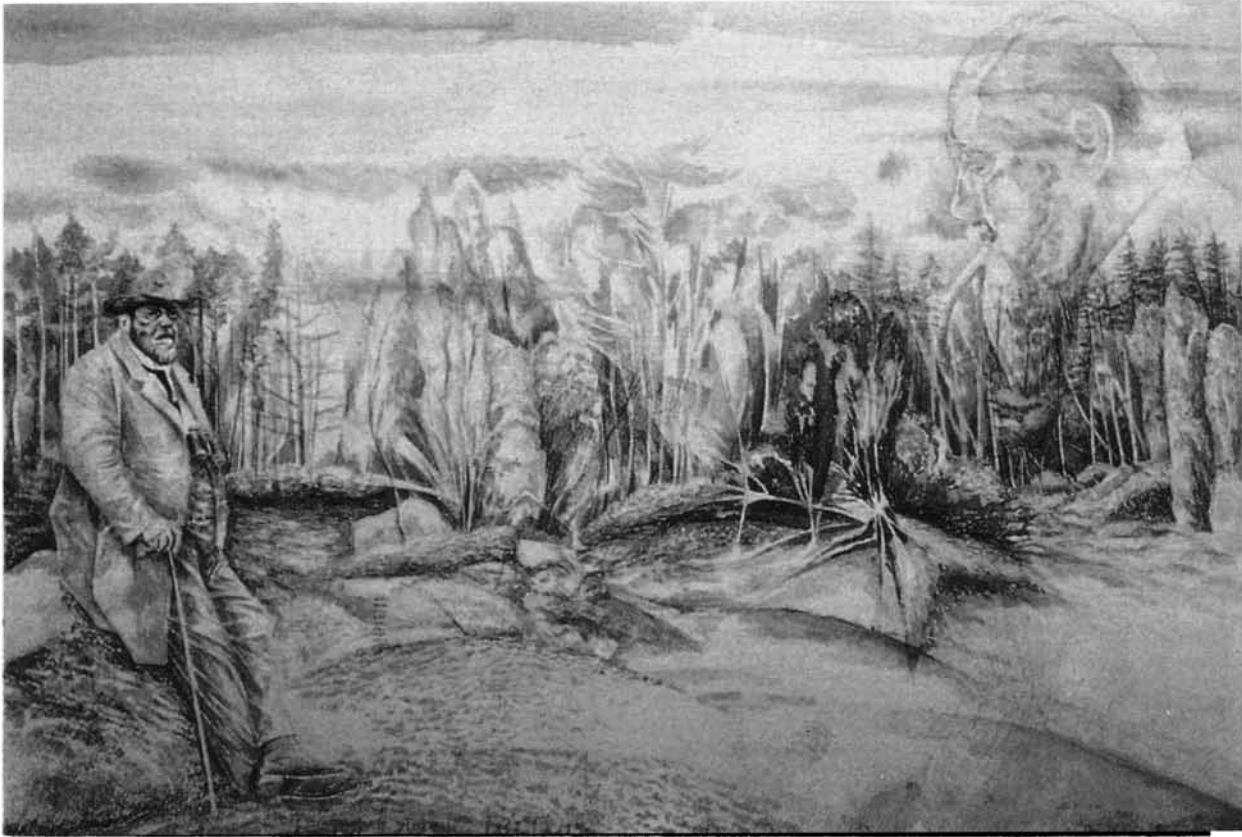# Pastor Bode Lecture

Wilsede, June 20, 1990

N. Avrion Mitchinson:
Escape from the Red Queen

„Heidepastor" Wilhelm Bode

Michel Weidmann (Aquarell)

Wilhelm Bode was born on October 20, 1860, in Lüneburg, in Germany, as the third of ten children. His father was a teacher at the seminary in Lüneburg. There is a legend that the father, on the night of the birth of each of his sons, took the child and, placing hin in the wide pocket of his coat, diaper and all, walked up the nearby Kalkberg hill. There, he held up the child facing the town spread out peacefully below, and said, "Behold, my son! This is your home country! Remain true to it, hold it dear to your heart, and protect it!"

Wilhelm, the third son, inherited his father's inclination towards nature and his enthusiasm for it, and indeed for everything unspoiled and free, more strongly than any of the other children. Wilhem often accompanied his father on the long excursions he habitually took in the school holidays. And he showed from the first a particular love of nature lore and science.

The youth grew up in a tightly knit family. The father's favorite saying was, "The rich man is not the one with many possessions, but the one with few needs." In 1880, upon fishing school, the 19-year-old Wilhelm started theological studies, first in Göttingen, then in Strasbourg. Even as a student, his interests ranged wide: zoology, botany, history, and German romantic literature fascinated him in addition to his main subject of study. For several weeks during one holiday, he even joined a wandering circus.

After completing his theological studies, he was assigned to the parish in Egestorf, six miles to the east of Wilsede Hill. This was to become the scene of his life's work. His first serom, on August 15, 1886, was delivered on the theme *We together*. "You are my parishioners," he said, "and I am your pastor; and if two people are going to live together, and take up housekeeping together, it is a good thing for each to have a clear notion of the rights and duties that each has towards the other." "Do not demand that I demonstrate all the social graces," he went on, "or that I be worldly wise, or a flashy speaker, or anything else other than a servant of the true Teaching! Take care what is said from this, your pulpit, and watch jealously that it not be profaned! The parish that requires nothing of its pastor is asleep; but the one that requires much is alive... The first premise for beneficial cooperation is an unreserved and mutual give and take between us. We shouldn't say; 'Here are the parishioners, and there is the pastor,' but rather 'We together!' This is may task."

Pastor Bode tried to make lessons in the schools more interesting, and checked to see that the teachers really began lessons on time. He himself organized programsfor official school celebrations; he arranged for the children to be provided with their school books, with the exception of Bible and psalm book, at the cost of the school district. He advocated putting an atlas and a book on science and languages in the hands of each pupil; and he considered sports, gymnastics, to be one of the most important subjects. It was Pastor Bode, with his farmers, who in 1888 founded the first savings and loan bank in the Lüneburg Heath. Later, a cooperative for the insurance of farm animals, the *Kuhkasse* or "cow found," was added. The cooperative purchase of feed and fertilizer was organized, followed by a water cooperative, which used wind power to provide the village with running water.

This was the one side of his work: practical, active help so that the people entrusted to him could improve their standard of living.

Pastor Bode's other side seems marked by a sort of natural piety: his sermons breathe the air of freedom and nature. His passion for the heath is not an ideology; rather, it was a part of his pastoral teaching to win each of his farmers to an appreciation of the land that he farmed. On a walking trip with his father, the young Bode had passed from Egestorf via Aue and Radenbach to Wilsede, through the untouched natural beauty of the open heath with its juniper bushes, with the lustrous dark green of

the bordering pine woods. At one point, his father said, "My son, if a man could preserve this landscape for future generations, he would have accomplished a great work, a good work."

Many years later, when Bode found that a considerable parcel of land, the Totengrund, was to be sold and used for construction, he tried to prevent the sale. After many fruitless attempts, he found a valuable ally in Professor Thomsen from Münster: this man was prepared to supply funds for the purchase of the Totengrund, thus saving it from the development that threatened it. After very difficult negotiations, Bode succeeded in purchasing the Totengrund in 1906 for the sum of 6000 marks. This piece of land was to become the seed from which the Lüneburg Heath Nature Park was to grow.

Bode carried out his next project in cooperation with a Herr Dageförde, a teacher from Tangendorf. This teacher had assembled an extensive anthropological collection which filled the schoolhouse to overflowing. On the initiative of Pastor Bode, a piece of land was purchased in Wilsede. Thus, Bode became one of the founders of the Wilsede Heath Museum Society. Dageförde acquired (quite cheaply, as it was going to be torn down) a fine old farmhouse in Hanstedt dating from 1750. This house was disassembled, and then rebuilt on the lot in Wilsede. It opened on August 15, 1907, as "The Old House", or in the North German idiom, "*dat ole Huus.*" Tourism increased. The Society, only recently formed, enthusiastically erected an inn, the "Inn at the Heath Museum." Pastor Bode wrote the advertising pamphlets himself, and argued: "No paved road! No nickelodeon!"

As Pastor Bode learned that a dance hall was to be built on Wilsede Hill, he managed to delay the sale of the land. District Counsellor Ecker from Winsen/Luhe, a member of the Nature Park Society, sent the author of *Kosmos*, Dr. Curt Floericke, to look over the situation. Impressed, Floericke wrote a decisive report. Ecker, as representative in the Prussian Legislature, succeeded in arranging for public funds to be made available: the Nature Park Society was then able to purchase this parcel as well.

When Pastor Bode died on June 10, 1927, he was mourned by large numbers of people. It was his request that his ashes be scattered to the winds from the top of the Wilsede hill. This wish was granted him.

Hanne-Lore Neth

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Pastor Bode Lecture

Escape from the Red Queen

N. A. Mitchison [1]

Immunological diseases follow a characteristically fluctuating course of relapse and remission, such as is illustrated in Fig. 1. This is true most obviously of diseases such as rheumatoid arthritis which have a major autoimmune component, but it holds equally well for chronic infectious diseases such as leprosy in which hypersensitivity plays an important part. It is likely, but not definitely established, that the fluctuations reflect an imperfect balance between opposing forces within the immune system, and that these in turn reflect the activity of opposing control genes. Among such control genes, those of the major histocompatibility complex (MHC) are likely to be the most important.

Studies on the MHC and disease have tended to focus on detrimental genes, that is, those which are positively associated with the disease in question, predispose for it, and presumably act as causal factors. Some of the autoimmune diseases are tightly associated with particular HLA genes, such as is ankylosing spondylitis (and certain forms of reactive arthritis) with HLA-B27. For others the tightness of the association has become apparent only as seemingly unrelated predisposing genes have been discovered to share sequences in common. Thus an epitope shared between HLA-DR1 and HLA-Dw4 explains well why both of these genes predispose for rheumatoid arthritis [1]. The existence of a tight association suggests that the disease process may be driven by presentation of a self-peptide by the HLA molecule. Not only does this provide an attractively simple picture of how the disease develops, but it also points the way forward to new modes of treatment. From the tight associations spring the present flurry of excitement concerning HLA-blocking peptides and monoclonal antibodies.

In comparison, beneficial HLA genes have suffered neglect. This seems a pity, if only because it makes sense to try to understand what makes a patient get better. The negative associations between HLA and disease seem on the whole to be weaker than the positive ones, although this has not been categorically established. Another reason for neglect is that it is less obvious how an MHC gene could inhibit an immune response, in the way that these beneficial genes seem to do.
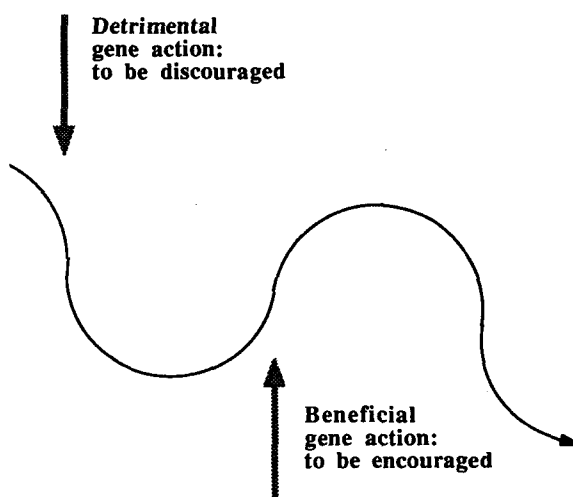

Fig. 1. The disease pattern of relapse and remission, characteristic of immunological diseases, suggests that opposing activities operate within the immune system

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One has to think seriously about suppressive activity and suppressor cells, and those are subjects that immunologists have learned to be cautious about. Nevertheless they are the subject of this paper.

Inhibitory MHC Genes

Examples of inhibition of immune responses by MHC genes are not hard to find. Our recent survey lists some 20 in mouse and man [2]. What that listing did not include are the significant but only moderately impressive negative associations between HLA and autoimmune disease that have often been recorded, usually as by-products of surveys aimed principally at verifying positive associations. Figure 2 gives an example, showing the apparently beneficial effects of three HLA-DR genes on rheumatoid arthritis in a recent study [3].

If I had to choose just one example of a disease study, it would be the joint work carried out by groups from Leyden and Caracas on HLA and lepromatous leprosy [4]. Not only does this contain beautiful data, but also it provides an amusing sidelight on paternity and family

life in Venezuela. Since then leprosy has become an arena for testing ideas about genetic control of suscepbility to chronic infectious disease, and more recent presentations of the topic are available [5]. Rather than go over the whole list of inhibitory genes in this and other areas again in detail, it seems more useful on the present occasion to offer the following generalizations.

1. As evidence of an immunoinhibitory effect, a negative association between HLA and an autoimmune disease (or other immunological disease, such as allergy) is equivalent to a positive association with an infectious disease.

2. Evidence of such associations often springs initially from population surveys. Such data need eventually to be supported by the stronger evidence that multiple-case family studies can provide. In the mouse, studies on panels of recombinant inbred mice provide the equivalent of family studies in man. It should be noted, however, that families with multiple cases tend to have a high susceptibility background, and that this will diminish the impact of protective genes (I am
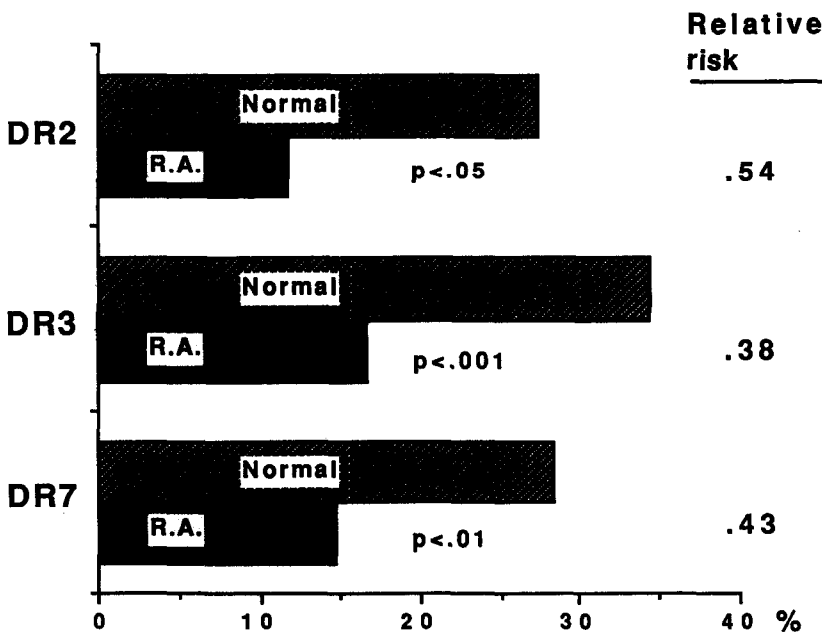

Fig. 2. Negative associations between class II HLA genes and rheumatoid arthritis, detected in a UK survey

grateful to H. O. McDevitt for pointing this out to me).

3. As mentioned above, many immunological diseases have strong positive HLA associations. This will tend to produce negative associations for other HLA genes, and the more frequent such a gene is in the study population, the more likely is this negative association to reach significance.

4. Although a negative MHC association may be taken as prima facie evidence of immunoinhibition in an immunological disease (and likewise a positive one in an infectious disease), detailed immunological study would be needed to substantiate the claim. This might involve exploring the possibility of relieving the inhibition by in vitro (or in the mouse by in vivo) treatment with anti-MHC monoclonal antibodies, or other procedures.

5. The clear-cut inhibitory MHC genes have all so far turned out to belong to class II. This is surprising, in view of the fact that T cells able to mediate an inhibitory effect often have the CD8 phenotype. One can think of explanations, for instance, along the lines of the phenomenon known in inbred mice where, when an active H-2K allele (in a cytotoxic response) is replaced by an inactive one, the previously inactive H-2D allele become active (and vice versa). But the absence of class I genes still seems odd, and perhaps further research will change the picture.

6. No MHC gene has been found to mediate inhibition exclusively. All the genes which inhibit a response act positively in others (this statement requires some qualification as regards HLA-DQ in man, where most of the evidence for a positive effect comes from in vitro studies with cloned T cells of "helper" phenotype).

7. Nevertheless a certain bias in the location of inhibitory activity within the MHC is evident, both in mouse and man. This is respectively towards H-2E and HLA-DQ. These genes are not, of course, homologous in evolution, but they do share certain features in common. Both seem to be secondary class II genes, with relatively few T cells restricted by them, with relatively low expression, and with relatively low polymorphism (none of these features are definitively documented, unfortunately). Function seems to have flipped from one gene to another during the evolutionary divergence of the two species.

One of the important issues of the day in this area is the claim that the presence of asp-57 in HLA-DQ protects against insulin-dependent diabetes. The most recent publication on this subject amounts to a vigorous rejection of this claim on the basis of a segregation study in multiple-case families [6], but the qualification about this type of study, mentioned in point 2 above, means that judgement should be suspended. I doubt if we have yet heard the last word on this matter.

Finally let me mention the recent study that raised my interest in the present issue [7]. It showed that substitution of $H-2A^b$ for $H-2A^k$ strongly inhibits the response of mice to F liver antigen and does so more weakly for their response to Thyl antigen. This provides a promising system for further study of mechanism.

Mechanisms of Inhibition

A comprehensive conceptual framework within which to consider mechanisms of inhibition is much needed, and the main purpose of this paper is to present one in the outline form shown in Fig. 3. In doing so, I gladly acknowledge the benefit derived from discussions with C. S. David and H. O. McDevitt, and from the trenchant commentary of Nepom [6].

This classification begins with a distinction between intracellular and intercellular mechanisms, so that only in the former does the inhibitory MHC product operate within the same cell as the positive MHC (immune response, Ir) product. Intercellular mechanisms corre-
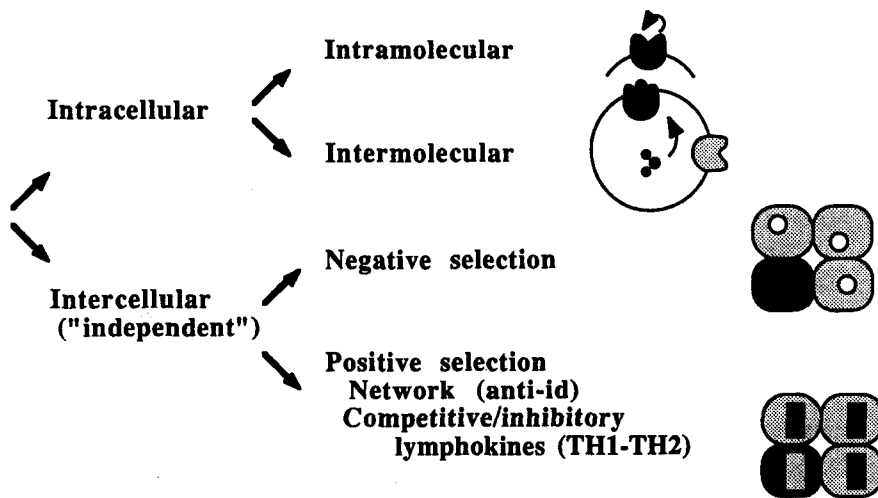
Intracellular

Intramolecular

Intermolecular

Intercellular
("independent")

Negative selection

Positive selection
Network (anti-id)
Competitive/inhibitory
lymphokines (TH1-TH2)

Fig. 3. A classification of immunoinhibitory mechanisms mediated by class II major histocompatibility complex molecules. The inhibitory molecule or repertoire is *shaded darker*

spond roughly to what Nepom designates as "independent" inhibitory activity, a category whose existence he questions.

Intracellular mechanisms further subdivide into intra- and intermolecular ones. Intramolecular inhibition, for instance, might involve an amino acid substitution in the $\alpha 1$ helix inhibiting the activity of an Ir gene previously defined by substitution in the $\alpha 2$ helix. This is a makeshift, as eventually the combination would be designated simply as a new neutral allele. On the other hand, the category of intracellular, intermolecular inhibitions has several examples, mostly involving class I genes in the mouse. These I have discussed some time ago [8]. The phenomenon of competition in the antiviral cytotoxic response between H-2K and H-2D mentioned above belongs here, as also does the competition between heterozygous alleles at H-2K or H-2D that has been noted in the same type of response. More relevant to our present discussion of class II inhibitory genes, perhaps, is the competitive suppression that my group has studied in the anti-Thyl response [9]. There the presence of an allogeneic MHC molecule on a Thyl antigenic cell (but not on a neighboring cell) can inhibit the response. That this is truly a competitive inhibition is strongly supported by our (unpublished) data demonstrating loss of inhibition when the dose of antigen is increased. We do not known for certain whether the allo-MHC antigen in this experiment is presented by self-class II molecules in the usual way, but if it is then the gene(s) which encode them could be regarded as inhibitory for the anti-Thyl response. In summary, the known instances of intracellular, intermolecular inhibition boil down to antigenic competition.

The intercellular mechanisms subdivide into those that result from negative or positive selection. In negative selection the product of one MHC gene inhibits the activity of another by deleting a part of its repertoire. The ikon for this category in Fig. 2 depicts the T cell repertoire as subdivided into four parts according to their restriction elements (e.g. H-2A^a, H-2A^b, H-2E^a, H-2E^b); the part restricted by the inhibitory gene is shaded darker, and there are holes in the other parts of the repertoire. This phenomenon is now familiar in the context of superantigens, such as H-2E, or the *mls* product. It has not yet been identified (to the best of my knowledge) as a mechanism of inhibition resulting from class II allelic substitution, although that may well be disclosed in the future.

Suppression mediated by positive selection is the most challenging category,

for this is our old friend the suppressor T cell revived. In the formal sense used here, inhibition results from positive selection when the product of one MHC class II gene enables a group of T cells to develop that are able to inhibit the activity of another group of T cells that would otherwise perform a response. The ikon shows the part of the repertoire that is restricted by the inhibitory gene as biased towards inhibition, while the rest of the repertoire is biased away from that activity (note the patches of shading). As mentioned in the figure, current theory is that inhibitory T cells could operate in alternative ways. One would be, by engaging in inhibitory anti-idiotypic recognition, thus involving Jerne's network. An alternative would be the secretion of inhibitory or competitive lymphokines, such as do TH1 and TH2 cells in the mouse [10]. Other possibilities could be cited, such as antigen-specific suppressor factors, but these seem too remote to be included in the discussion.

This is not the place to discuss these last alternatives in detail. Inhibition via the network has a long history and much experimental support (see my reviews [11, 12]) and can be regarded from various points of view. As K. Rajewsky has pointed out to me, it could be no more than a form of mopping up, needed only to prevent inescapable network interactions getting out of control. Or, as I. R. Cohen proposes, self-macromolecules such as heat-shock proteins or myelin basic protein could induce a positive response within the immune system, which would normally be contained by anti-idiotypic suppression, but which would on occasion break out in the form of autoimmune disease. As regards lymphokines, the evidence in the mouse is convincing of mutual inhibition mediated by γ-interferon produced by TH1 cells, and interleukin (IL)-4 and IL-10 produced by TH2 cells. In man the position is less clear; perhaps atopy and its control by therapeutic vaccination may offer the best example of inhibitory T cell activity [13].

Now that we have this classification, are we yet in a position to assign any of the known immunoinhibitory effects to their correct slot within it? For the effects which matter in human disease, of the type shown in Fig. 2, the answer is, not yet. For mouse models some assignments can be made to the category of positive selection and others to that of negative selection. V-gene usage provides an important clue to the operation of negative selection, and enhancement of the response by anti-class II antibody does likewise for positive selection. But it must be emphasized that assignments made on these bases are only provisional, because it is always hard to exclude the possibility that some additional mechanism is operating.

This discussion has focussed on ways of carving up CD4 class II-restricted T cells, the main regulatory compartment of the immune system and arguably the single most numerous and most important group of lymphocytes. They can be subdivided according to restriction element, involvement in the network, lymphokine secretion profile, and positive versus negative effect (and also according to markers such as CD45R which discriminate between naive and memory cells). Some of these are lineage markers while others are not, and one needs to use ones wits when mixing the two [14]. It seems to me that the alignment of these various characteristics is one of the most important items on the agenda of cellular immunology.

Why Are Immunoinhibitory Genes so Frequent?

It is hard to believe that autoimmune disease occurs with sufficient frequency, or in a young enough age group, to have had much evolutionary impact. As we have argued elsewhere [15], the driving force is more likely to have been the hypersensitivity induced by chronic infection. Most or all of the major tropical diseases are associated with hypersensi-

tivity, and nowhere is this more conspicuous than in leprosy. In that disease immunopathological mechanisms are most threatening in borderline cases. It is as though individuals at either end of the spectrum are protected: at the tuberculoid pole (and in the much larger number of individuals who are infected but never show clinical symptoms) the immune system functions in its usual protective mode, while at the lepromatous pole its protective functions are inhibited and the parasite becomes free to multiply. Immunoinhibitory genes may thus occur in human populations in the developed world largely as a result of past selection for inhibition of infection-associated hypersensitivity.

The association noted above between immunoinhibitory activity of MHC genes, low expression, and low polymorphism now begins to make sense. The predominant activity of MHC genes is positive where they function as immune response genes. Such genes are driven to become intensely polymorphic, as a result of what the evolutionary biologists have come to call "the Red Queen strategy." By this is meant that any one species lives within an environment provided by other species, and as one evolves so must the others. The final result is a great deal of evolutionary change but little real progress, just as in Lewis Carrol's *Through the Looking Glass* where Alice and the Red Queen hold hands and run, without getting anywhere. Nowhere does this apply with greater force than in the coevolution of immune response genes in the host and the antigen genes in parasites to which they are opposed. This ceases to apply to MHC genes in respect of their inhibitory function. In that case the interests of the host and the parasite coincide; the Red Queen, so to speak, comes out of play. We can therefore expect immunoinhibition to associate with diminished polymorphism. The association with diminished expression may occur because, on balance, such genes prove less valuable in an evolutionary sense; they may even be on their way to total

elimination from the MHC gene pool. It is tempting to suppose that reduced class II expression may provide a mechanistic signal for suppression within the immune system, thus closing the evolutionary circle.

All this is of course highly speculative. The value of the evolutionary arguments is that they focus attention on particular mechanisms, and also that they identify the need for particular types of immunoepidemiological data.

New Therapies: Combatting or Enhancing Immunoinhibition

The proof of these ideas about inhibitory activity is whether they lead on to new forms of therapy. In this context three lines of current research look particularly promising. The first two concern chronic infectious diseases in which immunoinhibitory activity has long been suspected of preventing recovery, and where a novel form of therapy offers hope of breaking through that barrier. The third concerns the opposite problem, autoimmune disease in which the lack of adequate immunoinhibitory activity may help cause the disease, and where a novel form of therapy might rectify that defect.

This year a group from the Rockefeller University collaborating with local researchers in Addis Ababa published their results on sublesional administration of IL-2 in leprosy [16]. This is the first trial of lymphokine treatment in a chronic infectious disease, and it used the lymphokine at something approaching physiological concentrations (far less than has been used in cancer trials). The results were encouraging, as judged by the histological response determined in skin biopsies, and treatment with other lymphokines is planned. From the point of view expression above, treatment of this sort carries great promise as well as some hazard. If patients are to be shifted along the spectrum towards the tuberculoid pole, it is essential that they be moved out of the intermediate zone of hypersensitiv-

ity and not into it; that will require careful patient selection. While these results do not provide direct support for the TH1-TH2 concept, they are at least compatible with it.

Last year there appeared a full report on the treatment of cutaneous leishmaniasis by immunotherapy in the form of vaccination with bacille Calmette-Guérin (BCG) plus killed leishmania organisms [17], a form of treatment that has also been applied in leprosy. Results as good as those of conventional chemotherapy were obtained. That reports includes a detailed and thoughtful discussion of the possible mode of action; once again, while many other possibilities remain open, an interpretation in terms of competing lymphokines seems attractive.

The third attractive line of research is gene therapy. After long debate and much hesitation, we are about to witness the first gene therapy trials in man, starting probably with cancer and with congenital enzyme deficiencies. A strong case can be made for following these with trials in the hemoglobinopathies. If all goes well, it would seem reasonable to consider such therapy for cases of autoimmunity which have proved refractory to other forms of treatment. The type of gene that one would wish to implant are those shown in Fig. 2, or possibly an asp-57 HLA-DQ if the doubts mentioned above can be resolved. I am well aware of the difficulties: how to protect an implanted allogeneic major transplantation antigen, for example; and, for those genes which operate their inhibitory effect through positive selection, how to obtain expression in thymic epithelium. But with the technologies that are becoming available these obstacles do not seem insuperable. Now many be the time to start a serious research effort towards that goal.

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