The cognitive principle challenges clonal selection

Irun R. Cohen

Here, Irun Cohen argues that the clonal selection paradigm is no longer a convenient paradigm for organizing thinking about the immune system. He contends that most immunologists now investigate questions for which the clonal selection paradigm makes no provision and that one of its major tenets is contradicted by the prevalence of natural autoimmunity. Instead, he proposes a cognitive paradigm.

Mental paradigms are models that simplify complexity, ideas that help to make sense out of the infinitely complex continuum which is reality. No idea can represent reality as it is. A paradigm merely represents a fragment of reality in a way that allows the mind to deal with it: it encodes a part of the world to the mind's specifications. A paradigm is formed and retained because it is useful, not because it is real[1]. A scientific paradigm marks out a conceptual territory for exploration by observation and experimentation. It establishes a world view that defines which questions are worth studying and what answers might be expected. Thus, the prevailing paradigm will bias the way the scientist views and interprets the results of experiment. Certainly, the prevailing paradigm can determine the experiment's publishability. Paradigms must be taken seriously: they influence what we see and what we say. An antiquated paradigm is a hazard.

The paradigm which, for over three decades, has organized immunological thinking is clonal selection[2]. The clonal selection paradigm holds the antigens responsible for organizing the immune system; only those lymphocyte clones bearing receptors that match the antigens encountered by the individual flourish. To avoid autoimmunity, recognition of self is forbidden. Thus does the clonal selection paradigm explain the specificity of adaptive immunity and the tolerance for antigens of the self. The world view inculcated by the clonal selection paradigm has led many immunologists to believe that the primary function of the immune system is to distinguish between the self and the foreign. A textbook by Jan Klein embodies this belief in its title – *Immunology: The Science of Self–Nonself Discrimination*[3].

The clonal selection paradigm identifies autoimmune disease as an accident of self recognition originating from a random mutation of a lymphocyte receptor or from a failure to delete a forbidden clone[4]. Autoimmune lymphocytes arise by chance and express chance specificity; autoimmune diseases should have clinical expressions dictated by chance. Burnet makes the point clear: 'It is of the essence of our approach to immunity that no two cases of autoimmune diseases should be the same'[4].

Flaws in the clonal selection paradigm

Progress in immunology appears to have rendered the clonal selection paradigm incomplete, if not obsolete; true, it accounts for the importance of clonal activation, but it fails to encompass, require, or explain most of the subjects being studied by immunologists today: antigen processing and presentation, the structure and function of major histocompatibility complex (MHC) molecules, multicellular interactions, restrictions in T-cell receptor and immunoglobulin gene usage, superantigens, cytokine functions and networks, suppression, and anti-idiotypes. More importantly, what we have learned about autoimmunity directly contradicts a major corollary of the clonal selection paradigm: autoimmunity is not an aberration, but is a property of all healthy immune systems[5,6]. Moreover, the particular self-antigens recognized by natural autoimmune T and B cells are not random accidents but are a limited and predictable set of antigens (Table 1). Indeed, a particular class of B cells, the B-1 (formerly known as CD5) B cells, appears to specialize in making natural autoantibodies[7]. In contradiction of Burnet's assertion[4], pathological autoimmunity, too, is highly structured: there are only a few dozen autoimmune diseases, each immunologically quite typical[8]. Indeed, a large majority of the patients can probably be accounted for by less than ten different diseases. Thus, the

Table 1. Natural autoimmunity demonstrable in healthy individuals

Autoantibodies[6]	
Cell membrane components:	β_2-microglobulin, spectrin, band 3 protein, secretory component.
Intracellular components:	Actin, tubulin, myosin, keratin, DNA, myoglobulin, cytochrome c, collagen, myelin basic protein, protamine.
Plasma proteins:	Albumin, transferrin, IgG.
Cytokines and hormones:	Interferons, interleukin 1a, tumor necrosis factor, insulin, thyroglobulin.
T cells	Thyroglobulin[23], acetylcholine receptor[24], myelin basic protein[25], hsp65 (Ref. 26), insulin[27].

expression of pathological autoimmunity, like the expression of benign autoimmunity, is not accidental. In a follow-up paper in next month's *Immunology Today*[9], the relationship between natural autoimmunity and autoimmune disease will be discussed; here, I simply note that the existence of natural autoimmunity negates a central principle of the clonal selection paradigm and suggests that the evolutionary aim of the immune system is not to distinguish between self and nonself. In fact the aim of the immune system should escape no one; it is to enhance fitness.

Immunological fitness

Fitness is the term used by evolutionary biologists to describe success in surviving to generate fit offspring[10]. Children born without immune systems and adults who acquire defective immune systems, unless treated by very special measures, die of infection. Hence, it may be concluded that the forces most consequential in forging the immune system are those exerted by infectious agents. (This assertion is true even if some infectious agents like *Treponema pallidum* or Group A Streptococci may make us sick with autoimmunity.) Therefore, the immune system enhances fitness by preventing death from infection. To carry out this function, the immune system (like any other adaptive system) must solve three problems: (1) the signal/noise problem, or how to focus recognition; (2) the context problem, or when to act; and (3) the response problem, or how to choose the most suitable set of immune effects.

The signal/noise problem

Any biological macromolecule can be seen as a conglomerate of potentially antigenic epitopes. Theoretically, if a minimal T-cell epitope is a processed peptide of nine amino acids[11], then any protein could have as many overlapping epitopes as it has amino acids, minus eight. B-cell epitopes are created by the mosaic of conformational features of the protein. A standard bacterium with 10^4 genes could confront the immune system with perhaps 10^6 potential epitopes, at least theoretically. Theoretically too, the receptor repertoire of the immune system should be able to muster lymphocyte clones to recognize all of them. Thus, inherent in any immune response is noise, a paralyzing degree of polyclonal activation. Indeed, some parasites neutralize the immune system by activating it polyclonally[12]. The large numbers of potential epitopes present on every antigen could never be allowed a free hand in selecting all potentially reactive lymphocyte clones. The system must have discriminating filters. To make sense out of the input is to filter out the inessential noise and to concentrate on a manageably small part of reality. Focusing creates signal.

The context problem

But to rescue a signal from noise is not sufficient for fitness; we have to know the context in which the signal arrives. Context bestows meaning. The context tells us if the gun we see is likely to be a toy or a weapon, if it is theater or murder. A processed peptide presented in the pocket of an MHC molecule may constitute an antigenic epitope for a T cell[11], but fitness cannot be promoted without more information. Has the epitope originated from an infection or not? An epitope in the context of infection might best be attacked; the same epitope in the context of repose (no sign of infection) might best be ignored or tolerated. It is not sufficient merely to distinguish whether the antigen is self or foreign: an unnecessary immune response to harmless foreign antigens can incapacitate by allergy; at the very least, such a response can squander limited resources. Appreciation of context is the beginning of wisdom.

The response problem

Contrary to the world view of the clonal selection paradigm, the immune response is not a monotonic reflex triggered by antigen recognition. Indeed, the nature of the response – its quality, quantity, timing and location – is what gives effective meaning to the recognition. For example, the striking differences between polar lepromatous leprosy, polar tuberculoid leprosy and successful rejection of *Mycobacterium leprae* are not due merely to recognition or lack of recognition of the microorganism. In all three cases the microbe is recognized by the immune system; the differences, tragic or happy, are a consequence of the types of cells and cytokines activated after recognition[13].

A formidable feature of the immune system is the richness of its repertoire of responses. The many and diverse types of B cells, antibodies, T cells and cytokines that create the response repertoire can be seen in textbooks and reviews. The biological outcome of an immune response is determined by adjusting the

response repertoire – what the system can do – to the receptor repertoire – what the system can see. The handiwork of the immune system is the product of the two repertoires. The job of the system is not merely to recognize but to mix-and-match repertoires. A suitable mix-and-match outfits the individual ideally to the occasion. There can be no single response that is appropriate to all that is foreign, and the absence of recognition cannot always be appropriate for all that is like self. The naked epitope cannot tell an inexperienced lymphocyte which type of response is appropriate; information about the context is necessary.

The cognitive paradigm

Unstructured encounter with antigens as visualized by the original clonal selection paradigm is indifferent to the problems of focus, context and response. The fact that the immune system solves these problems suggests that we might be better off with another paradigm. I propose that a cognitive paradigm can encompass many of the features of the system now studied by immunologists, features that are beyond the ken of the clonal selection paradigm. In emphasizing the shortcomings of the clonal selection paradigm, I do not mean to imply that clonal activation of lymphocytes does not occur; clonal activation of lymphocytes is a fact. I argue here that clonal activation is only one element in the larger world of immune cognition.

Cognitive paradigms are founded on the idea that any system which collects and processes information will do its job most efficiently by having an internal representation of its subject[14,15]. Simply put, a cognitive system is a system that extracts information and fashions experience out of raw input by deploying information already built into the system; in a sense, a cognitive system is one that knows what it should be looking for. This internal information, which precedes and imposes order on experience, can be seen conceptually as a blueprint for dealing with the world. In the abstract, cognitive systems can be said to behave with a sense of direction; their internal organization endows them with a kind of intentionality[16]. Cognitive systems, then, are not passive processors or recorders of information; they are designed to seek very particular information from the domain in which they operate.

The nervous system, too, uses a cognitive strategy of internal images to structure individual experience[15]. The eye, for example, is not merely a passive recorder of photons; it is wired to seek edges and contours. Preformed images also operate at the highest neural levels: anyone who interacts with infants can readily observe that the human brain begins life imprinted with an internal picture of the human face. Babies soon after birth will gaze intently at human faces, or at any representation that features eyes and a mouth in a suitable alignment ('smiley' is universal)[17]. Babies smile at smiles and cry at frowns, even before they distinguish between individual faces. The brain's internal image of the human face directs the infant to seek out and respond to other humans. This germ-line image is the foundation for the capacity to learn to recognize, interact, and bond to other individuals.

The internal images encoded in the brain function not only to organize the information entering from the external environment; the brain contains a picture of the individual's own body, the neurological homunculus. A common but enigmatic aberration of the brain's image of the self is the phantom limb, the vivid and often painful sensation of the continuing existence of a limb that has been amputated or even of a limb that has been absent from birth[18]. Study of the phantom limb phenomenon has led some neurologists to conclude that the brain's picture of the self is formed by the activities of networks of neurons[18]. In the next issue[9] I shall discuss the immunological homunculus[5,19], the immune system's picture of the self, which also appears to be encoded in cellular networks.

By encoding the environment, images internal to the system define the niche within which the system is designed to act. Bees are born with a hard-wired internal image of the essential flower and its essential nectar; this internal representation allows the bees to recognize and deal with real flowers[20]. Obviously, the genes of real flowers have encoded in the structure and behavior of the flowers an image of the structure and behavior of the bees. The internal organizations of the bees and of the flowers endow them, in an abstract sense, with intentionality; they seek each other. The definition and creation of information by internal representations, the intentionality of a system, is the cognitive principle[14,15].

Note that the word cognitive here does not imply consciousness. The human central nervous system often manifests consciousness; the lymphocytes, the bees and the flowers never do. Likewise, the property of intentionality is devoid of personality; the immune system intends to fight infection not because there exists a little man inside it who whispers in its ear, but because the internal organization of the system is about fighting infection. The system has evolved to behave that way. Note too that an internal code, like any code, is only information. Its existence is independent of any particular material: a bacterial protein may be effectively encoded by a different molecule (a nucleic acid sequence), by a convention (the words 'bacterial protein'), or even by a function (its being bound by a certain antibody). In fact, the antibody to the protein is a kind of negative or mirror image of the protein. Which code is the correct one depends on its utility in the particular context.

It is worth digressing to note that, just as the immune system is adapted to our parasites, our parasites are adapted to the immune system. Their life depends on it. The open-ended antigenic variation of parasites is the parasitic internal image of the effectively open-ended repertoire of antigen receptors. The parasites' internal image of the host may also include host antigens and host immune system regulatory molecules, internal images that enable the parasites to survive in the face of host immunity. Microbial adhesion molecules actually encode the microbe's image of the host's anatomy. Whether the host or the parasite is the information system or the environment is relative to one's point of view.

Varela, Coutinho and their colleagues too have called attention to the cognitive properties of recognition, learning and memory as fundamental to immune behavior[21,22]. My purpose here is to show, however briefly, that the principle of internal images applies to adaptive biological systems generally, be they neurological, ecological or immunological, and to illustrate that a cognitive paradigm can encompass the search for context, the extraction of signal from noise, and the deployment of the response repertoire in the service of fitness characteristic of the immune system.

Epilogue

This paper has pointed out the incompleteness of the clonal selection paradigm and has introduced the idea of a cognitive paradigm. A cognitive paradigm for immunology states that the immune system must know how to focus on particular antigens and how to evaluate their context before it actually encounters the antigens; the immune system seeks certain antigens in a certain context. Thus, the cognitive paradigm differs from the clonal selection paradigm in proposing that the immune system is not passively selected by the antigens, it is selective of the antigens; clonal selection is structured by antigen selection. It remains to discuss how antigen selection operates through internal images of infection and of the self (the immunological homunculus). These images in part are encoded in the germ line, refined in the thymus, and primed by mother[9].

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The cognitive paradigm and the immunological homunculus

Irun R. Cohen

In last month's issue of Immunology Today, *Irun Cohen discussed the inadequacies of the clonal selection paradigm and proposed a cognitive paradigm in which preformed internal images guide and restrict the process of clonal activation. Here he clarifies the nature of these internal images, drawing on concrete examples from the image of infection and the image of self, the immunological homunculus.*

Contrary to the expectations of clonal selection, the germ-line effectively encodes a primitive internal image of bacteria, viruses, and the context of inflammation[1]. These images do not depend on the antigen receptors of lymphocytes. Components of complement can recognize some microorganisms directly, targeting them for phagocytosis or lysis[2]; natural killer (NK) cells can respond to bacteria[3]; macrophages and other white blood cells have invariant germ-line receptors for lipopolysaccharides, muramyl dipeptide cell wall elements, and other distinctly bacterial molecules; many different cells recognize viral nucleic acids and the interferons that are elaborated as a consequence of viral infection. This primitive information arms cells with the capacity to recognize and respond to invaders: to secrete cytokines; to migrate, adhere, and penetrate tissues; to engulf bacteria and viruses; to activate enzyme systems and generate toxic molecules and free radicals that can kill invaders[3].

The germ-line picture also encodes the organ or site in the body in which invasion has taken place. The patterns of lymphocyte migration, determined by molecules encoded in the germ line, compartmentalize the body[4]. Specialized types of monocytes are resident in various tissues – skin, liver, lungs, gut, eye, nervous system – and each type of monocyte processes the information of invasion in specialized ways.

The germ-line picture of infection and infectious agents developed over evolutionary time as a result of the fact that parasites are not only packages of antigenic variation; they are constrained by invariant structures and programs dictated by their ecology – their need to exist in defined anatomical and biochemical niches, to reinfect new hosts, and so forth. These obligatory manifestations of parasitic life were exploited by the germ-line to evolve an internal picture of infection. Charles Janeway[5] reasons that the immune system evolved to discriminate infectious nonself from noninfectious self.

Figures 1 and 2 illustrate the main features of the clonal selection and cognitive paradigms. The diagram of the clonal selection paradigm (Fig. 1) shows its appealing simplicity. The diagram of the cognitive paradigm is more complicated (Fig. 2) but it serves as an outline and a summary of this article.

Sensing context

Processing and presentation

Antigen presenting cells (APCs) can, according to the context, modify expression of cell interaction molecules, major histocompatibility complex (MHC) molecules, and adhesion molecules; these molecules determine how antigen signals are heeded by T cells[6]. The presence or absence of stress or inflammation influences the uptake of external molecules and the degradation, processing, and presentation of both external and self epitopes. Indeed, immunologists discovered empirically that the immunogenicity of most antigens

including self antigens is augmented by the presence of bacteria. Complete Freund's adjuvant (killed mycobacteria in oil) empowers self antigens to induce experimental autoimmune diseases[7]. Apparently, a destructive effector response to the self is legitimate when the self antigen is in the context of infection staged by the adjuvant. In this case, the immunologist has learned how to lie to the immune system. Note, however, that the healthy immune system usually can be fooled only once. Autoimmune diseases often go into remission spontaneously and cannot be induced a second time[8]. The system can learn to interpret context.

The importance of context is, likewise, illustrated by immunization in the absence of an adjuvant signal. A foreign protein molecule administered without adjuvant usually induces no immune response, and may even induce tolerance to the antigen: there will be little or no response in the future to the antigen administered with an adjuvant. Indeed the immune system may be tolerant of a viral antigen when it is expressed as a self antigen (early in development and no sign of infection) in a transgenic mouse[9]. But tolerance to that pseudo-self antigen is lost when the mouse is later infected with the virus. The context of infection can be more decisive for the response than the foreign or self identity of the antigen; the 'second' signal may be more fundamental than the epitope[5]. Thus, the immune system is driven not by antigens, but by antigens-in-context. The intentionality of the system, expressed by the signals accompanying antigen presentation, is to fight infection[1].

Filtering and focusing

The APCs[6] report the context of the antigenic encounter and, by processing and presenting, they serve as a filter and a lens: a filter that destroys molecular noise, and a lens that focuses the attention of lymphocyte receptors on particular molecular signals. Stable binding of the processed peptide fragments of antigens to MHC molecules requires that the peptides contain certain amino acid motifs at particular positions in the peptide sequence[10]. Thus, only a fraction of any antigen is preserved as a potential signal for lymphocytes. The APC is the germ-line's way of focusing attention on priority objectives. Like the retina[11], the APC acts as a feature detector; it processes information with intent.

Priming the repertoire in the thymus

The germ line, as we have seen, deals with the problems of focus and context; on this basis the receptor repertoire, generated somatically, is now able to act. However, before it confronts the outside world, the receptor repertoire is primed by the self. During the maturation of T cells in the thymus, the thymic environment drives some clones to expand (positive selection) while it activates other clones to die a programmed death (negative selection). (Many clones are thought to die a neutral death because of lack of positive selection.) The clonal selection paradigm has led to the supposition that these processes, negative selection in particular, exist to produce self tolerance, that is to rid the T-cell repertoire of potentially self-recognizing lymphocytes[12]. The cognitive paradigm suggests that the shaping of the lymphocyte repertoire during ontogeny is to help inscribe internal images for recording later antigenic experience; it may include the positive selection of some self-recognizing T cells, along with the negative selection of others. Some T cells that do not recognize self may die a neutral death. Analysis of the specific molecular environment in the thymus, the peptidic self[13], will clarify the thymic contribution to a selective image of the self, the immunological homunculus.

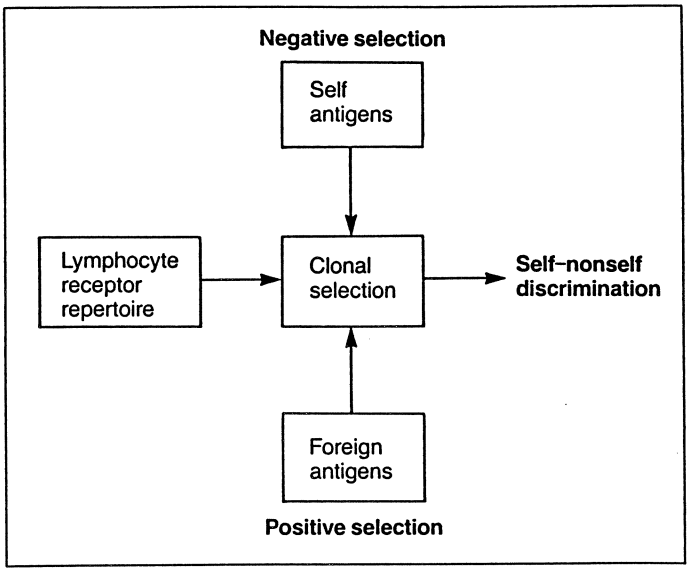

Fig. 1. *The clonal selection paradigm. This paradigm proposes that the receptor repertoires of B and T cells are organized by two antigenic forces: the self antigens, which negatively delete or anergize potentially autoimmune clones, and the foreign antigens, which positively select the remaining clones that have complementary receptors. The output of the system is the discrimination between the self antigens, which are ignored, and the foreign antigens impinging on the system, which are rejected.*

Help from mother

Antibodies binding to a particular antigen greatly enhance the uptake and processing of that antigen; preformed antibodies thus flag specific antigens for special attention[14]. Mother effectively primes her offspring's immune system by transferring a sample of her antibodies[15]. Her antibodies to infectious agents protect the baby during the early period of parasitization; newborn ungulates deprived of maternal antibodies die of infection[16]. Since Mother has experienced and survived the local parasitic environment, her image of that environment carries a warranty. Mother thus provides a more detailed image of the immediate external environment to augment the primitive image of infection carried by the germ line. Moreover, her natural autoantibodies can also help the child develop his/her own immunological homunculus.

But Mother gives more than her antibodies; babies usually, probably always, receive a transfusion of maternal blood in the course of normal birth. The blood transfusion contains living T cells, B cells, monocytes, and antigens. Although the mechanism is

not clear, blood transfusions have a profound influence on immune reactivity; transfusions of white blood cells have been discovered to reduce the rejection of allografts[17]. Mother's milk too contains lymphocytes, antibodies and antigens. Indeed, congenital exposure to maternal HLA antigens that the individual has not inherited appears to influence susceptibility to autoimmune disease later in life (J.J. Van Rood, submitted). Thus, our immune system, like our mitochondrial DNA, is imprinted matrilineally.

Antigenic experience and receptor images

The somatically generated receptor repertoire records the antigenic experience of the individual and so expands and refines the threefold set of primary internal images: the germ-line image of context and infection, the thymic image of self, and Mother's image of the environment. These primary images constitute a reference point that defines the intentionality of the immune system: which antigens it should seek out and remember. Thus, clonal activation is determined decisively by the primary internal organization of the immune system. Clonal selection by itself does not organize the immune system; rather, it is the state of organization of the immune system which organizes clonal selection. I wish to comment on two organizational elements: immune regulatory networks in general and the immunological homunculus.

Immune networks

Like a brain or a computer, the power of the immune system to rank signals, make decisions, and deploy effector forces must come from its many connected elements, its networks. Jerne promoted the idea of regulatory networks in his anti-idiotypic theory[18], a theory advanced by the work of many others (for example, see Refs 19 and 20). V-region-connected networks such as Jerne's can generate cognitive attributes like recognition, learning and memory[21]. However, theories based entirely on V-region networks miss the images of context and infection which are the products of evolutionary experience and which precede V-region connectivity. Not only the V-regions of antigen receptors (idiotypes), but germ-line-encoded cytokines[22], adhesion molecules[23], cell trafficking patterns[4], and, possibly, superantigens[24] organize immune behavior. Because these elements influence one another, the immune system can be seen to be composed of many networks connected by a variety of ligands.

The immune system, like the brain[11], uses parallel processing. Any package of antigens (cells, microorganisms, viruses) interacting with the immune system is dealt with simultaneously along different network channels. The germ-line elements (complement, NK cells, APCs, and so on), the B cells, and the T cells each analyse different features of the antigenic entity and extract the special information they intend to see: the signals of infection, the native conformation of macromolecules, the motifs and structure of processed peptides. These parallel channels, along which information is processed, interconnect through the interactions of monocytes, T cells, B cells and their products. For example, a B-cell receptor may recognize an antigen molecule by reason of the molecule's conformation, but the B cell won't be activated to secrete IgG antibodies, unless a T cell confirms that it can recognize a peptide sequence of the molecule processed and presented by the B cell. For safety and reliability, immune decisions are made by committees, not by single cells. Obviously, which particular cells comprise the committee determines the outcome. Note that immunologists have learned to influence committee decisions by immunizing with carriers and adjuvants.

Immunological homunculus regulation of autoimmune disease

The immunological homunculus is an internal image of the self acquired by early recognition of self antigens, both in the thymus and in the periphery. The self image is, in fact, composed of the committees of T and B cells that deal with the dominant self antigens[25–27].

At the outset, one may ask why the immune system bothers making internal images of self. If the intention of the immune system is to fight infection and if self tolerance based on clonal deletion is so logical to immunologists[12,28,29], why has evolution been forced to accommodate natural autoimmunity? Some may claim that natural autoimmunity is a mistake, a leakiness in thymic clonal deletion and anergy. However, natural autoimmunity is a universal phenomenon that has persisted throughout evolutionary time, and so must serve some useful purpose. I propose that the selective pressure for organized natural autoimmunity has been exerted by the molecular conservation of the biosphere. Cellular life depends on the functions of certain critical, and therefore highly conserved, molecules. Since molecular structure is the raw material of antigens, our conserved molecular self cannot be totally different immunologically from the conserved molecules of our parasites. This means that the immune system is constantly bombarded by self-like foreign molecules (such as the 65 kDa heat shock protein: hsp65) which arrive with parasites in the context of infection[30]. Autoimmunization which cannot be avoided must be dealt with.

Happily, besides posing a problem, the conservation of critical molecules can provide an immunological opportunity. Conserved molecules shared by different invaders can serve as common antigens. For example, hsp65 is hyperexpressed during infection both by microbial cells and by host cells; it is a trustworthy sign of infection[30]. Indeed, the immune response to many infectious agents often focuses on the most highly conserved, self-like antigens of the invader[27,30]; the immune system is capable of using autoimmunity to an hsp molecule to help reject an invading microbe[31]. I propose that the immunological homunculus organizes and regulates autoimmunity naturally to hsp65 and to other conserved molecules so that autoimmunity can be used to fight infections, reject tumor cells, or repair tissue damage without paying the price of chronic, progressive autoimmune disease. Considering our enterprising parasites, I dare say that an immune system incapable of autoimmunity is an immune system

incapable of guardianship. Autoimmunity is not merely a burden and an opportunity, it is a necessity.

Natural autoimmunity is benign because the immunological dominance of the major self antigens comprising the homunculus is encoded by two committees of cells: naturally-autoimmune T and B cells and their anti-idiotypic regulatory cells[25–27]. Dominant self antigens, in short, are self antigens anticipated by committees. The advantage is that dominance is welded to regulation; activation of homunculus autoimmune cells, even in the context of infection and inflammation, automatically activates a regulatory network. The autoimmune reaction to homunculus autoantigens is thus controlled; it withdraws from the effector mode when it is not needed. Consider that disease is not caused merely by recognition of self, but by an aggressive effector response that may (or may not) result from such recognition[27].

Moreover, the immunological dominance of the self antigens encoded within the homunculus acts as a protective attractor: by automatically diverting to themselves the brunt of any autoimmune process that happens to visit the organ, the dominant autoantigens spare the need for active tolerance to the other, non-dominant self antigens. Hence tolerance to the non-dominant self antigens is a side effect of the dominance encoded by the homunculus. Each tissue may have one or more dominant guardian self antigens: myelin basic protein in the central nervous system, myosin in muscle, collagen type II in joints, hsp65 in inflammation in general. The few dominant antigens of each organ constitute an immunological signature of the organ. This signature is encoded in the interactions of the networks of autoreactive cells centered around the dominant antigens. The nervous system, too, uses a signature strategy to define the organs that belong to the body[32]. It is the signature that defines the healthy self. Sercarz and his associates have directed attention to the fact that the non-dominant 'cryptic' epitopes (a counterfeit signature?) can be dangerous when they are noticed[33]. The homunculus concept explains the curious fact that natural autoimmunity is limited to relatively few self antigens; these self antigens are selected for their contribution to fitness.

The structuring of natural autoimmunity, which is the homunculus, also explains why there are so few autoimmune diseases and why their choice of target antigens seems to be so uniform. The relatively rare development of a chronic, progressive, and destructive autoimmune disease results from defective regulation of dominant natural autoimmunity. For example, systemic lupus erythematosis can be unleashed by immunization of mice to an idiotype of an anti-DNA antibody administered with a strong bacterial adjuvant[34]. Likewise T-cell autoimmunity to hsp65 is naturally benign[35] but, when it fails to get toned down by regulatory cells, anti-hsp65 autoimmunity can cause type I diabetes in mice[36] or arthritis in rats[37]. If weak regulatory connections contribute to the transition of natural autoimmunity to autoimmune disease, then a rational therapy for autoimmune disease may involve strengthening homunculus regulatory cells by active measures such as T-cell vaccination[38–41]. Indeed, endogenous T-cell vaccination may occur as the result of suffering a bout of an experimental autoimmune disease[8]. Perhaps much human autoimmunity, too, is self-curing and, therefore, undiagnosed.

Natural autoimmunity, the homunculus, promises to be a revealing field of inquiry. It remains to be discovered why the homunculus is composed of just certain self-antigens (the self signature), how the regulatory T and B cells get organized around the natural autoimmune T and B cells, how the regulatory cells control the effector state of the autoimmune cells, and if and how T-cell receptor restriction[42] fits into the homunculus. The immunological homunculus is not some 'little man' sitting outside of the system who rules autoimmunity; the homunculus is the characteristic organization of autoimmunity itself.

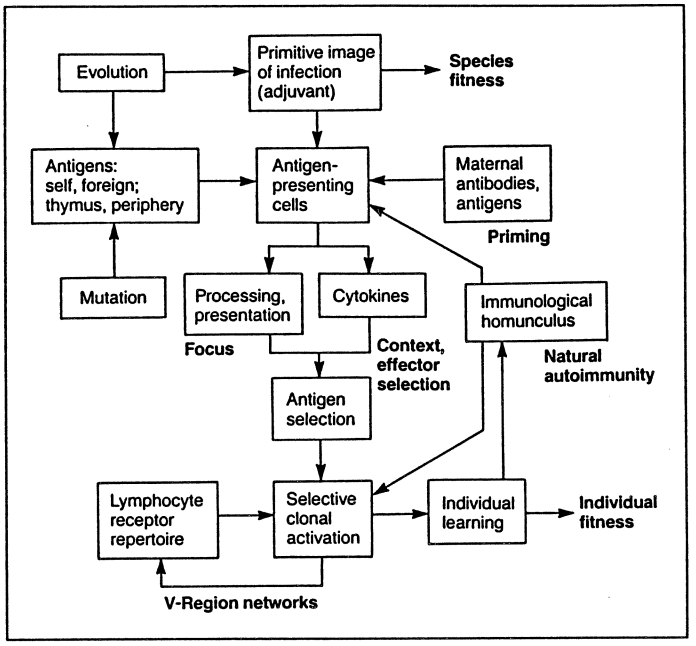

Fig. 2. *The cognitive paradigm. This paradigm proposes that clonal activation, which is tailored by the antigenic experience of each individual, is subject to the intervention of antigen selection, a process which expresses the evolutionary adaptations of the species. Antigens, self and foreign, are determined by evolution and by mutations. Evolution has also encoded, within the germ line, mechanisms of innate immunity that constitute a primitive image of infection. The agents of this primitive image include the APCs: macrophages, dendritic cells, endothelial cells, tissue cells and even B and T cells themselves. These cells ignore, destroy, or process and present certain epitopes and elaborate various cytokines. These activities provide focus, sense context and activate particular effector mechanisms. The outcome is the selection of certain antigens and molecular motifs as signals that function to activate selected clones. This form of antigen selection, in addition, is primed by maternal antibodies (an image of the infectious environment) and by maternal antigens. The immunological homunculus (an image of the key self antigens) is formed by contact with self antigens in the thymus and in the periphery. It includes T and B cells that recognize a limited number of dominant self antigens and the regulatory cells that interact with the autoimmune T and B cells. The homunculus is the expression of natural regulated autoimmunity; it influences the functioning of the APCs, the specificity of clonal activation, and the behavior of the regulatory networks, some of which are connected by V-region idiotypes. The output of the system is fitness, which profits from both foreign and self recognition.*

Epilogue

The evolutionary adaptations of the germ line, which defines the fitness of the species, culminate in suitable antigen selection by the apparatus of processing and presentation. The immune fitness of the individual is the outcome of selective clonal activation as it is constrained and guided by the process of antigen selection. Thus does the cognitive paradigm (Fig. 2) differ from the clonal selection paradigm (Fig. 1). Internal images allow the system to encode the essential fragments of the antigenic world to the system's specifications and utility; adaptation is fitting antigen selection and suitable response. Consider it this way: the cognitive paradigm is an immunologist's paradigm of the immune system's paradigm of the molecular world.

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