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The Self, the World and Autoimmunity

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The Self, the World and Autoimmunity

Autoimmunity—in which the immune system recognizes and attacks the self's own tissues—is not as simple as it seemed. Self-recognition appears to be at the heart of health as well as of certain diseases

by Irun R. Cohen

It is generally assumed that the main job of the immune system is to distinguish between what is "self" and what is "not self." Once the distinction has been made, "self" is preserved and "not self" is destroyed. At the most general level, of course, this is true, and human beings remain alive and healthy only because it is so. Recently it has become clear, however, that at a finer level of detail the distinction between self and other is not absolute. One of the paths to this insight has been provided by the autoimmune disorders, in which the immune system attacks normal, healthy tissue. Autoimmune disease, which may be crippling or fatal, can strike any tissue or organ. Its victims are often in the prime of life, and for unknown reasons they are more frequently women than men.

Work in my laboratory on a form of autoimmune arthritis shows that the basis of autoimmunity may be a resemblance between a specific foreign molecule and a molecule of the self. What is more, our work is consistent with a model of the immune system in which the immune-system receptors that perform the work of recognition can themselves be recognized by other receptors. Such "self-recognition," which was strictly outlawed by older models of the immune system, may form the basis of a network whose equilibrium keeps the body healthy. When it is disrupted, as it is in autoimmunity, disease results. This new picture, in which self and world are no longer absolutely distinct, has already begun to yield practical benefit in the form of vaccines that may ultimately ease the substantial suffering caused by autoimmune diseases.

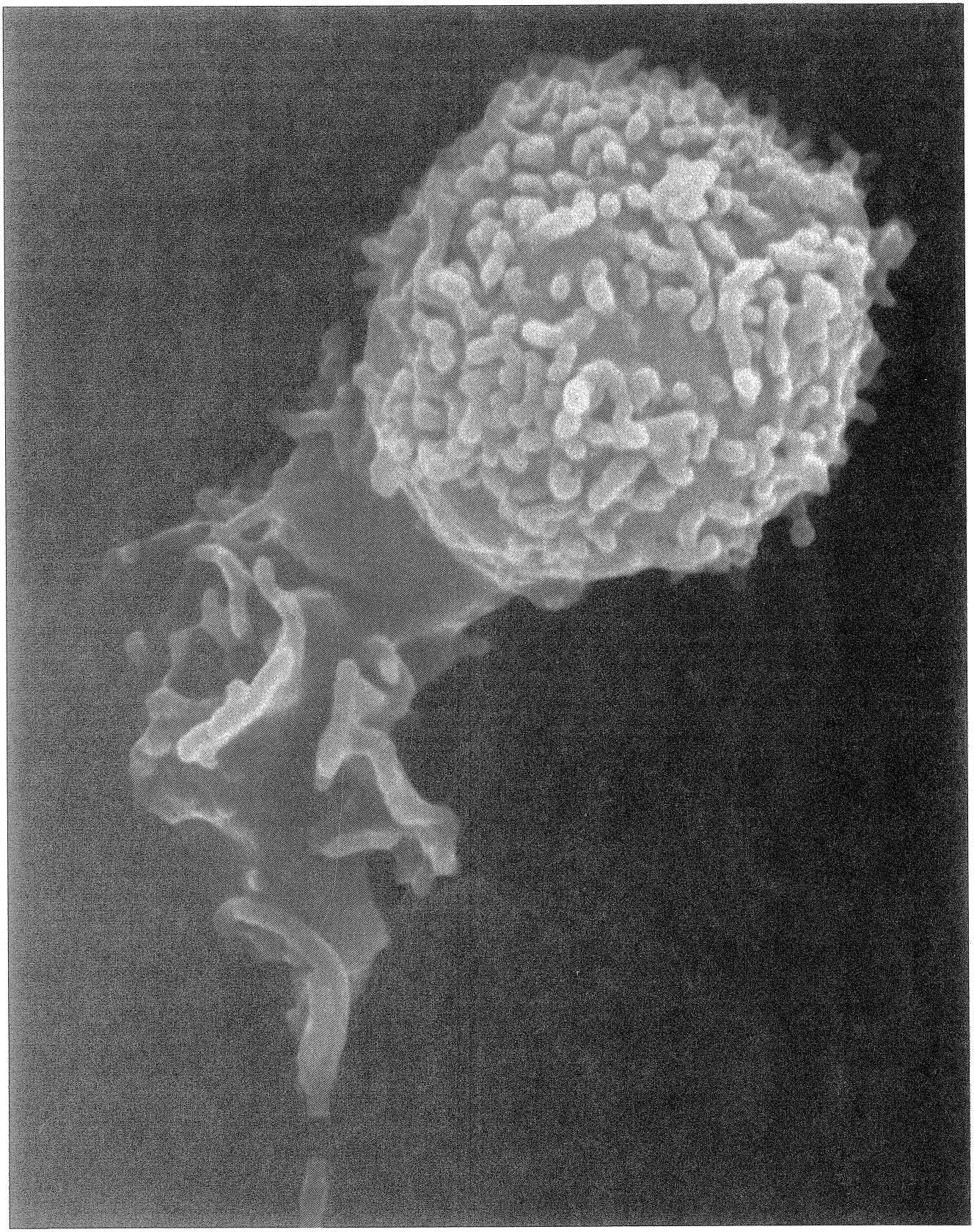
The list of autoimmune diseases is both long and disturbing. It includes multiple sclerosis, in which the tissue attacked is myelin (a substance that sheathes nerves in the central nervous system); myasthenia gravis, in which the target is a receptor molecule for the important neurotransmitter acetylcholine; rheumatoid arthritis, whose target is the peripheral joints; type I (juvenile) diabetes mellitus, in which the cells producing insulin are destroyed, and systemic lupus erythematosis, in which DNA, blood vessels, skin and kidneys are attacked. In contrast to AIDS, which is marked by an inactivation of key cells in the immune system, in all these diseases the immunological response is strong and well focused; it is, however, directed at some essential component of the body. The immune system is itself the culprit. How can that be?

Clearly the answer lies in the problem of recognition. That problem in turn touches on the cells that mediate recognition in the immune system: the lymphocytes. The immune system includes two such classes of cells, which are called *T* lymphocytes and *B* lymphocytes. Both types arise from stem cells in the bone marrow. The stem cells, however, lack the receptors that enable *B* and *T* cells to recognize specific molecules as targets for immune attack. Such immune receptors appear as the multipotential stem cells mature. As a result of the process of maturation, each *B* or *T* cell ultimately comes to have many copies of one immune receptor on its surface and therefore is able to recognize only one other molecule. Any molecule so recognized is called an antigen.

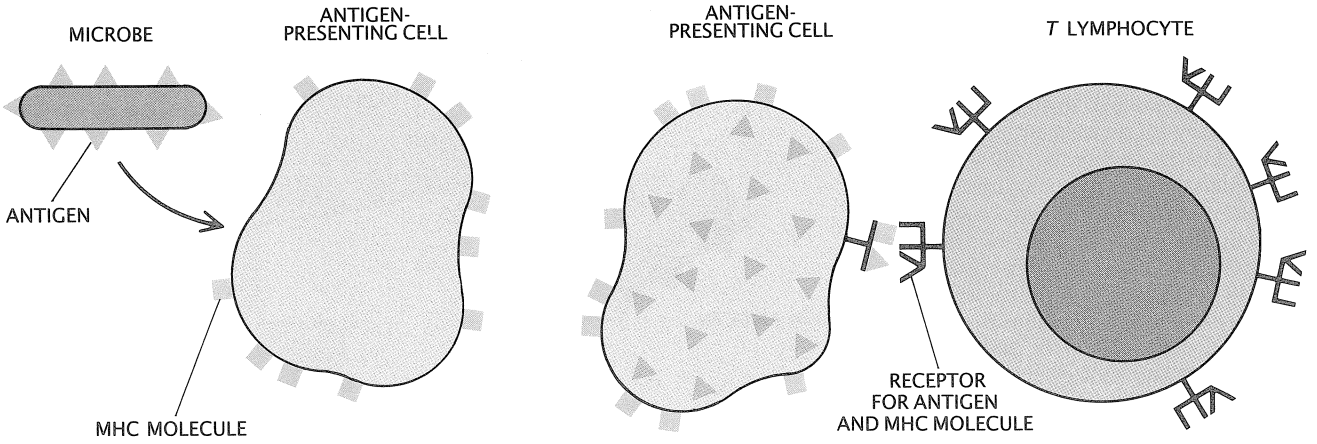
One of the remarkable features of the process of recognition is that it requires not the whole antigen but only a small piece known as an epitope. If (as is often the case) the molecule to be recognized is a polymer such as a protein or a sugar chain, the epitope frequently consists of as a few as from four to six of its thousands of monomeric subunits (amino acids in proteins, sugar units in sugar chains). The shape and the electric charge of each epitope are such that it will best fit a particular receptor. When an epitope finds its complementary receptor, they form a reversible association that generates a signal in the *T* or *B* cell.

At the heart of this process is the fact that each lymphocyte bears receptors with but a single specificity. For the immune system to be able to recognize a wide range of pathogens, however, there must be a great diversity of receptors, and indeed new receptors are constantly being produced at random by a process of genetic recombination in the progenitor stem cells. Not all the receptors created in this way are equally useful, and the immune system weeds out the unnecessary ones by a process called clonal selection. The lymphocyte whose receptor happens to have the closest fit to an epitope on a microbial antigen enjoys an advantage over its competitors: it replicates faster, and soon it may come to predominate over the other *T* and *B* cells in its vicinity.

The descendants of the progenitor make up a clone that not only increases in size but also differentiates into specialized forms. *B* cells may become plasma cells, which secrete antibodies (molecules with the same shape as the clone's antigen receptor), or memory cells, which persist



T LYMPHOCYTE, a white blood cell that forms an essential part of the immune system, is shown magnified 30,000 diameters. The villi (surface protuberances) are caused by the ruffling of the cell's outer membrane; they increase the surface area available for transactions with the environment. The stalklike structure extending from the cell body (known as a uropod) appears to have a role in cell mobility. The cell shown here is a *T4* "helper" lymphocyte; it facilitates the action of other immune-system cells. By recognizing and attacking joint cartilage, helper *T4* cells cause an experimental autoimmune disease called adjuvant arthritis. The micrograph was made by Yaakov Naparstek and Dorit Gurfel of Hadassah University Hospital in Jerusalem.



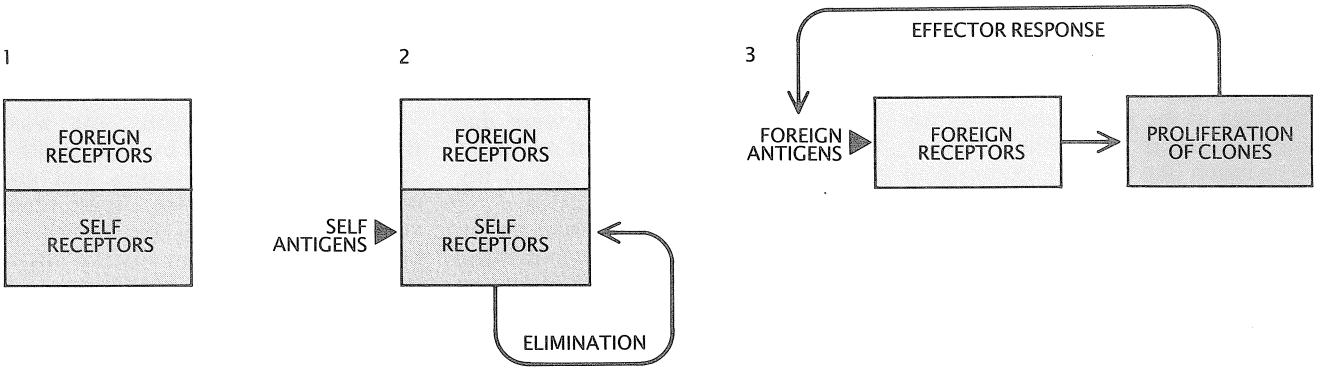
T CELL RECOGNIZES ANTIGEN presented by a specialized cell. An antigen is any molecule that is recognized by a receptor on a lymphocyte or by an antibody. When the antigen-presenting cell encounters a microbe, it digests the invader and presents its components to the *T* cell, along with molecules of the major histocompatibility complex, or MHC, which belong to the antigen-presenting cell itself. The fit of the antigen and MHC molecules with the *T* cell's receptor triggers a response in the lymphocyte.

to identify the epitope with increased efficiency if the pathogen returns. *T* cells mature into one group bearing a surface marker known as *T*4 and another bearing a marker known as *T*8. Within each group are cells that act directly ("effectors") and others that act by influencing other immune-system cells ("regulators"). *T*8 effectors are cytotoxic: they kill cells bearing a specific antigen. *T*8 regulators are suppressive: they inhibit the activities of other *T* or *B* cells. *T*4 effectors damage tissue by activating other white cells; *T*4 regulatory cells are "helpers" that facilitate the action of both *B* and *T* cells.

Now, the random generation of new receptors and their winnowing by clonal selection endows the immune system with great flexibility. The number of possible receptor structures is enormous: perhaps millions of different *T*-lymphocyte clones and hundreds of millions of *B*-lymphocyte clones. From the randomly generated receptors that are continually being produced, clonal selection narrows the field to a few dominant types for each antigen. From a theoretical point of view clonal selection can be seen as a form of digital processing, in which the system is able to direct its attention to the most relevant information (the receptor that best fits an epitope) and disregard the rest (all, or almost all, competing receptor-epitope pairs).

Yet that very flexibility is the source of a problem: self-recognition. If the immune system can recognize almost anything, why not the molecules that belong to the self? F. Macfarlane Burnet of the University of Melbourne, author of the theory of clonal selection, proposed a solution to the problem of self-recognition. During prenatal development, Burnet argued, all the antigens that were present would be self antigens. If recognition of an epitope during gestation triggered clonal suicide, the immune system would be purged of all self-recognizing clones. Recognition of epitopes after birth would induce active immunity, but by then the immune system would be blind to self structures. Burnet explained the appearance of autoimmune disease by exposure after birth to self-antigens that had been accidentally sequestered during gestation.

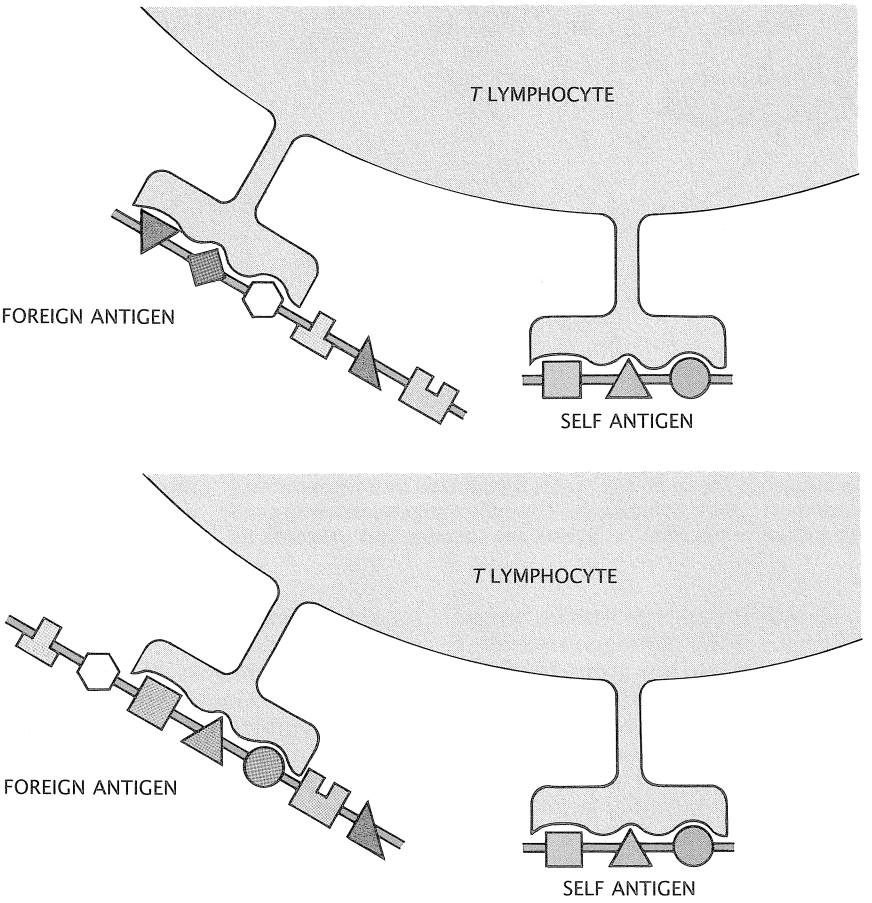
To be reliable, however, clonal elimination requires distinguishing absolutely between self and not-self: receptors that recognize self must be eliminated and those that do not must be spared. Yet it seems clear



CLONAL SUICIDE was a theory developed to account for the absence of autoimmune disease in most people. A clone is a group of cells descended from the same progenitor and hence genetically identical. The immune system can create clones capable of recognizing both self and foreign antigens (*1*). In clonal suicide all clones having receptors for self antigens are eliminated before birth (*2*). Clones that recognize foreign antigens persist. On encountering the corresponding antigen, they proliferate and differentiate to combat the invader (*3*). This theory was formulated in the 1950's by F. Macfarlane Burnet of the University of Melbourne. Recently it has become clear that self and foreign antigens cannot be distinguished by such a simple mechanism.

that such an absolute distinction cannot easily be made. One reason is that although the receptor-antigen relation is generally thought of as a lock-and-key affair, in reality the fit is not exact or exclusive. Within certain limits a single receptor can combine with many different epitopes, each of which it fits with greater or lesser precision. The capacity of millions of different receptors to bind many epitopes enlarges the functional repertoire so greatly that it is difficult to imagine that any biological molecule could pass unrecognized by at least one receptor—including the molecules of the self.

The challenge is compounded by the fact that the self and the invader are made up of the same building blocks: proteins, carbohydrates, nucleic acids and lipids. What is more, molecules such as enzymes or hormones that perform key biological functions tend to be conserved in evolution so that self and invader may have identical—or at least very similar—molecules. Finally, it seems that some pathogens actually make hostlike antigens as a means of disguise. For example, leishmania parasites (some types of which cause trypanosomiasis) synthesize antigens similar to those of the red blood cells of their mammalian hosts. It appears that antigenic "mimicry" is a persistent feature of the struggle between self and pathogen.



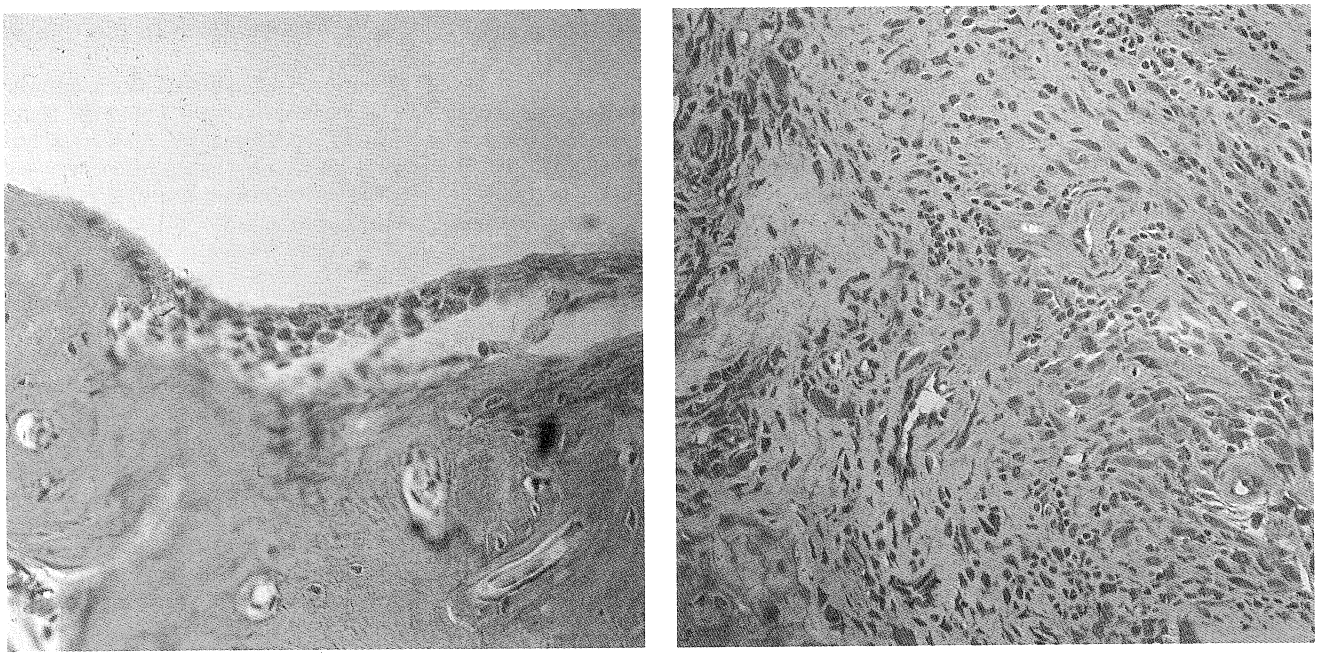
ANTIGENIC MIMICRY is based on a resemblance between a self antigen and a foreign one. Antigens are often polymers such as proteins or sugar chains; the sequence of monomeric subunits underlies the lock-and-key fit with the receptor of a lymphocyte or an antibody. If a self antigen and a foreign one resemble each other, both may fit the same receptor. The resemblance may arise because different monomers have similar shapes (*top*) or because different polymers share a sequence of subunits (*bottom*).

To understand the role of antigenic mimicry in autoimmunity my colleagues and I studied an experimental disease of rats called adjuvant arthritis, which was first observed by Carl M. Pearson of the University of California at Los Angeles in the 1950's. Pearson noted that rats inoculated with a mixture of mineral oil and killed organisms of *Mycobacterium tuberculosis* (the tuberculosis agent) developed arthritis. Adjuvant arthritis caused degeneration of the cartilage in the joints, and its symptoms, Pearson and others noted, were much like those of rheumatoid arthritis. Rheumatoid arthritis is typically manifested as a progressive inflammation of hands and feet. Unlike osteoarthritis (which often accompanies aging), rheumatoid arthritis typically strikes young women, and it can lead to tragic deformity.

Since both rheumatoid and adjuvant arthritis were assumed to be due to autoimmunity, my co-workers and I hoped that explication of the disorder in rats would help us to understand the human disease. The tissue damage seen in adjuvant arthritis was characteristic of *T* lymphocytes rather than *B* lymphocytes or other immune components, and so our strategy was to isolate the clones of *T* cells that were attacking the cartilage in the rats' joints. Although the strategy sounds simple, in actuality it required some substantial technical advances, most of which were due to the pioneering work of Avraham Ben-Nun, who was then one of my graduate students.

Ben-Nun's work was based on another induced autoimmune disorder, known as experimental autoimmune encephalomyelitis (EAE). Considerably more was known about EAE than about adjuvant arthritis. It could be induced in laboratory animals by inoculation with basic protein, a component of myelin in the central nervous system. The immunity to basic protein is manifested by paralysis (often fatal) and inflammation in the region of the brain and spinal cord where the nerve fibers are sheathed in myelin. Some workers consider EAE to be the best laboratory model of multiple sclerosis, and much work had gone toward characterizing the epitopes of basic protein that are responsible for EAE in rats, guinea pigs and mice as well as in other experimental animals.

Like adjuvant arthritis, EAE was thought to be caused by *T* cells rather than *B* cells or antibodies, and our strategy was to isolate clones of *T* cells that responded specifically to basic protein. Ben-Nun worked out a method for growing such clones. *T* cells from rats immunized against basic protein were grown in a culture medium containing the basic-protein antigen. Although the cells that recognized basic protein were a small minority, the presence of their antigen stimulated them to proliferate at the expense of the other lymphocytes: it was clonal selection in tissue



CARTILAGE DAMAGE, hallmark of adjuvant arthritis, results when *T* lymphocytes attack joint cartilage. The micrograph at the left shows rat joint tissue eight days after inoculation with an "adjuvant" containing ground-up *Mycobacterium tuberculosis* (the tuberculosis pathogen) in mineral oil. Lymphocytes have begun to invade the cartilage (*upper layer of tissue*). The micrograph at the right, made 27 days later, shows the normal cartilage architecture extensively disrupted by white blood cells.

culture. That procedure enabled us (in this work Ben-Nun and I collaborated with Hartmut Wekerle, then at the Max Planck Institute for Immunobiology in West Germany) to obtain pure clones of *T* cells that respond to basic protein; all the clones isolated so far have been of the *T*4 type.

Further work showed unequivocally that these *T*4 cells cause EAE. Yaakov Naparstek showed that they accumulate in the brain and spinal cord just before the onset of paralysis. Moreover, we were able to retrieve anti-basic-protein *T* cells from immunized rats and, by injecting them, cause EAE in other rats. This was the first time a specific clone of *T* cells had been shown without question to be responsible for a known autoimmune disorder. Paradoxically, although the *T* cells from the immunized rats were able to cause disease, in some instances the rats they were taken from had already recovered from their severe paralysis and seemed to be clinically well. That perplexing finding implied the existence of mechanisms for holding autoimmunity in check—a subject to which I shall return.

Soon after these experiments were done, Joseph Holoshitz, who was spending a leave in my laboratory, suggested that we apply our experience with EAE to adjuvant arthritis. It seemed a sound idea. The catch was that in the case of EAE the antigen that caused the disorder—basic protein—was well known to begin with. In the case of adjuvant arthritis, however, the relevant antigen was not known. It was assumed that the antigen must be one belonging to *Mycobacterium tuberculosis,* but *M. tuberculosis* includes many thousands of antigens. How could we find the antigenic needle in this immunologic stack?

We reasoned that only the human investigators on the case were ignorant of the right antigen. Surely the *T* lymphocytes that cause the disorder recognize the relevant antigen. Accordingly, Holoshitz cultured cells from arthritic rats with pulverized *M. tuberculosis* organisms. If antigenic mimicry was indeed at work and there existed bacterial antigens resembling the self antigens that were under attack in the arthritic rats, the disease-causing *T* cells might pick them out from among all the other bacterial antigens. When that happened, the relevant clone would predominate by clonal selection. That is just what happened. The second *T*-lymphocyte line that was obtained was found to induce arthritis when injected into rats. Holoshitz went on to isolate a clone called A2b that caused even severer disease.

Having induced the bacterial antigen to pick out the relevant *T*-cell clone, we could now employ the *T* cells to find the antigen itself. That work was undertaken by Willem van Eden, who came to my laboratory as a postdoctoral fellow from the Netherlands. Van Eden cultured clone A2b with fractions of ground-up *M. tuberculosis* organisms and with various components of joint tissue. As expected, A2b recognized a mycobacterial fraction (one prepared by my colleague Ayalla Frenkel). In addition the clone recognized proteoglycan, a joint-cartilage molecule that includes sugar and protein components; as it happens, the epitope recognized by A2b was on the part of the proteoglycan molecule called the core protein.

This double recognition was exciting, because it amounted to antigenic mimicry in the test tube: a clone of *T* cells with a single specificity had recognized both a foreign antigen and a self antigen. Adjuvant arthritis could now be explained as the result of a resemblance between those antigens.

But what were the precise epitopes involved? Van Eden's initial work had identified only a fraction of ground-up bacterium, not a specific epitope. To identify a specific epitope we needed to separate *M. tuberculosis* organisms into their component molecules and determine which molecule was recognized by A2b. Once the molecule had been identified we could break it down into progressive-

ly smaller pieces until we found the smallest defined piece A2b would recognize, which would constitute the relevant epitope.

Although the process is simple to describe, it might not have been possible without a useful trick of genetic engineering. Mycobacteria are notoriously difficult to study biochemically. Hence biochemists have resorted to inserting their genes into *Escherichia coli,* a well-behaved and much studied laboratory pet. When the genes are expressed by *E. coli,* large amounts of mycobacterial antigens are made available for study. The availability of such "expression libraries" of *M. tuberculosis* proteins offered us a relatively simple way of identifying the antigens that had been recognized by clone A2b.

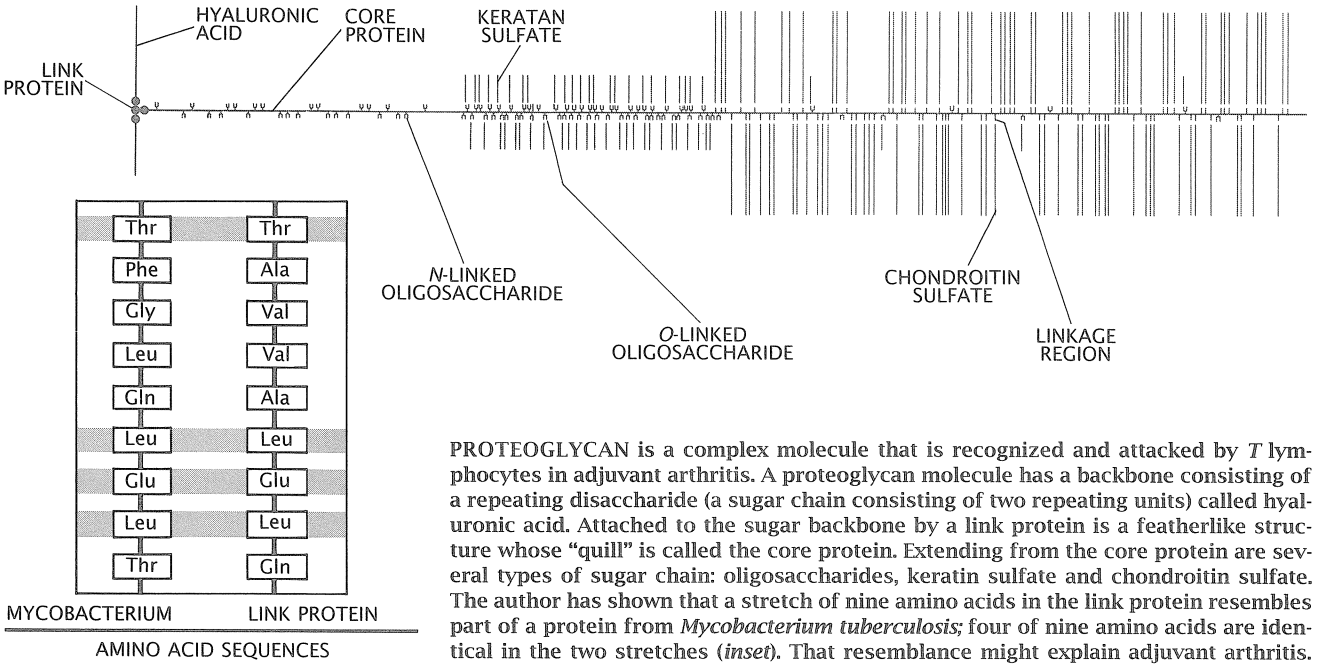
Van Eden tested the responses of A2b to an expression library prepared by Jan D. A. van Embden and Jelle E. R. Thole of the National Institute of Public Health and Environmental Hygiene in the Netherlands. To our delight A2b responded to one of the mycobacterial gene products, a protein with a molecular weight of about 65,000 (a hydrogen atom has a molecular weight of 1), the amino acid sequence of which had already been worked out. Thole and Embden obtained fragments of the protein and tested them against A2b. Ruurd van der Zee of the State University of Groningen then synthesized amino acid chains spanning the area of the protein likely to contain the relevant epitope. The chains were tested and the epitope, consisting of nine amino acids, was identified.

The precise resemblance between the bacterial epitope and the protein part of the proteoglycan remains to be specified. Fortunately the amino acid sequences of proteoglycans have been worked out quite thoroughly. The nine amino acids of the bacterial epitope were compared with published core-protein sequences, and a resemblance was found to a stretch of the link protein that joins the core protein to the proteoglycan's sugar backbone. Four of the nine amino acids in the two stretches are identical. We are currently testing whether that resemblance could account for the double recognition of the two epitopes by clone A2b and therefore for the autoimmunity that underlies adjuvant arthritis.

Does such molecular mimicry also have a role in causing rheumatoid arthritis in human beings? Although there is no definitive answer, early findings are suggestive. We investigated immune responses of some 50 patients suffering from rheumatoid arthritis or from a nonautoimmune degenerative disease of the joints. *T* lymphocytes from both groups were exposed to a mycobacterial fraction containing the cartilage-mimicking epitope. The cells from the rheumatoid arthritis patients underwent a markedly augmented proliferation; those from the others showed a much lower rate of proliferation that was comparable to the rate in healthy people.

Rheumatoid arthritis does appear to be associated with a specific reactivity of *T* cells to a mycobacterial antigen. Such findings, however, by no means establish a causal relationship. The reactivity of the *T* lymphocytes might be the result of arthritis rather than its cause. For example, rheumatoid arthritis might trigger a response of *T* cells to cartilage proteoglycans. The *T* cells might then cross-react to mycobacterial epitopes that happen to resemble the cartilage antigens. There is certainly no obvious connection between *M. tuberculosis* infection and the subsequent development of rheumatoid arthritis. Yet nonvirulent mycobacteria are ubiquitous, and perhaps a clinically invisible exposure might later lead to autoimmunity.

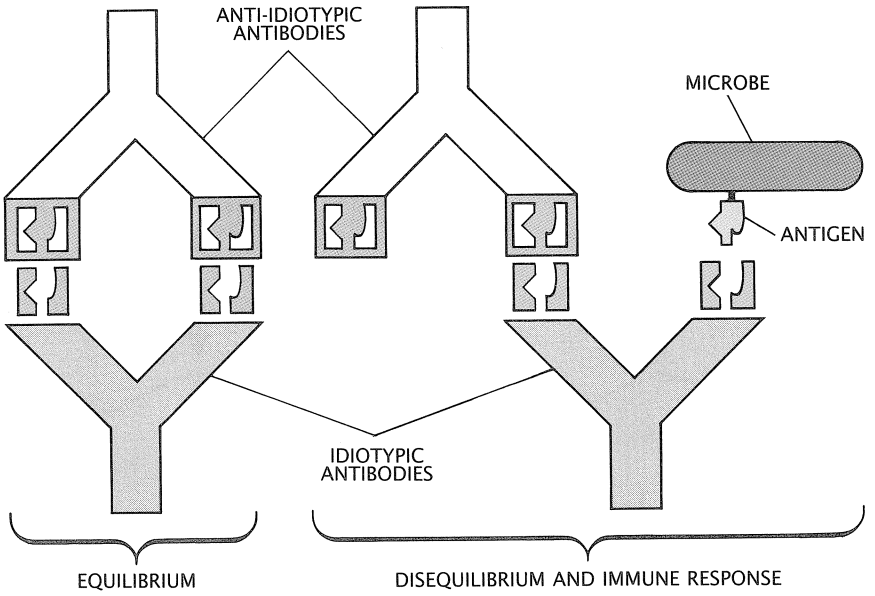
Such connections are known for other pathogens. Acute rheumatic fever, for example, a condition characterized by inflammation of the heart, joints and nervous system, is almost always preceded by an acute infection (usually of the throat and tonsils) with a type of streptococcal bacterium. In the 1960's Melvin H. Kaplan of Case Western Reserve University showed that antibodies made by rabbits against streptococcal antigens also bind to human heart tissue. It should be noted, however, that although all the streptococci of a particular strain may carry human-mimicking epitopes, only a small minority of infected people ever come



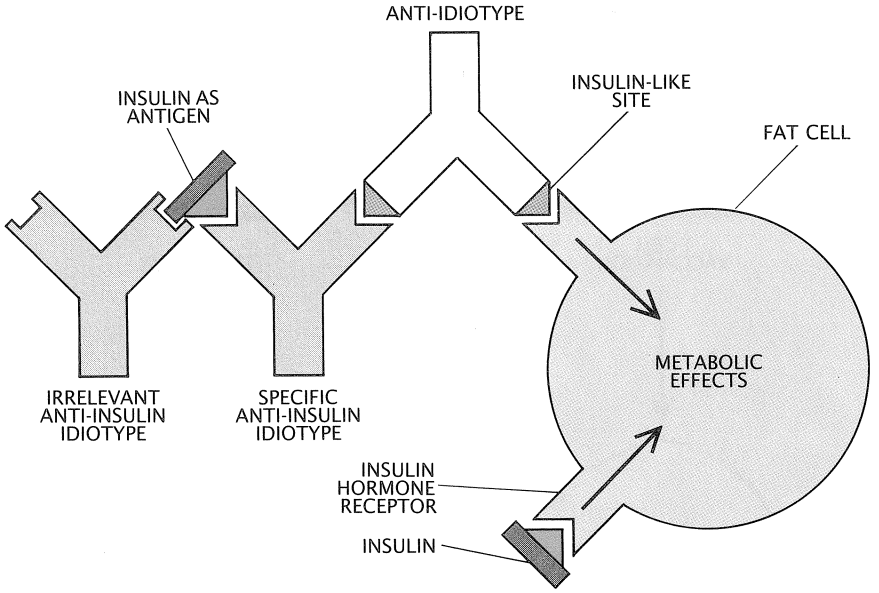
PROTEOGLYCAN is a complex molecule that is recognized and attacked by *T* lymphocytes in adjuvant arthritis. A proteoglycan molecule has a backbone consisting of a repeating disaccharide (a sugar chain consisting of two repeating units) called hyaluronic acid. Attached to the sugar backbone by a link protein is a featherlike structure whose "quill" is called the core protein. Extending from the core protein are several types of sugar chain: oligosaccharides, keratin sulfate and chondroitin sulfate. The author has shown that a stretch of nine amino acids in the link protein resembles part of a protein from *Mycobacterium tuberculosis;* four of nine amino acids are identical in the two stretches (*inset*). That resemblance might explain adjuvant arthritis.

down with acute rheumatic fever. Moreover, the autoimmune attack is generally brief. It would seem that the immune system has the capacity to regulate autoimmunity. How?

Surprisingly, the great scope of the receptor repertoire, which causes the problem by encompassing both the self and the world, may also provide a solution. In the early 1970's Niels Kaj Jerne of the Basel Institute for Immunology formulated a theory of immunity based on observations by several investigators that antigen receptors could themselves be recognized by other receptors on lymphocytes or antibodies. A receptor could also be an antigen! Therefore in addition to receptors for each epitope (as postulated by Burnet), Jerne's conception included receptors for each receptor [see "The Immune System," by Niels Kaj Jerne; SCIENTIFIC AMERICAN, July, 1973]. The original Burnetian specificity of the receptor is referred to as its idiotype, and the specificity of the receptor's receptor is called the anti-idiotype.



ANTI-IDIOTYPE NETWORK may underlie the immune system's response to disease. The idiotype is a receptor's specificity for an antigen. The anti-idiotype is a second receptor's lock-and-key fit with the first. Under ordinary, equilibrium conditions, idiotypic and anti-idiotypic receptors may bind, holding each other in check (*left*). If a microbial antigen is present, it binds to an idiotypic receptor, creating a disequilibrium that leads to the immune response (*right*). It is also possible that the equilibrium between idiotypes and anti-idiotypes somehow restrains the harmful effects of autoimmunity.

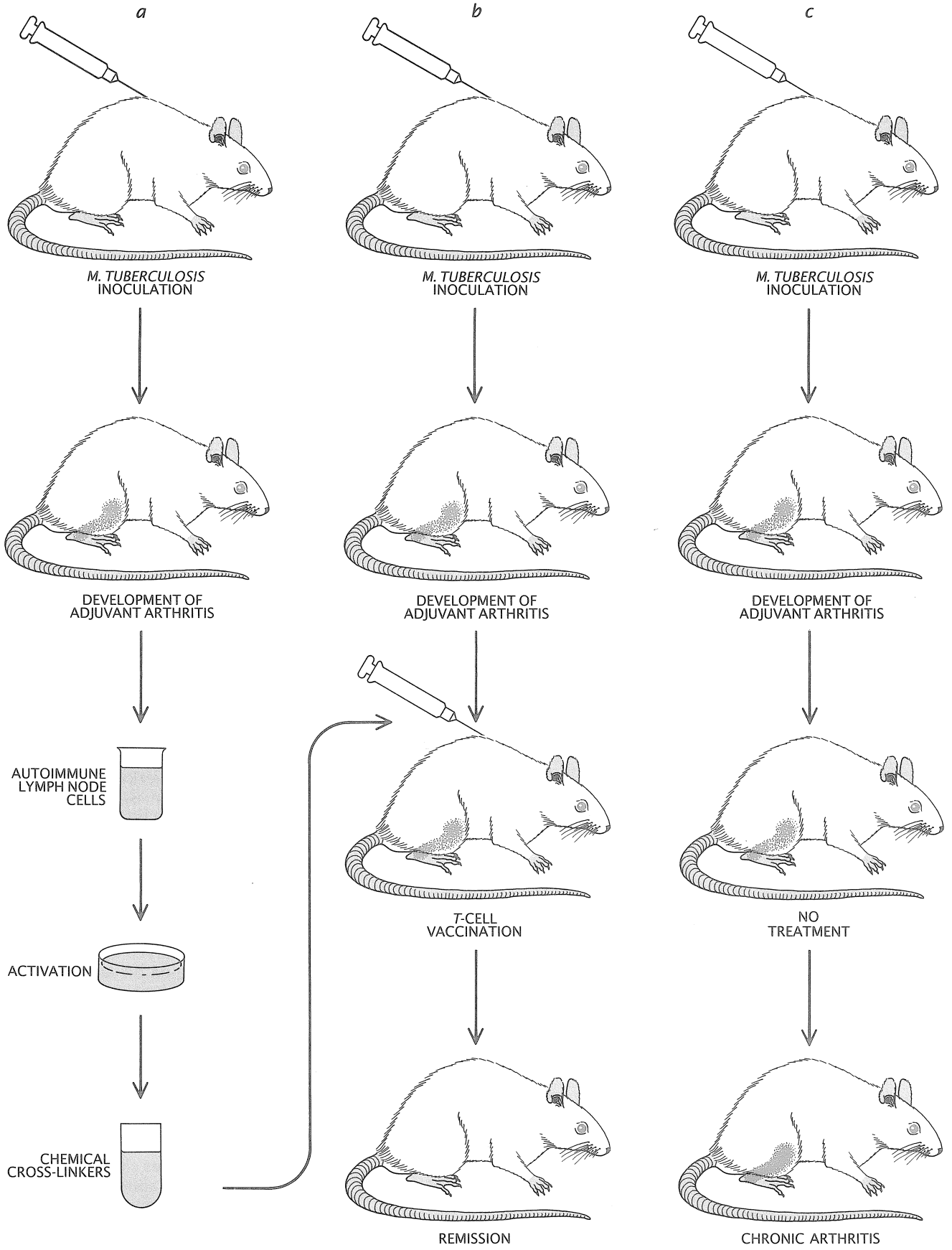


HORMONES CAN BE SHORT-CIRCUITED by the effects of the idiotype-anti-idiotype network, as is shown in a schematic representation of work done in the author's laboratory. Mice immunized to the hormone insulin develop antibodies to several structures on the insulin molecule, including the part (*red*) that binds to the insulin receptor of fat cells. The mice then spontaneously develop anti-idiotypic antibodies that bind to the idiotypic receptor. The receptors of the anti-idiotypic antibodies resemble the configuration of the part of insulin that binds to the insulin receptor. Hence the anti-idiotypic receptors also bind to the insulin receptor, causing a condition similar to diabetes.

That concept has some remarkable implications. If the epitope is thought of as a key and the idiotypic receptor as a lock, what of the anti-idiotypic receptor? Because it is complementary to the idiotype (the lock), the anti-idiotypic receptor must have the form of the key. The key, however, is also the form of the epitope. Hence the epitope and the anti-idiotypic receptor may have the same shape. Jerne argued that in addition to a set of receptors complementary to the antigenic world, the immune system contains a set of receptors (the anti-idiotypic ones) that are homologous to the antigenic world: the system contains not only itself but also the world. This self-recognizing network establishes an equilibrium that regulates the behavior of the immune system, according to Jerne.

Jerne's ideas have generated many experiments, and results are accumulating that support the network concept. Several workers have found that immunization with an epitope leads to the production of antibodies complementary to the epitope, followed thereafter by the production of anti-idiotypic antibodies that mimic the shape of the epitope. Yoram Shechter, Ruth Maron, Dana Elias and I carried out such experiments in mice. We employed an insulin epitope and obtained an anti-idiotypic antibody that resembles the relevant part of the insulin molecule. (In fact, we are now finding anti-idiotypic, insulin-mimicking antibodies in the blood of some people suffering from the autoimmune form of diabetes. What these antibodies are doing there is still a mystery.) On a more practical level, it is hoped that anti-idiotypic antibodies can be exploited for vaccines: the anti-idiotype mimics the shape of a microbial epitope (and so induces immunity) but is harmless.

If recognition of self through the formation of anti-idiotypic receptors is central to the immune system,



VACCINE AGAINST AUTOIMMUNITY was developed by the author and his colleagues. Three groups of rats were inoculated with an adjuvant containing *M. tuberculosis;* all three developed adjuvant arthritis. Autoimmune cells from the lymph nodes of one group (*a*) were removed, processed to increase their immunogenic effects and then injected into the second group (*b*). After inoculation the vaccinated group experienced remission of the disease. The untreated group (*c*) developed chronic arthritis.

what distinguishes between healthy self-recogition and autoimmune disease? Immunologists who accept Jerne's ideas would propose that an equilibrium between idiotypic and anti-idiotypic receptors somehow yields a tolerance to self-epitopes and prevents autoimmune disease. Harmful self-recognition, they would argue, is checked by the mesh of the network and not merely by the presence or absence of a specific antigen. Indeed, it does seem that the immune system can live with and control autoimmunity. As I mentioned above, *T* lymphocytes capable of causing EAE can persist in rats that have recovered from the disease, and people do recover from rheumatic fever and other autoimmune disorders.

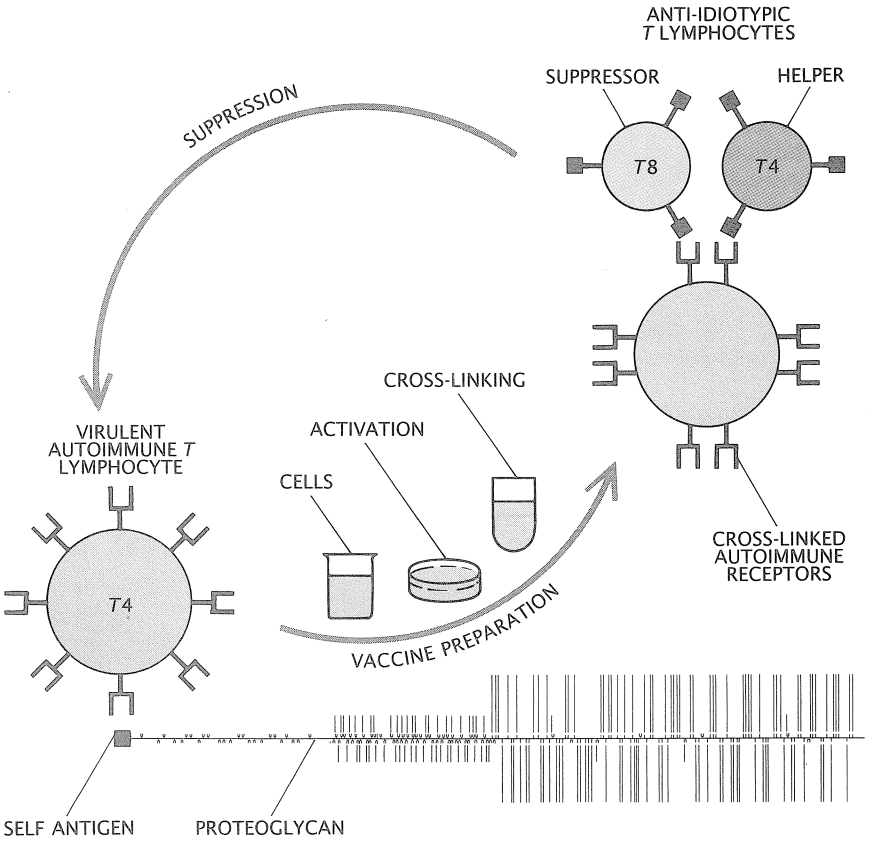
Although the network model offers a convincing interpretation of autoimmunity, it has not been conclusively established. Even without full theoretical understanding, however, the first practical steps have been taken toward preventing and treating autoimmune diseases. Having in hand the specific *T* lymphocyte clones responsible for EAE, adjuvant arthritis and some other experimental diseases, we decided to find out whether they could be used as "vaccines" against autoimmunity.

The first step was to take the line of anti-basic-protein *T* cells responsible for EAE and subject them to gamma radiation. The treated cells lost their virulence and were no longer able to induce EAE when they were injected into rats. The animals into which the *T* cells were injected, however, acquired permanent resistance to EAE: immunization of the rats with basic protein no longer triggered an attack on tissues of the central nervous system. The rats were perfectly capable of responding to other antigens and could even develop adjuvant arthritis when they were exposed to *M. tuberculosis* antigens. We had achieved an experimental vaccine. Its basis was immunizing the rats against the *T* cells, which had receptors for basic protein.

Vaccination with *T* lymphocytes was quickly extended to adjuvant arthritis. In collaboration with my colleague Meir Sinitzky we found that the potency of the "vaccine" could be considerably enhanced by aggregating the receptors of the *T* lymphocytes into a mass; this was accomplished either physically (through hydrostatic pressure) or chemically (through agents that cross-link cell-surface receptors). Apparently, aggregating the receptors makes them much more potent in generating anti-idiotypic lymphocytes. Even more striking, the vaccine also serves as a form of therapy: rats receiving cross-linked *T* lymphocytes taken from other sick rats quickly underwent permanent remission of their autoimmune disease.

It is not yet known exactly how *T*-cell vaccination induces resistance to the autoimmune process, but some suggestive data are being accumulated. Our most recent work confirms that in response to vaccination anti-idiotypic *T* lymphocytes emerge that specifically recognize the receptors of the disease-causing *T* cells. The anti-idiotypic lymphocytes include both cells with the *T*4 marker and those with *T*8. The *T*4 cells are helpers and the *T*8 cells are suppressors, which inhibit the growth of clones of other lymphocytes. We do not know which type is responsible for resisting the autoimmune disease. It is conceivable that the two groups work in concert to regulate the lymphocytes that cause the autoimmune disease.

The effectiveness of *T*-lymphocyte vaccination in activating lymphocytes capable of modulating autoimmunity is certainly compatible with the general idea of a Jernian network. Our observations, however, by no means establish the physiological role of the network proposed by Jerne; much more work will be required for that. Yet the work done so far has established that the border between the self and the external world is not nearly as clear as was once thought. Self-recognition is not merely a sin punished by autoimmune disease, as Burnet and others believed. On the contrary, it is central to health as well as to illness. The immune system is much more complex than it seemed when immunologists thought it perceived only the external world. That knowledge may ultimately be of very real help in easing the pain of autoimmune disease.



POSSIBLE MECHANISM of the vaccine against adjuvant arthritis is illustrated schematically. The critical cells are the virulent autoimmune *T*4 cells—with receptors for proteoglycan—that are removed from arthritic rats. Preparation of the vaccine entails aggregating the receptors, a process that increases their potency. When they are injected into other rats suffering from adjuvant arthritis, the aggregated receptors evoke anti-idiotypic *T*4 and *T*8 cells. The *T*8 cells are "suppressors" that may inhibit the proliferation of the autoimmune lymphocytes. The *T*4 cells are "helpers." Helpers facilitate the growth of *B* and *T* cells; their function in the vaccinated rat is not as yet understood.

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