Adv. Int. Med.
29:147-165,
1984.

Autoimmunity: Physiologic and Pernicious

IRUN R. COHEN, M.D.

Department of Cell Biology, The Weizman Institute of Science, Rehovot, Israel

THIS CHAPTER is a sequel to "Autoimmunity and Suppressor T Lymphocytes," a review that appeared in *Advances in Internal Medicine* 2 years ago.[1] The authors of that earlier review catalogued nonspecific suppressor cell functions in a number of autoimmune diseases but concluded that this approach

> resembles that of a man who searches for his lost key beneath a lamp post because 'that's where the light is.' We believe that satisfactory explanations of the origin of autoimmune diseases will not develop from the studies of nonspecific phenomena that presently dominate the field. Our review thus tends towards pessimism, but there is an optimistic note. New developments, such as hybridoma technology and the ability to maintain cloned lymphocytes in tissue culture, have already had a powerful impact on basic immunology. They are just now finding applications to studies of autoimmune disorders. . . .

The present chapter summarizes recent investigations employing hybridoma antibodies, long-term cell cultures, and other techniques for isolating and studying specific immunologic effectors. These methodologies, combined with a deeper appreciation of the organization of the immune system, have made it possible to investigate the autoantibodies and autoreactive T lymphocytes that are the specific agents of autoimmune disorders. Isolation of the pathogenic agents of disease is a significant step toward their specific control.

Physiologic Autoimmunity

Autoimmunity in its most general sense refers to the recognition by antigen receptors of the immune system of normal

0065-2822/84/0029-0147-0165-$4.00

components of the individual. It was once taught that recognition of self was inadmissible, as it would surely threaten the body with self-destruction by autoimmune disease.[2] However, it is now quite certain that far from being forbidden, recognition of self is essential to the normal physiology of the immune system.[3] Physiologic autoimmunity is evident in two aspects of immune behavior: recognition of self antigens of the major histocompatibility complex (MHC), and recognition of antigen-binding receptors in network regulation of the immune response by anti-idiotypic immunity.

Receptor-bearing T lymphocytes normally respond to their specific foreign target antigens in association with products of self MHC genes.[4] For example, cytotoxic T lymphocytes responsive to viral antigens will kill virus-infected target cells only when the target cells also present self MHC antigens.[5] Recognition of self MHC antigens has been documented in the responses to a wide variety of antigens and seems to be a general rule for T lymphocytes.[6–8] Even target self antigens in autoimmune disease are recognized in specific association with MHC allelic products. Autoimmunity to thyroglobulin can be easily induced in most strains of mice. However, whether a target thyroid gland is susceptible or resistant to autoimmune attack was found to be determined by the nature of the self MHC.[9]

Another requirement for recognition of self MHC antigens can be observed in interactions between antigen-presenting macrophages and T lymphocytes[10] or between helper T lymphocytes and the B lymphocytes whose antibody production they regulate.[11] Different loci in the MHC appear to specialize in regulating particular types of cell interactions. Self class I genes (HLA-A, B, or C in humans; H-2K or D in mice) are recognized by cytotoxic T lymphocytes as they attack their target cells, while self class II genes (HLA-DR or H-2I) are recognized by T lymphocytes of the helper and delayed hypersensitivity types.[4, 12]

How the molecular products of MHC genes work is not clear, but the logic of the phenomenon can be understood if one considers the critical role of self-recognition in any organized society, be it of lymphocytes, insects, or humans. Transfer of information between individuals requires that each recognize its fellows and their places in the hierarchy of the society. An army of people or ants cannot carry out orders and fight effectively against the enemy unless each soldier is able to recog-

nize the uniform and rank of his superior and inferior associates, as well as the colors of the enemy. Self-recognition is a prerequisite for organized transfer of information between the individual components of any system. In a general sense, we may say that the products of MHC genes function as physiologic signals that help organize the transfer of information between cells in the immune system.

One may ask, therefore, why call recognition of self MHC autoimmunity? Isn't recognition of self MHC conceptually similar to other, clearly not autoimmune forms of signal transfer between cells, such as those governing the endocrine system, differentiation of stem cells, etc.? The answer is that the process of recognition of self MHC structures, although in the service of cell cooperation bears the hallmarks of true adaptive immunity. The receptors that recognize self MHC seem to be clonally distributed among classes of lymphocytes. Heterozygotes at the MHC, that is, most outbred individuals, have alternate subpopulations of T lymphocytes that recognize the universe of antigens; each subpopulation sees the antigenic universe exclusively in association with one or another MHC allelic product as a self signal for cell cooperation.[13] In theory, the T lymphocyte receptor repertoire for target antigens is redundant for each self MHC gene allele (Fig 1). In practice, particular target antigens may be recognized more readily in association with one of the individual's MHC allelic products than with the other.[14] If this turns out to be a general rule, it would explain the advantage in being a heterozygote at the MHC; if one MHC allelic product doesn't "associate" well with an invading antigen, the other might. A homozygote with the same MHC gene on both chromosomes lacks this insurance. For everyone to be an MHC heterozygote requires a very large degree of MHC polymorphism in the species, and this is the case.[4, 12]

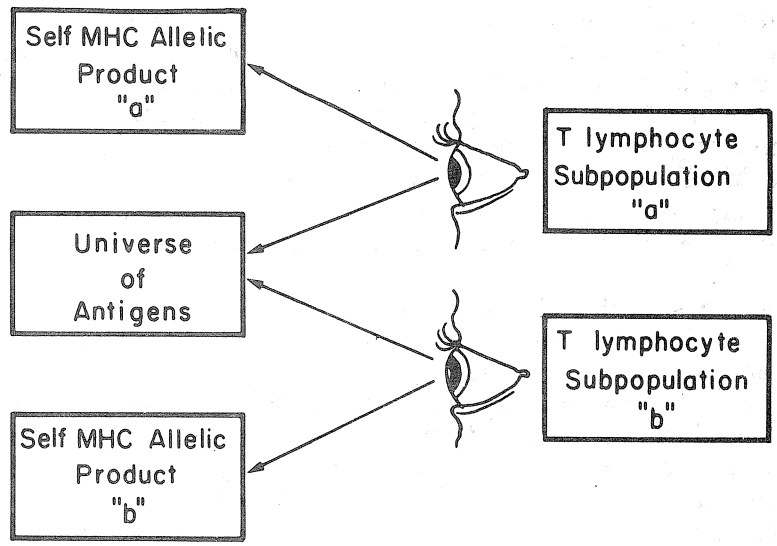
Another singular characteristic of the MHC is that its function as a signal for cell cooperation is plastic and influenced by the environment in which the lymphocytes have differentiated.[9, 15, 16] Lymphocytes can "learn" to relate to particular MHC products as legitimate interaction signals. Under certain circumstances foreign MHC antigens, usually the most irresistible targets of immune attack,[12] can be observed to function as self MHC signals for cell cooperation.[17] This adaptive flexibility and clonal diversity of recognition distinguishes self MHC

products from other physiologic recognition systems and defines the MHC as a subject of immunologic recognition. Thus, recognition of self MHC is true autoimmunity, even though it may produce healthy cell cooperation rather than disease. Why this is so is a mystery.

The anti-idiotypic network is a second example of physiologic autoimmunity. It appears that lymphocytes can recognize the antigen receptors or antibodies (idiotypes) produced by other lymphocytes.[18] The resulting response to specific idiotypes may be expressed as anti-idiotypic antibodies or T lymphocytes (Fig 2). The essence of the network idea is that anti-idiotypes regulate the expression of idiotypes.[19] The network notion of regulation has yet to be verified in all its details, but it is certain that idiotypes can function as self antigens and that anti-idiotypes are a form of autoimmunity that can influence the nature of immune responses to antigens.[20, 21]

Anti-idiotypes can be seen as a necessary result of the astronomical number of diverse antigen receptors generated by the mutation and recombination in lymphocytes of the relatively small number of primary genes carried in the germ cells.[22] It is estimated that hundreds of millions of different receptors

Fig 1.—Separate subpopulations of T lymphocytes are restricted to recognizing antigens in association with specific MHC allelic gene products.



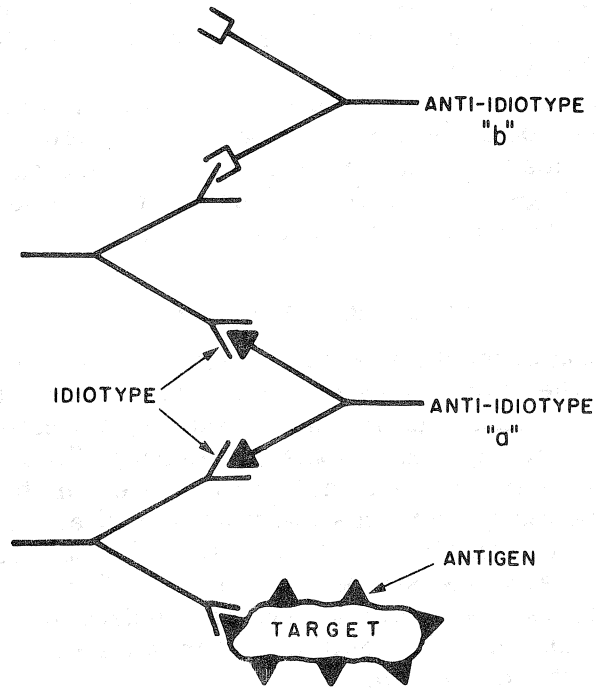


Fig 2.—Anti-idiotypic antibodies interact with the variable regions of idiotypic antibodies. Anti-idiotype "a" is complementary to the antigen-binding site of the idiotype and so mimics the structure of the antigen. Anti-idiotype "b" interacts with the variable region of the idiotype outside the binding site for antigen and does not mimic the structure of the antigen.

and antibodies can be produced by these processes. The power and uniqueness of the immune system are founded on the virtually unlimited number of structures that can be potentially recognized, that is, bound, by such a vast repertoire of receptors. Antigens are defined operationally by their binding to immunologic receptors. There are so many different receptors for antigens that any biologic structure should be able to be recognized as an antigen by one or more complementary receptor combining sites. By the same logic, antigen receptors themselves should be recognizable as antigens (idiotypes) by combining sites of one or more other, anti-idiotypic receptors. Different parts of the variable region of a receptor may be recognized as idiotypic, including the binding site for antigen.[23] An anti-idiotype that is complementary to the idiotype of the

binding site for antigens could mimic the structure of the antigen (see Fig 2) and enhance[24] or suppress[25] the idiotypic response to that antigen.

Network autoimmunity differs from MHC autoimmunity in that the idiotype is the target antigen, while MHC gene products are cellular interaction signals seen in association with some other target antigen. Both of these autoimmune processes are physiologic and tend to promote health.

Pernicious Autoimmunity

When recognition of target self antigens produces disease we may define the autoimmune reaction as pernicious rather than physiologic. Disease usually results from damage caused by inflammation, edema, phagocytosis, cytotoxicity, fibrosis, calcification, and other processes that are triggered in the wake of immunologic recognition. In some situations disease can follow the binding of autoantibodies to very sensitive structures such as hormone receptors (see below), but most forms of autoimmune disorders are inflammatory. The molecular connection between immunologic recognition and inflammation is beyond the scope of this discussion.

Molecular Mimicry and Pernicious Autoimmunity

Some evidence suggests that certain foreign antigens may trigger an autoimmune disorder because they look like, or mimic the structure of self antigens. This might be the case for DNA antibodies in systemic lupus erythematosus (SLE). Shoenfeld and his colleagues isolated monoclonal hybridoma DNA antibodies from SLE patients by fusing peripheral blood or splenic lymphocytes with a suitable human lymphoblastoid line.[26] Of 30 monoclonal antibodies selected for their binding to denatured DNA, 18 also reacted with other polynucleotides and 10 bound both nucleic acid antigens and the phospholipid cardiolipin. DNA and cardiolipin both have a sugar-phosphate backbone, and it is likely that the shared antigenic determinant is made of appropriately spaced phosphodiester phsophate groups.[27] This cross reactivity could explain the biologically false positive test for syphilis, due to cardiolipin antibodies, that occurs frequently in patients with SLE.[28] More importantly for our discussion, the immunologic cross reactivity be-

tween DNA and cardiolipin implies that production of antibodies that recognize DNA does not require immunization with DNA itself. This conclusion is supported by the finding that mice immunized with cardiolipin produced antibodies that bound DNA as well as cardiolipin.[29] Hence, it is conceivable that the DNA antibodies in the blood of some SLE patients may have arisen in response to cardiolipin or some related antigens introduced by microbial infection.[26] In any case, monoclonal techniques provide a powerful tool to analyze the fine specificities of individual autoantibodies.[30]

Adjuvant arthritis is an autoimmune disease of rats that is strikingly similar in pathology and clinical course to human rheumatoid arthritis.[31, 32] In this case the autoimmune arthritis is triggered by immunizing MHC genetically susceptible rats[33] with a mixture of *Mycobacteria tuberculosis* bacteria emulsified in oil, known as complete Freund's adjuvant.

Adjuvant arthritis is an autoimmune process because the disease can be transferred to normal recipient rats by lymphocytes in the absence of bacterial antigens.[34] An important question is the origin of the autoimmunization: do mycobacteria have antigens that cross-react with self-antigens of rat joints, or does the inflammation caused by the mycobacterial adjuvant expose the rats to their own self antigens? To answer this question it was necessary to isolate the lymphocytes producing adjuvant arthritis and to study their capacity for recognition. From rats immunized with complete Freund's adjuvant, Holoshitz and his colleagues in my laboratory isolated T lymphocytes that responded to mycobacterial antigens and grew the lymphocytes as antigen-specific cell lines.[35] We found that such antibacterial T lymphocytes produced arthritis on intravenous inoculation into normal recipient rats. Single clones of T lymphocytes responding to specific mycobacterial antigens were also capable of producing severe and prolonged arthritis,[36] proving that the same T lymphocyte can be bacterially immune and perniciously autoimmune at one and the same time. The target antigenic determinant has not yet been identified but it is presumably a molecule whose structure is shared in part by *M. tuberculosis* and a substance in the joints of rats. Hence, adjuvant arthritis might be explained by molecular mimicry between the host and a bacterial parasite. Lines of T lymphocytes selected for their reactivity to tuberculin did not produce arthritis, suggesting that the putative cross-reactive antigen is

not tuberculin.[36] Trentham and co-workers have suggested that the autoantigen in adjuvant arthritis is collagen type II. This conclusion was based on the observation that rats with adjuvant arthritis demonstrate immunity to collagen type II[37] and that direct immunization to collagen type II itself can induce autoimmune arthritis.[38] Patients with rheumatoid arthritis also show immunity to collagen type II.[39] However, Iizuka and Chang concluded that adjuvant arthritis and collagen type II arthritis were distinct entities, because rats can be rendered resistant to adjuvant arthritis while remaining susceptible to collagen type II arthritis.[40]

Why only rats of some MHC genotypes respond to *M. tuberculosis* inoculation by arthritogenic autoimmunity is unknown but may be related to the nature of antigenic determinants selected to be the targets of the immune response. The process of selection of antigenic determinants appears to be regulated in some way by MHC gene products.[41] The association of some types of arthritis in humans with the HLA-B27 and with microbial infection[42] is worthy of note.

The HLA-B27 allele occurs in 6%–8% of the human population of European origin, but it is present in 95% of individuals suffering from ankylosing spondylitis and in a high frequency of patients with Reiter's syndrome.[43–45] Infection with enteric bacteria, such as *Shigella*[46] or *Yersinia,*[47] or with *Chlamydia*[48] has been associated with development of Reiter's syndrome. Ankylosing spondylitis has a peculiar association with *Klebsiella*. Not only is arthritis related to infection, but certain isolates of *Klebsiella* seem to share antigenic specificity with antigens on the lymphocytes of ankylosing spondylitis or Reiter's syndrome patients bearing the HLAB27 allele.[49] Antisera to these *Klebsiella* organisms were found to be cytotoxic for the lymphocytes of B27-positive patients. The reason for this is not clear, and it appears that B27 lymphocytes might actually become modified by contact with bacterial antigens.[50] In any case, there is strong circumstantial evidence implicating infection in the onset of some forms of arthritis, probably autoimmune, in individuals of certain genotypes. Thyroid disease of autoimmune nature also has been associated with antibodies to *Yersinia*[51] and with immunization to streptococcal antigens.[52] Rheumatic fever is another disease of possible autoimmune etiology that is triggered by bacterial infection[53] and might involve an immunologic relationship between cardiac muscle and

the group A streptococcus.[54] One way to explain these phenomena is based on the likely supposition that many bacteria, viruses, and other foreign substances in the environment bear foreign antigenic determinants together with antigenic determinants that mimic the structure of a self antigen of the host. Most individuals respond to the foreign antigenic determinants and not to the self cross-reactive determinants; but some, by chance or by possession of an unfortunate constellation of MHC or other genes, mount a strong response against the self-mimicking determinants and so acquire an autoimmune disorder. According to this argument, adjuvant arthritis and ankylosing spondylitis are archetypical autoimmune disorders. The fact that most individuals ignore self antigens even when presented on foreign invaders might explain why many well-adapted parasites disguise themselves with a coat of antigens that mimic those of their hosts.[55]

Structural mimicry can give rise to pernicious autoimmunity in yet other ways. As discussed above, an anti-idiotypic antibody can mimic the structure of the antigenic determinant recognized by the idiotype (see Fig 1). This fundamental principle of the idiotype–anti-idiotype network was found to be responsible for autoimmunity to a hormone receptor. It was observed that mice immunized to pork or beef insulins developed autoantibodies to their own insulin receptors, as well as antibodies to the immunizing insulin.[56]

It was obvious why the mice made insulin antibodies, as insulin was the immunogen. The autoantibodies that they made to the insulin hormone receptor turned out to be anti-idiotypes directed to specific idiotypes among the insulin antibodies.[57, 58] These idiotypic antibodies apparently were complementary to the conformation of that part of the insulin molecule that fit into the insulin hormone receptor. Hence, the anti-idiotypic antibodies that were complementary to these idiotypes mimicked the conformation of insulin itself and so could bind to the insulin receptor, as it were, by accident (Fig 3). The anti-idiotypes suppressed production of the idiotypic insulin antibodies and, from this point of view, were a classic example of positive physiologic autoimmunity generated by the network. However, these same anti-idiotypes induced diabetes in the mice by binding to insulin receptors and disrupting their normal function. From this point of view, the anti-idiotypic antibodies were perpetrators of pernicious receptor autoimmunity; note, in the ab-

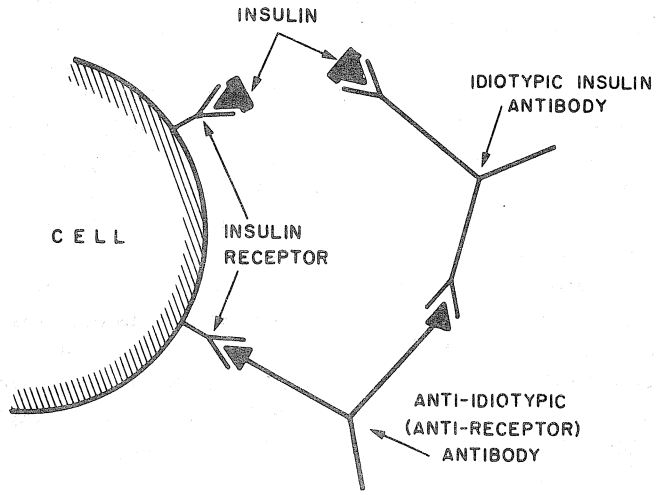


Fig 3.—An anti-idiotypic antibody to an idiotypic insulin antibody can act as anti-receptor antibody to the insulin receptor. The anti-idiotypic antibody mimics the structure of insulin and so can bind to insulin receptors. Such an anti-idiotype is physiologic when it regulates expression of the idiotype and pernicious when it causes diabetes by interacting with the insulin receptor.

sence of inflammation. In short, physiologic autoimmunity and pernicious autoimmunity were operationally defined by their contrasting effects, although these effects could have been mediated by a single molecular species. Network generation of pernicious autoimmunity has not yet been discovered in human disease, but the mouse study would suggest that an individual with Graves' disease,[59] for example, may have produced TSH receptor antibodies as anti-idiotypes to TSH autoantibodies or to other antibodies made in response to an antigenic determinant that mimics the conformation of TSH.

Covert Autoimmunity

Recent experiments indicate that potential agents of pernicious autoimmunity can exist in a quiescent state in well individuals. By using labeled self antigen it has been possible to demonstrate that healthy humans and animals of various species are populated with lymphocytes that bind self antigens.[60] Moreover, it has been shown that treatment of populations of normal lymphocytes with nonspecific, polyclonal activators can induce the secretion of autoantibodies to a variety of self anti-

gens.[61] Gleichmann and his associates have been able to induce a number of autoimmune diseases in mice in whom they caused chronic graft-versus-host reactions.[62] These findings imply that autoreactive lymphocytes are ubiquitous and can be turned on by nonspecific signals.

What is the natural hisotory of autoreactive lymphocytes? How are they held in a state of subclinical quiescence? Does turning them on always lead to disease? Information providing partial answers to these questions is beginning to accumulate. My associates and I have adapted relatively new cell culture techniques to grow autoimmune T lymphocytes as cell lines. The development of a T lymphocyte line requires that the lymphocytes have a history of having been activated by immunization to the specific antigen. Therefore, isolation of a T lymphocyte line in vitro is itself evidence that the original progenitor cells of the line had been in a state of immune differentiation.

Much of our work has centered on a disease called experimental autoimmune encephalomyelitis (EAE) in rats. This disease, characterized by mononuclear cell infiltration of the CNS and paralysis, can be induced by immunizing genetically susceptible animals to the basic protein (BP) antigen of myelin.[63] EAE is usually clinically acute, and affected rats either die or spontaneously recover from paralysis. Rats that have recovered from EAE acquire specific resistance to subsequent attempts to induce the disease by repeated immunization to BP. We found that potential EAE effector T lymphocytes could be rescued in vitro as cell lines from the lymphoid organs of rats that had recovered from EAE and that were resistant.[64] Thus, recovery and resistance took place in the face of persisting autoreactive T lymphocytes. That these recovered anti-BP T lymphocytes could be pernicious was proved by the fact that they caused EAE on intravenous inoculation into normal recipient rats. Suppression of the resident anti-BP effector T lymphocytes and acquired resistance to EAE were attributable to the presence of other lymphocytes that recognized specifically the anti-BP T lymphocytes, suggesting that suppression of EAE might result from a process of anti-receptor or anti-idiotypic immunity to lymphocytes with receptors for self-BP. Thus, physiologic network autoimmunity appeared capable of suppressing cellular agents of pernicious autoimmunity.

We also succeeded in isolating covert anti-BP effector T lym-

phocytes from well rats that were genetically resistant to active EAE[65] and from rats that had been immunized to BP in an innocuous form.[64] Hence, potential producers of EAE could be seen to develop covertly and remain silent in healthy rats.

To trace the migrations and organs of residence of EAE effector T lymphocytes, we tagged anti-BP line cells with a radioactive label and injected them into recipient rats.[66] The rats came down with EAE and spontaneously recovered. As expected, onset of disease was accompanied by the accumulation of line cells in the brain and spinal cord, as well as in the liver and spleen. Line cells reactive to other antigens were never found in the CNS. Unexpectedly, some of the line cells migrated to the thymus and persisted there for months after the rats had recovered from EAE. The line cells were rescued and found to cause disease in new recipient rats.

These experiments made possible by T lymphocyte line methodology indicate that autoreactive lymphocytes may cause transient autoimmune disease and persist despite clinical remission, that development of potential autoimmune effector T lymphocytes does not necessarily lead to clinical disease, and that subclinical autoimmunity occurs in a variety of circumstances.

Physiologic Autoimmunity Against Pernicious Autoimmunity

More evidence is needed to ascertain whether spontaneous anti-idiotypic immunity is a natural barrier to pernicious autoimmunity. In any case, it is worthwhile investigating whether anti-idiotypic autoimmunity can be used as a medical procedure to modify or suppress autoimmune diseases. One strategy would be to isolate pernicious autoantibodies or autoreactive lymphocytes and exploit them as immunogens to induce suppression of endogenous idiotypes. Binz and Wigzell used anti-idiotypic immunity to receptors for MHC antigens to produce partial tolerance in rats to specific allogeneic grafts.[21] Until now this approach has been used in experimental models of autoimmune disease in two variations: passive administration of preformed anti-idiotypic antibodies, and active immunization of the experimental subject to the idiotypes.

Autoimmune tubulointerstitial nephritis is produced in guinea pigs by immunizing them with tubular basement membrane.[67] The disease is characterized by mononuclear cell infil-

tration in the renal cortex, which seems to be mediated by autoantibodies to the tubular basement membrane. Brown and co-workers succeeded in inhibiting the development of disease by passive transfer of anti-idiotypic antibodies administered at the time of immunization to basement membrane.[67]

Zanetti and Bigazzi alleviated the spontaneous autoimmune thyroiditis of Buffalo strain rats by administering to sublethally irradiated rats rabbit anti-idiotypic antibodies directed against rat thyroglobulin antibodies, the etiologic agents of disease.[68] Although repeated inoculations with anti-idiotypic antibodies were required, the results are encouraging because they show that ongoing, spontaneous autoimmunity can be partially suppressed by passive administration of anti-idiotypes.

A third autoimmune disease that has been successfully modified by anti-idiotypic immunity is experimental autoimmune myasthenia gravis. This model of human myasthenia gravis is caused by autoantibodies to the acetylcholine receptor. Fuchs and her colleagues actively raised anti-idiotypes in outbred rabbits by immunizing them repeatedly with allogeneic or autologous antibodies specific for the acetylcholine receptor.[69] Some of the rabbits became refractory to disease subsequently induced by immunization to the acetylcholine receptor. This study shows that effective anti-idiotypic immunity can be induced in the autoimmune subject and need not be transferred from without.

My laboratory has used lines of autoimmune T lymphocytes to actively vaccinate rats and mice against experimental autoimmune disorders of the CNS, joints, or thyroid. The EAE and adjuvant arthritis models in rats have been described above. Experimental autoimmune thyroiditis is induced in MHC-susceptible mice by immunizing them with mouse thyroglobulin.[70] It is characterized by mononuclear cell infiltration of the thyroid gland and high titers of thyroglobulin antibodies. Similar to the encephalomyelitis[71] and arthritis models,[35] this form of thyroiditis appears to be produced by autoreactive T lymphocytes.[9] From animals actively immunized to the appropriate antigens we have succeeded in isolating autoimmune T lymphocytes and propagating them as long-term cell lines. The unique feature of the T lymphocyte lines is that each is functional in producing a specific autoimmune disorder. As few as 10^4–10^5 anti-BP line cells induced encephalomyelitis within several days of intravenous inoculation into syngeneic rats, some clones of anti-mycobacterial lines produced severe polyar-

thritis in irradiated rats within 5 days of intravenous inoculation,[36] and antithyroglobulin line cells mediated thyroiditis in mice.[72] These functionally active autoimmune lines have been very helpful in uncovering pathogenic processes underlying organ specific autoimmune disease, but their contribution to this discussion is their ability to prevent and possibly to treat disease. A single inoculation of anti-BP line cells attenuated by inhibition of DNA synthesis induced resistance to EAE in about two thirds of recipient rats.[73, 74] Likewise, a single injection of irradiated antithyroglobulin line cells inhibited autoimmune thyroiditis in all recipient mice.[72] Antimycobacterial line cells inhibited the development of adjuvant arthritis[35] and, more importantly, could be used to treat adjuvant arthritis after it had reached its peak development.[36] The mechanism of specific resistance induced by T lymphocyte line cells is being investigated, and preliminary results suggest that protection results from anti-receptor autoimmunity.

Prospects for Therapy

Will anti-idiotypic immunity to antibodies or lymphocytes have any clinical use for autoimmune disease? The answer will depend on resolution of several issues.

- Treatment of existing autoimmune disease and not prophylactic vaccination is the major clinical challenge. The results that have been reported should encourage the development of more experimental models suitable for investigation of this question.
- Is it more efficacious to treat with preformed anti-idiotypic antibodies or to induce active anti-idiotypic immunity by immunizing with idiotypes? Active immunization with idiotypes would be expected to be longer lasting and possibly more effective, because anti-idiotypic T lymphocytes might be generated in addition to anti-idiotypic antibodies.
- Should the idiotypic immunogens be antibodies or T lymphocytes? Although it is much easier to prepare and store antibodies, immunization with T lymphocytes seems to offer a powerful means of suppressing autoimmune diseases. The issue should be studied using the same disease models for treatment.
- The MHC barrier to cell transfer[4] suggests that im-

munization with allogeneic T lymphocytes will not be feasible. Moreover, it would be very inconvenient to raise autologous T lymphocyte lines for each and every patient. An alternative to immunization with whole cells would be to immunize patients with isolated T lymphocyte receptors of autoantigens, a procedure that might allow immunization with allogeneic receptors. Perhaps a pool of receptors isolated from many persons would cover the range of idiotypes prevalent in the population for the particular autoantigen. For example it may be necessary to raise only a few tens of T lymphocyte lines from individual patents with myasthenia gravis, isolate the receptors, and pool them so as to obtain a reagent which hopefully could be used to produce anti-idiotypes to the myasthenia gravis idiotypes of most persons. However, this approach will be feasible only when techniques are developed for easy isolation of the receptors of T lymphocytes.

Immunology is in a period of technological and conceptual advance, and I expect that definitive solutions to these issues will emerge in the near future and may provide the foundation for network manipulation in clinical medicine. Control of infectious disease was aided considerably by the successes of Pasteur, Koch, and others in isolating the pathogenic microbial agents. Whether or not anti-idiotypic immunity will prove to be the answer, isolation of the internal agents of autoimmune disease will certainly generate new approaches to diagnosis and therapy.

Acknowledgments

Work carried out in my laboratory was supported by NIH grants NS18168 and AM32192. I am the incumbent of the Mauerberger Professional Chair in Immunology.

REFERENCES

1. Miller K.B., Schwartz R.S.: Autoimmunity and suppressor T lymphocytes. *Adv. Intern. Med.* 27:281, 1981.
2. Burnet F.M.: *The Clonal Selection Theory of Acquired Immunity*. Nashville, Vanderbilt University Press, 1959.
3. Wigzell H.: Positive autoimmunity, in Talal N. (ed.): *Autoimmunity: Genetic, Immunologic, Virologic, and Clinical Aspects*. New York, Academic Press, 1977.

4. Snell G.: T cells, T cell recognition and the major histocompatibility complex. *Transplant. Rev.* 38:5, 1978.
5. Zinkernagel R., Doherty P.C.: MHC-restricted cytotoxic T cells: Studies on the biological role of polymorphic major histocompatibility antigens determining T cell restriction-specificity, function and responsiveness. *Adv. Immunol.* 27:51, 1979.
6. Shearer G.M., Schmidt-Verhulst A.M.: Major histocompatibility complex restricted cell-mediated immunity. *Adv. Immunol.* 25:55, 1977.
7. Gordon R.D., Samuelson L.E., Simpson E.: Selective response to H-Y antigen by F1 female mice sensitized to F1 male cells. *J. Exp. Med.* 146:606, 1977.
8. Wettstein P.J., Frelinger J.A.: H-2 effects on cell-cell interaction in the response to single non-H-2 antigens: II. Donor H-2D region control of H-7.1-specific stimulator function in mixed lymphocyte culture and susceptibility to lysis by H-7.1-specific cytotoxic cells. *J. Exp. Med.* 146:1356, 1977.
9. Maron R., Cohen I.R.: H-2K mutation controls immune response phenotype of autoimmune thyroiditis: Critical expression of mutant gene product in both thymus and thyroid glands. *J. Exp. Med.* 152:1115, 1980.
10. Shevach E.M., Rosenthal A.S.: Function of macrophages in antigen recognition by guinea pig T lymphocytes: II. Role of the macrophage in the regulation of genetic control of the immune response. *J. Exp. Med.* 138:1213, 1973.
11. Kindred B., Shreffler D.: H-2 dependence of cooperation between T and B cells in vivo. *J. Immunol.* 109:940, 1972.
12. Klein J.: The major histocompatibility complex of the mouse. *Science* 203:516, 1979.
13. Paul W.E., Shevach E.M., Pickeral S., et al.: Independent populations of primed F1 guinea pig T lymphocytes respond to antigen-pulsed parental peritoneal exudate cells. *J. Exp. Med.* 145:618, 1977.
14. Pan S., Wettstein P.J., Knowles B.B.: H-2K^b mutations limit the CTL response to SV40 TASA. *J. Immunol.* 128:243, 1982.
15. Bevan M.J.: In a radiation chimera, host H-2 antigens determine immune responsiveness of donor cytotoxic cells. *Nature* 260:417, 1977.
16. Maron R., Cohen I.R.: Thymic reconstitution of H-2-linked T-cell responses to thyroglobulin or insulin. *Immunogenetics* 17:95, 1983.
17. Ishii N., Baxeranis C.N., Nugy Z.A., et al.: Responder T cells depleted of alloreactive cells react to antigen presented on allogeneic macrophages from nonresponder strains. *J. Exp. Med.* 154:978, 1981.
18. Nisonoff A., Bangasser S.A.: Immunological suppression of idiotypic specificities. *Transplant. Rev.* 27:9, 1975.
19. Jerne N.K.: Towards a network theory of the immune system. *Ann. Immunol. (Paris)* 124C:373, 1974.
20. Eichmann K.: Expression and function of idiotypes on lymphocytes. *Adv. Immunol.* 26:195, 1978.
21. Binz H., Wigzell H.: Specific transplantation tolerance by autoimmunization against the individual's own naturally occurring idiotypic, antigen-binding receptors. *J. Exp. Med.* 144:1438, 1976.
22. Leder P.: The genetics of antibody diversity. *Sci. Am.* 246:72, 1982.
23. Nisonoff A., Lamoyi A.: Implication of the presence of an internal image of the antigen in anti-idiotypic antibodies: Possible application to vaccine production. *Clin. Immunol. Immunopathol.* 21:397, 1981.
24. Lifshitz R., Parhami B., Mozes E.: Enhancing effect of murine anti-idiotypic serum on the proliferative response specific for poly(LTyr,LGlu)poly(DLAla)—poly(LLys)[(TG)-A—L]. *Eur. J. Immunol.* 11:27, 1981.
25. Eichmann K., Rajewsky K.: Induction of T and B cell immunity by antiidiotypic antibody. *Eur. J. Immunol.* 5:661, 1975.
26. Shoenfeld Y., Rauch J., Massicotte H., et al.: Polyspecificity of monoclonal lupus autoantibodies produced by human-human hybridomas. *N. Engl. J. Med.* 308:414, 1983.

27. Lafer E.M., Rauch J., Andrezejewski C. Jr., et al.: Polyspecific monoclonal lupus autoantibodies reactive with both polynucleotides and phospholipids. *J. Exp. Med.* 153:897, 1981.
28. Schleider M.A., Nachman R.L., Jaffe E.A., et al.: A clinical study of the lupus anticoagulant. *Blood* 48:499, 1976.
29. Rauch J., Tannenbaum H., Stollar B.D., et al.: Monoclonal anticardiolipin antibodies bind to DNA. (Submitted for publication.)
30. Eilat D.: Monoclonal autoantibodies: An approach to studying autoimmune disease. *Mol. Immunol.* 19:943, 1982.
31. Pearson C.M.: Development of arthritis, periarthritis, and periostitis in rats given adjuvants. *Proc. Soc. Exp. Biol. Med.* 91:95, 1956.
32. Pearson C.M.: Experimental joint disease: Observations on adjuvant-induced arthritis. *J. Chronic Dis.* 16:863, 1963.
33. Battisto J.R., Smith R.N., Beckman K., et al.: Susceptibility to adjuvant arthritis in DA and F_{344} rats. *Arthritis Rheum.* 25:1194, 1982.
34. Whitehouse D.J., Whitehouse M.W., Pearson C.M.: Passive transfer of adjuvant-induced arthritis and allergic encephalomyelitis in rats using thoracic duct lymphocytes. *Nature* 224:1322, 1969.
35. Holoshitz J., Naparstek Y., Ben-Nun A., et al.: Lines of T lymphocytes induce or vaccinate against autoimmune arthritis. *Science* 219:56, 1983.
36. Holoshitz J., Cohen I.R.: Unpublished data.
37. Trentham D.E., McCune W.J., Sussman P., et al.: Autoimmunity to collagen in adjuvant arthritis of rats. *J. Clin. Invest.* 66:1109, 1980.
38. Trentham D.E., Townes A.S., Kang A.H.: Autoimmunity to type II collagen: An experimental model of arthritis. *J. Exp. Med.* 146:857, 1977.
39. Stuart J.M., Postlethwaite A.E., Townes A.S., et al.: Cell-mediated immunity to collagen and collagen alpha chains in rheumatoid arthritis and other rheumatic diseases. *Am. J. Med.* 69:13, 1980.
40. Iizuka Y., Chang Y.H.: Adjuvant polyarthritis: VII. The role of type II collagen in pathogenesis. *Arthritis Rheum.* 25:1325, 1982.
41. Barcinski M.A., Rosenthal A.S.: Immune response gene control of determinant selection: I. Intramolecular mapping of the immunogenic sites on insulin recognized by guinea pig T and B cells. *J. Exp. Med.* 145:726, 1977.
42. Wright V.: Seronegative polyarthritis, a unified concept. *Arthritis Rheum.* 21:619, 1978.
43. Brewerton D.A., Caffrey M., Hart F.D., et al.: Ankylosing spondylitis and HL-A27. *Lancet* 1:904, 1973.
44. Schlosstein L., Terasaki P.I., Bluestone R., et al.: High association of HL-A antigen, W27, with ankylosing spondylitis. *N. Engl. J. Med.* 288:740, 1973.
45. Morris R., Metzger A.A., Bluestone R., et al.: HL-AW27—a clue to the diagnosis and pathogenesis of Reiter's syndrome. *N. Engl. J. Med.* 290:554, 1974.
46. Good A.E.: *Shigellae* and Reiter's syndrome. *Ann. Rheum. Dis.* 38(suppl. 1):119, 1979.
47. Ford D.K.: *Yersinia*-induced arthritis and Reiter's syndrome. *Ann. Rheum. Dis.* 38(suppl. 1):127, 1979.
48. Keat A.C., Maini R.N., Nkwazi G.C., et al.: Role of *Chlamydia trachomatis* and HLA-B27 in sexually acquired reactive arthritis. *Br. Med. J.* 1:605, 1978.
49. Edmonds J., Macauley D., Tyndall A., et al.: Lymphocytotoxicity of anti-*Klebsiella* antisera in ankylosing spondylitis and other related arthropathies: Patient and family studies. *Arthritis Rheum.* 24:1, 1981.
50. Geczy A.F., Alexander K., Bashir H.V., et al.: A factor in *Klebsiella* culture filtrates specifically modifies an HLA-B27 associated cell surface component. *Nature* 283:782, 1980.
51. Shenkman L., Bottone E.J.: Antibodies to *Yersinia* enterocolitis in thyroid disease. *Ann. Intern. Med.* 85:735, 1976.
52. Tonooka N., Leslie G.A., Greer M.A., et al.: Lymphoid thyroiditis following im-

munization with group A streptococcal vaccine. *Am. J. Pathol.* 92:681, 1978.
53. Stollerman G.H.: Streptococcal immunology: Protection versus injury, editorial. *Ann. Intern. Med.* 88:422, 1978.
54. Dos G.A., Gaspar M.I.C., Barcinski M.A.: Immune recognition in the streptococcal carditis of mice: The role of macrophages in the generation of heat-reactive lymphocytes. *J. Immunol.* 128:1514, 1982.
55. Bloom B.R.: Games parasites play: How parasites evade immune surveillance. *Nature.* 279:21, 1979.
56. Shechter Y., Maron R., Elias D., et al.: Autoantibodies to insulin receptor spontaneously develop as anti-idiotypes in mice immunized with insulin. *Science* 216:542, 1982.
57. Shechter Y., Elias D., Maron R., et al.: Mouse antibodies to the insulin receptor developing spontaneously as anti-idiotypes: I. Characterization of the antibodies, unpublished manuscript.
58. Cohen I.R., Elias D., Maron R., et al.: Immunization to insulin generates anti-idiotypes that behave as antibodies to the insulin hormone receptor and cause diabetes mellitus, in Köhler H., Cazenave P.A., Urbain J. (eds.): *Idiotypic Manipulations in Biological Systems.* New York, Academic Press, Inc., 1983.
59. Hearn M.T.W.: Graves' disease and the thyrotropin receptor. *Trends Biochem. Sci.* 5:75, 1980.
60. Steinman L., Cohen I.R., Teitelbaum D.: Natural occurrence of thymocytes that react with myelin basic protein. *Neurology* 30:755, 1980.
61. Rosenberg Y.J.: Autoimmune and polyclonal B cell responses during murine malaria. *Nature* 274:170, 1978.
62. Gleichmann E., Van Elven E.H., Van der Veen J.P.: A systemic lupus erythematosus (SLE)-like disease in mice induced by abnormal T-B cell cooperation: Preferential formation of autoantibodies characteristic of SLE. *Eur. J. Immunol.* 12:152, 1982.
63. Paterson P.Y., Drobish D.G., Hanson M.A., et al.: Induction of experimental allergic encephalomyelitis in Lewis rats. *Int. Arch. Allergy Appl. Immunol.* 37:26, 1970.
64. Ben-Nun A., Cohen I.R.: Spontaneous remission and acquired resistance to autoimmune encephalomyelitis (EAE) are associated with suppression of T cell reactivity: Suppressed EAE effector T cells recovered as T cell lines. *J. Immunol.* 128:1450, 1982.
65. Ben-Nun A., Eisenstein S., Cohen I.R.: Experimental autoimmune encephalomyelitis (EAE) in genetically resistant rats: PVG rats resist active induction of EAE but are susceptible to and can generate EAE effector T cell lines. *J. Immunol.* 129:918, 1982.
66. Naparstek Y., Holoshitz J., Eisenstein S., et al.: Effector T lymphocyte line cells migrate to the thymus and persist there. *Nature* 300:262, 1982.
67. Brown C.A., Carey K., Colvin R.B.: Inhibition of autoimmune tubulointerstitial nephritis in guinea pigs by heterologous antisera containing anti-idiotype antibodies. *J. Immunol.* 123:2102, 1979.
68. Zanetti M., Bigazzi P.E.: Anti-idiotypic immunity and autoimmunity: 1. In vitro and in vivo effects of anti-idiotypic antibodies to spontaneously occurring autoantibodies to rat thyroglobulin. *Eur. J. Immunol.* 11:187, 1981.
69. Fuchs S., Feingold C., Bartfeld E., et al.: Molecular approaches to myasthenia gravis, in Schotland D.L. (ed.): *Disorders of the Motor Unit.* New York, John Wiley & Sons, Inc., 1982.
70. Vladutiu A.O., Rose N.R.: Autoimmune murine thyroiditis: Relation to histocompatibility (H-2) type. *Science* 174:1137, 1971.
71. Ben-Nun A., Cohen I.R.: Experimental autoimmune encephalomyelitis (EAE) mediated by T cell lines: Process of selection of lines and characterization of the cells. *J. Immunol.* 129:303, 1982.

72. Maron R., Zerubavel R., Friedman A., et al.: T lymphocyte line specific for thyroglobulin produces or vaccinates against autoimmune thyroiditis in mice. *J. Immunol.*, to be published.
73. Ben-Nun A., Wekerle H., Cohen I.R.: Vaccination against autoimmune encephalomyelitis using attenuated cells of a T lymphocyte line reactive against myelin basic protein. *Nature* 292:60, 1981.
74. Ben-Nun A., Cohen I.R.: Vaccination against autoimmune encephalomyelitis (EAE): Attenuated autoimmune T lymphocytes confer resistance to induction of active EAE but not to EAE mediated by the intact T lymphocyte line. *Eur. J. Immunol.* 11:949, 1981.