. The immune system is part of this microscopic struggle for life. Those who can fight illness leave more offspring in the next generation. Immunity preserves identity, not only of the individual, but of the species line; but every individual, every species, is *what it* is *where it* is, in a niche in an ecosys-

tern where it is at home, supported by that world without, within which these "fights" also take place.

Indeed, over the millennia of human history, the microscopic wars within have been as important as the political wars without A person has been much more likely to die of infectious disease than by attack of enemy soldiers. The micro-aggressors are a greater threat than the macro-aggressors: the fittest survive the battle within. Yet we have also learned that "the fittest survive" is not really the best way to characterize Darwinian natural history. The phrase is too gladiatorial, too adversarial. We must replace it with "the better adapted survive." Fighting is not the only—and usually not the best—adaptive technique: the better adapted may be those who can endure drought, or use food more efficiently, or cooperate with each other." At the microscopic level too, the better adapted may not always have to win a battle. Immunity is essentially the protection of individual biological identity in a world where life is maintained by the orderly control of what passes through membranes.

Immune systems guard individuals. But natural history is much more than individuals protecting themselves. Over evolutionary time ecosystems are strikingly historical. The selective forces in ecosystems produce and yet also transcend the lives of individual plants and animals; they produce new kinds of individual. Evolutionary ecosystems have increased the numbers of species on Earth from zero to 5 million or more. Extinction and respeciation have resulted in increasingly differentiated natural kinds. The diversity of individuals has increased.

Superimposed on this increase of diversity, the complexity of individual lives in the upper trophic rungs of ecological pyramids has risen. One-celled organisms evolved into many-celled, highly integrated organisms. Stimulus-response mechanisms became complex instructive acts. Warm-blooded animals followed cold-blooded ones. Neural complexity, conditioned behavior, and learning emerged. Sentience appeared—sight, smell, hearing, taste, pleasure, pain. Brains coupled with hands. Consciousness and self-consciousness arose. Persons appeared with their idiographic psychological selves, egos with their intense concentrated unity, and nature produced persons with the capacity to form transmissible cultures. Immunity defends the local self, but only as part of this developmental evolution.

Organisms defend only their own selves or kinds, using immunity to do so, but the system spins a further story. Organisms defend their continuing survival; ecosystems are the context of new arrivals. Species increase their kind, but in ecosystems there may be, and has been, an increase of kinds, and increases in the integration of kinds. Each of the organisms in this panorama of life defends its individuality, but they are all instances in a species line, evolving under ecosystemic pressures. In time, all organismic individuals die, all species go extinct or pass over into something else, In this more comprehensive picture of nature history, the particular individu-

ality, guarded by immunity, is the one thing that cannot be preserved for long, even at the species level, much less at the individual level. And the reason that it cannot long be preserved is that the evolving ecosystem, churned by climatic change, by novel mutations, by invasions of newcomer species, genetic drift, and other vicissitudes of natural history, is incessantly resulting in other individuals who differ in genome and kind. Protecting the idiographic particularity of a genetic set, the assignment of the immune system, is, at one level, absolutely vital to life; it is, at another level, a futile undertaking, because nothing is more certain to be lost—lost at both the individual and the species level. Any organism of any species is a loser in that battle. In that sense, any individual's immunity is only a momentary event in the flow of life over generations, over millennia, that has continued for billions of years.

The individual's battle, always lost, results in ongoing speciation turnover. Such speciation has, over the millennia, oddly resulted in increasingly idiographic individuality. In simpler life forms, for example, *Difflugia,* individuals can often be fused. But the evolutionary history that has produced increasing individuality has protected it with the evolution of more sophisticated immunity. If the cells from two different sponges are mixed and then left alone, the cells from each individual will separate out and re-aggregate, attempting to re-form the previous individuals. Earthworms reject grafts from other earthworms. In many invertebrates amoeboid cells (coelomocytes) identify and destroy foreign materials. Invertebrates express cell surface molecules that distinguish self from nonself, and such molecules may be the precursors of histocompatibility molecules in vertebrates. Later, the more discriminating and specialized defenses of acquired immunity evolve in vertebrates.

The immune system is philosophically interesting because of its blending of past and future, actuality and potentiality. The genetic system generates and tests novelties, which are explored in a search space that is nearby previous successes. When such novel organisms are made, the immune system, in counterpoint, protects that individuality. The immune system is the negative side of what genetic mutation is the positive side of. The one protects the individuality that the other generates.

To protect the new individuality that the genetic system generates, the immune system employs skills evolved across hundreds of millions of years and now stored in genetic memory. In the complement system, for instance, the classical and the alternative pathways are found both in mice and in humans, which indicates that both go back millions of years. In surveillance of this individuality, the lymphocytes (if we are to risk some cognitive language) "know what to expect," to some extent, since the immune system has coded within it a long-evolved innate immunity. And to some extent the lymphocytes acquire memory and "expect" the future on

the basis of the biographical past of any particular individual (acquired immunity). Finally, since, in a historical world, the future is often unlike the past, the lymphoctyes "make guesses"—sometimes educated and sometimes wild—about what might be coming in the future, in the generation of novel immunoglobulin molecules.

We have noted that evolutionary history makes possible increasingly idiographic individuality. But now we need the other side of that loop: individuality, though momentary on the scales of deep time, makes evolutionary history possible. Natural selection proceeds by selecting from the individuality generated by evolution with its genetic apparatus. So individuality, maintained by immunity, preserves selves, a good thing in itself; but this also preserves the diversity of selves upon which natural selection may act, a good thing systemically. Immunity, in the short view, is just defending a self against change; but in the long view, those selves defended against change are the pool of variant genotypes that can be tested for survival, making change possible. Immunity—self-defense—insures that the phenotype will be the faithful expression of the genotype, and this provides the individuality on which natural selection can work in its generate-and-test creativity.

In this sense, immunity makes evolution possible. And evolution escalates individuals in kind and complexity.

Information, Memory, and Education

Immunity is philosophically interesting because we hardly know what kind of cognitive account to give it. Although we should avoid intentional language, biological molecules are always informational molecules; there is an important sense in which they do know how to do something, if not individually then collectively. There are three cybernetic systems in the body. We regularly celebrate two of these, but slight the third. The first is the genes. We are impressed at the way that the DNA molecule is unzipped and read to construct all the proteins of life. The astronomical amount of information soaked through the body is used to conserve self-identity, which requires an informed organization of the 10^{28} atoms in the human body—more atoms than there are stars in the universe.

Secondly, information is also acquired, stored, and transmitted neurally—in the brain, one of the supreme achievements in evolutionary history. Again, the information potential is vast. There are 10^{11} neurons in the human brain, each of which may have hundreds or thousands of synapses, with hookups not simply linear and sequential but cross-wired and holographic. Each cell can "talk" to as many as a thousand other cells; the number of different synaptic connections that can be made on 10^{14} synapses is almost infinite. There is more operational organization in the three

pounds of the human brain than there is, so far as we know, anywhere else in the universe. Brains are cognitive systems that we do have to give account of in any full picture of natural history.

The third, little-appreciated cybernetic system is the immune system. That system depends on but exceeds genetics, because it too attains a form of acquired learning. Innate immunity is coded in the genes and "remembers" what has happened in the organism's evolutionary past. But acquired immunity "remembers" what has come along during the organism's biographical past, immunity is really a kind of remembrance, though not a neural kind. An organism gets the disease; then its body remembers, and it does not get the disease a second time. This bodily capacity to remember involves antigens. An antigen is anything to which the body responds differently the second time it meets it. In that sense, an antigen is a historical molecule, and the immune system is biographically informed.

Again, one has to use language with care; we should guard against overly cognitive language. But we do have to describe what is going on; and there is a kind of acquired learning in immunity, mechanical though the system also is. Immunologists use a term here that philosophers will find revealing. They speak of the "education" of a T cell or a B cell. When stem cells from the bone marrow mature in the thymus (T cells), this is called "thymic education" [4, p. 169]. Is this another case of moving terms from one level to another indiscriminately, like selfish genes, ant wars, queen bees and their slaves, and battles within? Or does it alert us to the fact that in the immune system there is a cognitive process at work?

Once such an educated T cell or B cell meets an alien microbe, it not only triggers defenses, it triggers a memory. What immunologists call "memory cells" are made; these are both long-lived and reproduce themselves, so that acquired immunity can continue for decades, even a lifetime. The body can remember what sorts of organisms it has met before and be ready for their return. From a philosophical perspective, we may wish to be circumspect about "memory" cells, as we are about "remembering"; and yet the vocabulary is widespread in immunology, and seems as equally legitimate, say, as the use of "memory" in computer science. These memory cells demonstrate a remarkable mixture of the genetic and the acquired capacity to cope.

Such capacity is much smarter than mere genetics: the body has defensive capacities far in excess of anything that could have been coded for in the genes. It can react to bacteriological and viral innovations that take place during its lifetime, and to new forms of bacteria and viruses that have never before existed on Earth. Nothing else approaches this cybernetic capacity other than the processes of acquired learning in the brain itself. This phenomenon may be viewed as a battle within; it can also be seen as a kind of creativity that skillfully searches the future for novelties that enlarge the

successes of the past. This immunological memory increases both the speed of learning and the learning capacity by several orders of magnitude.

Control and Complexity

Consider the complex task of the immune system. A host of metabolically and structurally different cells must live together harmoniously. There are more cells in the human body than there are people on Earth, and they have to be choreographed in organic unity. Further, invader cells, myriads of kinds of them, and insider cells gone wrong in many different ways—all these must be seen and eliminated. And this has to be done in microscopic and molecular ranges. So the body makes certain specialized cells that are capable of damaging and killing neighboring cells. (Immunologists make no effort to avoid the anthropomorphic language of "killing," though, again, there is no intentionally.) The major cytocidal cells are macrophages, natural killer cells, and cytolytic T lymphocytes (CTLs). These have to be carefully controlled, lest they kill the wrong thing.

The complement molecules work in a cascade reaction—15 to 20 different molecules, and 10 or more inhibitors, a total of some 30 to 40 molecules. Complement is always circulating in the blood and lymph, but not yet activated. Of the two activation pathways, the classical pathway uses antibodies; the alternative pathway does not. In the former, a C3 molecule has a fragment, C3a, cleaved off; then the remaining C3b triggers a cascade of about a dozen steps, many again with fragments cleaved to activate the remaining molecule, terminating in the lysis of the target cell. Such a cascade might seem overly complex, but it is really a sophisticated form of regulation; there are amplification circuits and stabilizing loops, shut-down provisions and backup pathways. It is, of course, a causal system, but it is more than that: the system is protecting a self.

Complement can be quite destructive and that is a good thing, but it is also a bad thing if it goes out of control. C3 is a powerful molecule. If all of it in the body somehow got activated and went to work killing body cells, a person would die in a few minutes. So it takes tight, fail-safe regulation. Immunologists use here the language of a fine-tuned mechanism: "Because of these regulatory mechanisms, a delicate balance of activation and inhibition of the complement cascades is achieved which prevents damage to autologous [self] cells and tissues but promotes the effective destruction of foreign organisms" [4, p. 268]; "The consequences of complement activation are so significant and potentially dangerous that the system must be very carefully regulated" [12, p. 200]. Only in a limited sense ought immunity in natural history to be portrayed as battles within from incessant assault without. War suggests things chaotic and out of control, the breakdown of order. But here there is orchestrated control.

In part, the war metaphor comes out of the infectious disease context in which immunology has had its historical development. But the immune system is at work in health as much as in disease, maintaining health by not allowing wars to start. There is just as much reason to interpret immunity as integrated control within, a control that sustains an appropriate relatedness to the ecological community without. The immune system is a sophisticated means of preserving biological identity at a high level of ideographic organismic diversity. We admire the control exemplified in brains and muscles as among the notable achievements of natural history. But we cannot see the complex control that is going on microscopically in our immune systems, also one of the remarkable achievements of evolution. True, life is a struggle, and that keeps the battle metaphor always relevant; but such struggle is the context of the discovery of ordered complexity. Immunity illustrates the evolution of order in the world quite as much as it does the pervasive threat of disorder.

Error

There is a downside. People and animals do get sick, and the last word is defeat: death. Can we pass any philosophical judgment on the frequent, inevitable, and final failure of the immune system?

One place to begin is to notice that, from an evolutionary point of view, for a microbe to cause disease is an error—in the sense that there is nothing to be gained, no selective advantage, in making the host sick. If an organism is an internal parasite, the more that an organism can live congenially with the health of its hosts, the more successful it will be. If its host species goes extinct, it does too. Microbes that kill their hosts, kill themselves, unless they can spread to new hosts; but if they only repeat this pattern in the next host, they are always on the run. So the co-evolutionary struggle produces some selection pressures that minimize virulence in pathogens. Nevertheless, the history of life is beset with diseases.

So the immune system fails and makes mistakes. There are infectious diseases; these can become epidemics. Cancerous cells go out of control, escape the dispatch of the immune system, and become tumors that kill. The closing chapters of an immunology text will be devoted to such troubles as hypersensitivity, when an adaptive immune response occurs in an exaggerated form causing tissue damage, The IgE response to pollen, an innocuous antigen, is hay fever, one of many allergies. There are numerous autoimmune diseases, such as rheumatoid arthritis, which result from the error of self-reactive cells. This is self-defense failed so that immunity self-destroys, the body at war against itself.

Such error and mistake puts us not only in a medical plight but also in a philosophical bind. Are we to praise the immune system, because it usually works so well? Or curse it because it sometimes fails? Or see it as just

there, neither good nor bad? Or have we framed the question uncorrectly? Perhaps the immune system is not so erroneous, even when it fails.

All problem-solving searches have to reckon with error, and this includes mental, genetic, and immunological searches. All creative cognitive and epistemic processes must explore; they proceed conserving what has been learned but with some variation and retention, hit and miss. Scientists and engineers, deliberate though their searches are, proceed to some degree in this manner—immunologists included, not in spite of themselves, but in the nature of their work. They generate and test ideas. They experiment, and fail, and succeed. Immunologists reach theories that are confusing webs of truth and error. They arrange partially successful solutions that have drawbacks. They remember previous successes and, searching about, they hit on things by chance.

Baruj Benacerraf, a Nobel laureate in immunology, summarized his career; "After more than 40 years in research and over 600 publications, I have learned that discoveries are determined primarily by chance observations and are conditioned by past experience and advances in technology" [13, p. 6]. J. H. Humphrey is impressed with the "serendipity in immunology" [14]. Recalling the history of immunologists trying to figure out how antibody-producing cells could make antibodies against virtually every conceivable antigen, Jan Klein remembers, "Many ingenious solutions to this riddle were proposed, but as experimental data accumulated against them each was discounted" [3, p. 26]. Finally, about 1957, after much trial and error, immunologists realized that the immune system itself, in making B cells and T cells, was generating variations, using a mixture of chance conditioned by past experience, and selecting the ones that worked (the clonal selection hypothesis): "The progress of the science has been slow and tortuous. There have been periods during which all of the carefully accumulated data seemingly contradicted each other, all was confusion, and nobody seemed to know what to do next. There have been blind alleys, irreproducible results, erroneously interpreted data, and misleading experiments. There have been controversies, skirmishes—yes, even battles. . ." [3, pp. 31-32].

No one familiar with recent philosophy of science, and certainly no immunologist, should think it irrational to search for solutions using elements of trial and error. We cannot say that the immune system is noncognitive, much less that it is faulty, on this count alone, for the seeming mistakes are an inseparable part of the search process. There is ingenuity and creativity both in immunology as a science and in the immunity in natural history that it studies. True, immunologists figure things out deliberately in ways not possible for the immune system at the cellular level; but the more immunologists are really on the frontiers of creativity, the more they are likely to be groping about as well. The errors in the immune system, analogously, are inevitable byproducts of the creative process.

Life has to be produced nonstop from the previous batch of life, and that means there will be some jury-rigging and provisional solutions. All the historical creativity that we find on Earth is like that. Creativity generates and tests novelties, and the trials are mostly going to be wrong to achieve a few that are right, even partly right. The human body is healthy most of the time, because the immune system is a finely tuned regulatory system patrolling bodily integrity; it knows how to do this on genetic inheritance. This includes a striking capacity to generate novel B cells and T cells, more trial and error against invading disorder in the body. That system usually works, but it sometimes goes wrong, and the possibility of going wrong is inseparable from the possibility of its working right.

Medical immunologists, after long years of research, make discoveries about how to cure diseases and learn to manipulate the human immune system to keep persons in better health. Their genius is to be admired. But when they do this they are discovering an immune system that, independently of any human knowledge of it, was already doing some remarkable medical work all by itself. One way of putting this is to say that the body is as smart as any of the immunologists who study it, and this remains true even when immunologists repair or enhance the immune system. Perhaps that runs the risk of anthropomorphism, but, at another extreme, to treat the immune system as nothing but a causal mechanism runs the risk of failing to understand the cognitive element of acquired learning that is in fact present.

Values Defended and Shared

Immunity in natural history is, from a concluding perspective, a defense of value. Venturing again to read into biology a vocabulary that we first employ in human experience, let us try terms such as "normative," "values," and "shared," most frequently met in philosophy and ethics, to complement the imagery of "the battle within" or "the selfish self," met in immunology and sociobiology. The molecules of the genetic set, given a chance and with life support from their ecology, develop in self-expression. They project a form of life. An organism, a self, is in that sense nondeliberately and nonmorally *normative;* there is a mechanism, a means, an information set by which it distinguishes between what *is* and what *ought to be.* The genome is a set of *conservation* molecules. So the organism grows, repairs its wounds, reproduces, and resists death. It regulates passage across its membranes and borders with its immune system. The biological state that the organism seeks, "idealized" in its programmatic form, is, in this biological sense, a valued state. Biologists regularly recognize this by remarking that a structure, metabolism, or behavior has "survival value." Every organism has a *good-of-its kind.*

The microscopic battle within is the organism defending its own form

of life. That is all it has the capacity to defend, all it has achieved that, from its perspective, is of value. Why not marvel when it does so with skill? The organism has constructed an immune system that surpasses the ingenuity of the genetic system with its novel explorations by T cells and B cells and its capacity for acquired memory. Organisms are not so much selfish beings as self-valuing beings, conserving their biological integrity.

This defense of the individual organism, invoking the immune system, has to take place spatially in an ecology and temporally in a transmitted species heritage over time. The immunity that defends a particular self from the skin in also has to be located in the evolutionary history in which the organism stands; its inclusive fitness is as important as its immunity. When we clarify biological identity in terms of a cybernetic flow of information in a species line, embedded in community—familial, populational, ecosystemic—the phenomenon under discussion is more appropriately viewed in an another gestalt. Fitness is the ability to contribute more to the welfare of others of one's kind, more relative to one's competitors. The system facilitates congruence between generations; sexuality and reproduction expand the individuality first protected by immunity.

All this is going on spontaneously, autonomously, without any animal awareness, much less any humans thinking about it. Now the nondeliberative element becomes important. This kind of value defense does not depend on deliberate cognition, on felt experiences, or human preferences or at all. Immunity is to be seen philosophically in terms of the organism's pursuit and sharing of its own *proper* life (L: *proprium,* one's own), which is all that the nonhuman individual organism can pursue, a life embedded in its population, species, and community. The organism has no other competence.

So the defense of the valued self is interlocked with the transmission of a valuable genetic heritage that makes organisms kindred even in their idiographic separateness. The mechanisms of immunity, though specific to each human person, have a generality that is shared with mice. The fact that immunologists can study mice and extrapolate the results to humans indicates a common heritage. One truth that comes out of immunology is that brother is unlike brother; another is that man is like mouse. Much that we value in our biology is widely distributed, or shared.

Immunology, the science, increases the human capacity for immunity, the biological phenomenon in natural history. A comprehensive account not only has to understand immunity in past natural history, but to understand immunology and immunologists at present. These activities too have to be naturalized, set in the context of the evolutionary natural history out of which both science and scientists come, transcend such history though these may. Immunologists, like immunoglobulins, have become protectors of the self all over again, and the possibilities for future development of such protection are immense. Immunology, a phenomenon in culture, is

itself part of the history of immunity, a phenomenon in nature. This continues the long history of things that are going on over our heads becoming things that go on in our heads, of the natural becoming rational. Immunologists, like our immune systems, help us defend our values, but that is just as much to share our values.

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