

# THE MAJOR HISTOCOMPATIBILITY COMPLEX IN MAN -- PAST, PRESENT, AND FUTURE CONCEPTS

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As George Snell (1) so rightly said, the supergene, the major histocompatibility complex (MHC), is like a page from the nature book read outside of the context.

Today this context is beginning to be better understood. We would here like to recall the evolution of concepts regarding these molecular structures found in the membrane of cells. First, attention was centered on the almost botanical description of their genetic polymorphism. Then the spotlight was turned, for several years, on their importance in transplantation. More recently, their role in the immune response has become more and more apparent. This, however, is probably not the last stage in our search. We, as well as others (2-5), have suggested that the essential function of these structures resides in self-recognition. These structures are, in fact, the identity card of the entire organism.

We will discuss these four viewpoints successively. Far from being mutually exclusive, they are landmarks in the stages of our thought process as we have gained deeper knowledge of the subject.

## **First concept: Polymorphism and Linkage Disequilibrium**

*Polymorphism:* Since Landsteiner's discovery of the first genetic polymorphism in man, knowledge of polymorphic genes has not ceased to increase and will continue to increase with DNA hybridization techniques. Most of these systems, however, are pauci-allelic and more often than not have one very frequent allele, one that is more infrequent, and a few variants. None of these can be compared with the extreme polymorphism of genes in the MHC of vertebrates, and particularly in the human lymphocyte antigen (HLA) complex

The definition of this polymorphism began to emerge in three laboratories: in ours where the first antigen Mac (HLA-A2) was defined (6), in Van Rood's laboratory (7) with the 4a 4b series (Bw4, Bw6), and Rose Payne's and W. Bodmer's (8) with the two alleles HLA-A2 and -A3. Then, thanks to an intense international effort that has spanned more than 15 years and included eight workshops, the web began to be disentangled. The importance of this international effort, launched by Amos in 1964 [see (9)], and followed by other workshops

directed by Van Rood (10), Ceppellini (11), Terasaki (12), Dausset (13), Kissmeyer-Nielsen (14), Bodmer (15), and again Terasaki (16), cannot be over-emphasized and is to the credit of the whole histocompatibility community. The four presently well-defined, closely linked loci, HLA-A, HLA-B, HLA-C, and HLA-D/DR, have each from 8 to 39 codominant alleles, and the number of haplotypical or genotypical combinations already amounts to several million. It is very likely that other closely linked polyallelic loci will be discovered, similar, for example, to the various loci in the I region of the mouse. If one adds to this complexity the polymorphism of other genes in the HLA region, coding, for example, for factors C2, C4<sup>s</sup>, C4<sup>f</sup>, and B<sup>f</sup> of complement, one reaches such levels of complexity that virtually every human has a different gene combination. If one considers all the genes of the human genome, it can be said that there is not and will never be on earth, apart from true twins, two identical people: every person is unique.

A question that immediately comes to mind is: Why is the MHC so complex? It is clear that a particular pressure was exerted on these genes to make them different and to maintain this differentiation. If it is true that these structures play a role in self-recognition and that they derive from primitive genes coding for surface molecules, then one can conceive of this diversity quickly becoming a necessity when living matter passed from the unicellular stage -- or from a syncytium of identical cells able to fuse without harmful consequences -- to the organized multicellular organism whose tissues must coexist and even cooperate and whose cells therefore cannot even merge with the cells of an organism of the same species.

Maintenance of this polymorphism is undoubtedly aided by the selective advantage given to the heterozygotes, possibly through the immune functions attributed to the MHC molecules in a subsequent stage of evolution.

The HLA system is now known to have two types of products that are very different from each other (their single nomenclature sometimes obscures this difference).

The products of the HLA-A, -B, and -C loci [Klein's class I (17)] are ubiquitous, being present at the surface of all (or almost all) cells of the organism. This wide distribution would suggest that they play a very general biological role.

In contrast, the products of the D/DR locus -- and probably of the "future" DR loci (class II) -- exist only at the surface of certain specialized cells, essentially immunocompetent cells, a valuable piece of information with respect to their functions.

We must not neglect another valuable piece of information afforded by the major similarities between the class I products and immunoglobulins: the light chain (the  $\mu$ 2-microglobulin) as well as one of the domains ( $\alpha$ 3) of the heavy chain have significant similarities with the immunoglobulins and therefore suggest the possibility of a common ancestral gene (18, 19).

The light and heavy chains of the class II products bear no similarity either with the class I products or with the immunoglobulins. It can be said, therefore, that the products of the HLA complex are *bipolar* and are probably derived, by duplication and successive mutation, from two very distinct genes, the function

and origin of which go far back in the evolution of the species.

At present, at least three variable regions on the heavy chain of the class I (20) products are known. In the most distal domain (a1) is the main variability zone (between amino acids 60 to 80), which probably corresponds to the serologically defined allelic epitope (individual antigenic determinant). This same domain also has (between amino acids 30 to 40) an apparently variable zone that is responsible for interaction with the influenza virus. In the median domain (a2) is a third variable zone (between amino acids 105 to 114).

The extreme frequency of cross-reactions between the various allelic molecules of each HLA locus is well known. Two interpretations that are not mutually exclusive are possible: the similarity in the structure of the allelic epitopes [see Colombani *et al.* (21)] or the existence of determinants common to two molecules but different from the epitopes; determinants which I, and Ivanyi (22), have called "antigenic factors" (also known as supertypal antigens or public antigens):

According to our hypothesis, the molecules having an identical epitope—let us say, for example, A2—are not identical in their composition. Some may have one or more different antigenic factors. This variability may be found in the same population but is more often found in different populations (23).

This concept suggests that the various parts of an HLA molecule might have different functions (as is the case for the different portions of the immunoglobulin molecule). It has recently been shown that the interaction between the HLA molecule and the influenza virus does not take place at the level of the serologically distinguishable determinant since this virus has a different interaction with molecules, which, nevertheless, have a serologically identical A2 determinant (24).

The same hypothesis could be applied to the DR molecules and could perhaps make it possible to solve the problem of the relations between the D and DR series. In effect, D might be no more than a variable part of the DR molecule having a stimulating function, since disassociated haplotypes do appear to exist—that is, where the determinant D is not the determinant usually found with the DR antigen (16, 25).

A second possibility, which should not be excluded, is that D in itself does not exist but is defined by an average of allostimulation due to a certain combination of alleles in the loci of region D, the linkage disequilibrium involving not only the DR locus but other loci as well, equivalent to IA, IJ, IC, IE of the mouse.

A second series of DR molecules is already in the process of being defined both by serological and cellular procedures. In particular an allelic SB series, centrometric in relation to the DR locus, has just been described (26, 27) through the use of mixed secondary lymphocytic cultures.

With regard to the genetic organization, we cannot yet grasp this in precise terms, but with the aid of modern DNA hybridization techniques it will not be long before we do understand it (28).

*Linkage disequilibrium.* The four loci of the HLA complex are closely linked on the short arm of chromosome 6 (21p). They are, however, sufficiently distant for relatively frequent recombinations to occur (0.8 percent between A and B and 1

percent between B and D/DR in man). This special situation seems presently to be virtually unique to human genetics. It is, moreover, accompanied by a particular phenomenon, which is the preferential gametic association between alleles of several loci of the same complex. A linkage disequilibrium is said to exist between these alleles. The phenomenon has given rise to numerous speculations.

Is this merely reminiscent of ancestral combinations (when populations were isolated some 2000 to 4000 years ago) that were revealed or increased by human migration? Could a mixture of populations temporarily set a certain haplotypal formula that would survive for only so long as was necessary for it to be dispersed through segregations occurring in successive generations (29)? Or is this linkage disequilibrium really a preferential association, that is to say, selected for the biological advantage or advantages it confers in a certain environment?

Of course, these two mechanisms can operate simultaneously.

One might ask whether the feature of linkage disequilibrium is specific to the MHC or whether it is a very general feature that recurs at other points of the genome.

HLA polymorphism and its linkage disequilibrium are valuable tools for anthropologists and epidemiologists. They allow the former to characterize a population; to discern its origin and draw up its genetic history. They allow the latter to compare HLA formulas and HLA haplotypes with the particular susceptibility of a population or groups of populations to certain diseases; and perhaps in the future they will be able to reconstitute major diseases and epidemics that have occurred in the past by observing the selections that have operated.

Finally, in formal genetics, the HLA complex is certainly the segment of the human genome that is best known and is a major example of our relating a human product to the sequence of the corresponding gene.

## **Second Concept: Transplantation Antigens**

It is in such terms that these membrane structures are most often defined, because at the same time that genetic polymorphism was being elucidated, transplantation in humans was assuming great importance in therapeutics.

Our understanding of allogenic response in man has evolved rapidly. When only the HLA-A and -B antigens were known, allogenic response amounted to cytotoxicity on targets A and B. Thanks to admirable volunteers, the correlation between the survival of skin grafts and the number of HLA-A and -B incompatibilities was clearly demonstrated (30-33). The same correlation was seen in recipients of related or non-related donor kidneys. This correlation, which was long debated, is no longer challenged; however, the benefit of compatibility limited to these two loci is very variable depending on the categories of patients.

When locus D was discovered (34,35), its importance in transplantation was immediately suspected (36, 37). In fact, it was shown *in vitro* that lymphocytic proliferation in allogenic culture was only possible when there was incompatibility at the D locus (38). Clinically, a correlation has been found between the intensity

of proliferation during the mixed lymphocytic reaction, that is, between the recipient and the related donor, and the survival of the graft. However, it has not been possible to apply this observation to the transplantation of nonrelated organs because of the time required for its elaboration.

In contrast, as soon as DR antigens (14, 15) could be detected by serological means - and thus rapidly - it became possible to use this new method of selection successfully. A DR incompatibility is accompanied by a drop in the survival rate of grafts, both skin (39, 40) and organ transplants (41, 42). In both cases there is a clear additive effect with those of the A and B incompatibilities (Fig. 1).

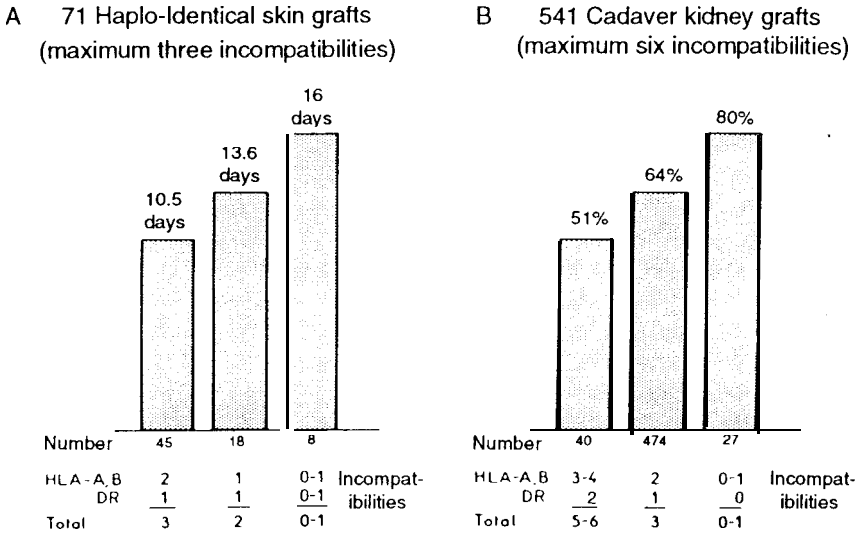


Fig. 1. Additive effect of HLA-A, -B and -DR incompatibilities. (A) Survival time (in days) of skin grafts done between HLA-haplo-identical (most often child to father). Survival of the grafts increases progressively as the total number of HLA-A, -B plus -DR incompatibilities diminishes (30, 39). (B) Percentage survival (at 2 years) of kidney transplant (done in the France-Transplant Network). The same tendency is observed, that is, survival is much improved where there are fewer total HLA-A, -B plus -DR incompatibilities.

Incompatibility is in most cases both DR and D, and thus has two consequences:

1) With DR incompatibility it provides a *target* for cytotoxic cells. DR antigens are true targets: they do not behave like minor antigens because they do not need the HLA-A and -B identity between the killer cell and the target (43).

2) It induces, by the D disparity, the appearance of auxiliary cells, some of which are helper cells and others suppressor cells. In the normal state, helper cells dominate suppressor cells. However, it must be made clear that in certain circumstances, the suppressor cells dominate the helper cells and the scale then tips in favor of tolerance.

It is possible that the indisputably beneficial effect of preoperative transfusions is due to the development of suppressor cells or factors in the recipient (44). In fact, with Sasportes and others (45, 46) we have shown that hyperimmunization against DR is accompanied by the *in vitro* appearance of a suppressive factor

capable of producing a specific feedback inhibition on its own cells. The exact circumstances that cause the suppression *in vivo* to sometimes dominate immunity are unknown. However, it is known that in the monkey the beneficial effect of transfusions has been observed only where the animals are also immuno-suppressed (47). Recipients of kidneys are, so to speak, always immunosuppressed due to their renal insufficiency; this would explain why, in the course of transfusions, the immune balance leans in favor of suppression.

On the basis of the preceding considerations we have proposed (48) a theoretical plan, of necessity provisional, for the choice of blood donors for transfusion and organ donors. Without going into detail, it is based on the following principles:

1) Before transplantation, a state of tolerance must be developed in the recipient and at the same time immunization against HLA-A and B-targets must be avoided. Thus, transfusions should be made with DR incompatible blood that is A, B compatible. The same DR incompatibility should be used constantly in order to increase the chances of the appearance of suppressive cells and factors of the allogenic proliferation.

2) In selecting the organ donor one must avoid providing targets against which the recipient could be immunized. Thus, priority should be given to HLA-DR compatibility in patients who have not produced antibodies against HLA-A and -B antigens in the course of transfusions (nonresponder recipients). On the other hand, priority should be given to HLA-A and -B compatibility in those who have been sensitized in the course of preoperative transfusions (responder recipients). Indeed, for the former there is little chance of immunization occurring against A or B antigens, but the appearance of helper cells and a supply of DR targets should be avoided. Conversely, in the responders, helper cells are already present and their action must be neutralized by not contributing incompatible A and B targets.

Very precise and detailed treatment protocols will be necessary to verify or disprove the validity of this plan.

### **Third Concept: Role in the Immune Response**

This third concept is essentially based on our knowledge of animals since systematic experiments are ethically difficult and thus rare in man (49). Nonetheless, to date, the parallel with the H-2 complex is striking. Here again we find the *bipolar* division of the functions of the products of the HLA complex:

1) Class I products appear to serve as targets when a cell is either infected by a virus or covered with a hapten.

2) Class II products appear to serve as a regulator between the various cell subgroups involved in the immune response.

In both cases, a phenomenon of restriction is most often observed, that is to say, an identity with class I or II products is apparently necessary between the cooperating cells.

Thus a phenomenon of restriction exists in the cytotoxicity of a killer T lymphocyte cell against a cell carrying a virus (50,51), a hapten (52) such as the

DNP, or a normal antigen such as the H-Y antigen (53). The killer cell must have at least one identity with the HLA-A and -B (class I) antigens of the target cell in order for the lysis to be effective, or else the killer must have matured in the presence of the histocompatibility antigens of the target.

Similarly, when an antigen such as PPD is presented by human macrophages (54), the presence of a DR identity (class II) is apparently necessary for the presentation to be effective and for lymphocytic proliferation to occur. This restriction is not absolute, however, and a certain number of proliferative reactions that can be explained by cross-reactions between DR antigens has been observed.

As in the mouse, where soluble factors carry antigens from the I region that convey a specific message to another T or B cell population, so in man there is evidence of a certain number of soluble factors of this type (55,56). Undoubtedly, when we have a better understanding of the various products of region D in man, numerous specific and aspecific factors, either restricted or unrestricted, will be described.

The restriction phenomenon is probably the most direct proof of the role of the products of the HLA complex in the immune response of man.

Indirect proof has been sought in the numerous associations between HLA and diseases. Based on the murine model, the first study of associations between HLA and disease was done in our laboratory on acute lymphoblastic leukemia (57). A slight but definite increase of A2 has now been demonstrated in numerous worldwide studies (58). Likewise, the A1 antigen is slightly increased in Hodgkin's disease. These two observations would suggest that genes acting on hematopoiesis may exist near locus A (58).

However, most of the diseases indisputably associated with HLA are neither tumorous nor obviously infectious (59). These are chronic or subacute diseases having a definite familial though mild character, that are of unknown etiology and are not included in any of the major classifications. For a good number of these there is an obvious autoimmune component.

We will give only two examples to illustrate once again the bipolar nature of the functions of HLA products. In the first example, class I products may still be considered as possible targets; in the second example, class II products may be considered as regulators of the immune response.

Articular and more especially sacro-pelvic disorders that are strongly associated with B27 seem to require the molecule HLA-B itself to play an essential role. In fact, the same B27 antigen is found in a series of disorders (Reiter's syndrome, ankylosis spondylarthritis, psoriatic rheumatism) which tend to affect the articulations of the sacrum and pelvis. Further, this same predisposition is found in all populations of the globe. However, it has now been clearly demonstrated that the same pathological manifestations can also affect a small number of individuals who are B27 negative. The B27 epitope is therefore not indispensable. At least two hypotheses may be advanced: either the responsible gene in all populations is strongly linked with the B27 antigen, or molecule B27 has a variable part (an antigenic factor) that is responsible for susceptibility; this antigenic factor would

not always be present on all B27 molecules and could be found on other HLA molecules probably having cross-reactions with B27 (in keeping with our concept explained above).

It seems, moreover, that for these diseases there is a factor that triggers infection. In fact, it is known that some acute intestinal infections caused by Gram-negative bacteria such *Shigella*, *Salmonella*, and *Yersinia* are complicated by ankylosing spondylarthritis mainly in patients who are B27 positive. Recently, a direct relationship was suggested between the B27 antigen and a type of *Klebsiella* (*Klebsiella* B43). The antibodies against *Klebsiella* would be capable of recognizing specifically an antigen present on the lymphocytes of B27 positive patients affected by ankylosing spondylarthritis. Further, lysates from this infectious agent would be capable of transforming lymphocytes in B27 normal individuals and of making them sensitive to the antibodies against *Klebsiella* (60, 61). Although clinically the link between a *Klebsiella* infection and ankylosing spondylarthritis is still unclear, this observation, not yet confirmed, suggests that certain infectious agents would be capable of modifying HLA antigens and of apparently making them similar to those in patients. It is not impossible that this type of mechanism may one day explain the linkages with other microorganisms referred to above. These microorganisms would be capable of modifying the B27 antigen and perhaps certain other HLA molecules as well (to take into account B27 negative patients), and of making them privileged targets for T-immune autolympocytes. Although this hypothesis is enticing, it cannot yet explain the very special localization of lesions, since the B27 antigen, like all HLA antigens, is practically ubiquitous.

If we now consider disorders associated with HLA-D/DR, one is at the outset struck by the large number of them that are associated with Dw3/DR3 and, more especially in Caucasians, with the A1, B8, DR3 haplotype. For the most part, there are diseases with a strong autoimmune component and a low family penetrance, such as myasthenia gravis, Graves' disease, Addison's disease, Sjögren's syndrome, disseminated lupus erythematosus, and active chronic hepatitis. It appears that this haplotype, in strong linkage disequilibrium, has a gene or perhaps a series of genes that are conducive to autoimmunization.

Insulin-dependent juvenile diabetes (IDD), itself associated with A1, B8, DR3 and also with B18, DR3, and B15, DR4 is in this respect very instructive (62, 63). The viral etiology of IDD is highly suspected: experimental models of the disease do exist and specific observations in some cases in man incriminate the B4 Coxsackie virus. One can therefore infer that the virus has destroyed a certain number of islets of Langerhans and triggered a process of cellular autoimmunity where cytotoxic lymphocytes persist in the organism against antigens modified by or associated with a virus. The disease would thus be self-sustained. In this hypothesis the D region products would have been incapable of inducing an adequate immune reaction against the virus causing the disease. In contrast, individuals who are DR2 positive (most frequently A3, B7, DR2), who appear to be "protected" against IDD would have a more effective immune response against the responsible agent.

This is only a working hypothesis which would have the advantage of applying



to other diseases associated with HLA-DR such as multiple sclerosis (DR2) and chronic polyarthritis (DR4) or juvenile rheumatism (DR5).

The reality, however, is certainly far more complex. In fact, in no case is the association complete with a DR antigen. This is generally explained by a linkage disequilibrium between a simple susceptibility gene for the disease and a DR allele. Here too, however, one might think there are polymorphic parts to DR molecules other than the epitopes presently known and that these might have a particular immune function. Even better, it could be assumed that the interaction of two (or more than two) genes from the D region would be conducive to an adequate immune response. This interaction could take place in the  $\epsilon$  position (64) between genes of the same haplotype (as in the interaction between I-A<sup>b</sup> and I-E<sup>b</sup> to form an I-E molecule in the mouse) or in the *trans* (65) position between two haplotypes (such as I-A<sup>k</sup> and I-A<sup>b</sup>) complementation in the mouse).

As a corollary to these gene interactions we propose that each HLA haplotype, and especially those in linkage disequilibrium that are found most frequently in the numerous diseases associated with HLA, has its own gene configuration that confers on it a particular capacity for immune response, which may be favorable in certain environmental conditions and unfavorable in others (for example the A3, B7, DR2) haplotype gives a susceptibility to multiple sclerosis and protects against IDD) Thus, each HLA complex would be composed of a set of genes that have subtle interactions among one another (such as gene C2 with the two C4 genes) thereby giving them a specific identity in immunological terms.

Likewise, every individual possessing two HLA haplotypes has his or her own immunological capacity which is conferred on him by the two particular haplotypal formulas inherited from his two parents, but which is also the result of the genetic interaction or complementation between these two complexes. Thus each individual has a personal immune response that makes him either susceptible or resistant to certain diseases. Here again each haplotypal combination may be beneficial or harmful depending on the type of challenge to which the individual is subjected.

In terms of the population, we can thus conceive that certain individuals are or were more exposed and thus are or were more easily eliminated than other individuals more resistant to past and present epidemic or endemic diseases. But it is not the same individuals who are susceptible or resistant to the different attacks; this is what makes the survival of a population possible, and thus the perpetuation of the human species.

#### **Fourth Concept: Self-Recognition**

MHC products are distributed on the surface of cells. Those of class I are virtually ubiquitous. Class II products may be found on immunocompetent cells but also on endothelial and other specialized cells. Their location suggests that they play a role in the social organization of cells of the same organism.

This assumption is strongly supported by the following observation: it appears to be necessary for MHC products to share an identity in order for cooperation to

be established between two populations of cells in the same organism or in two different organisms. This is the restriction phenomenon which we discussed above, and which is valid for the two classes of products. Results confirming this apparent need for identity are accumulating very rapidly in both animals and in man and are no longer limited solely to immunocompetent cells. The same is true, for example, in the adhesion phenomenon between fibroblasts and especially in the "homing" phenomenon in ganglia. Degos and others (66) have observed that splenocytes injected intravenously must share an identity with the cells of the capillary endothelium with regard to class I products so that homing can occur. The identity of class II products does not intervene (Fig. 2).

K	I					S	G	U	Mean r values
	A	B	J	E	C				
0	0	0	0	0	0	0	0	0	0.23
•	•	•	•	•	•	•	•	•	0.92
•	0	0	0	0	0	0	0	0	} 0.76
•	•	0	0	0	0	0	0	0	
•	•	•	•	•	0	0	0	0	
•	•	•	•	•	•	•	0	0	
•	•	•	•	•	•	•	•	0	
0	0	0	0	0	0	0	0	•	} 0.86
0	0	0	0	0	•	•	•	•	
0	0	0	0	•	•	•	•	•	
0	•	•	•	•	•	•	•	•	
0	•	•	•	•	0	0	0	•	
•	0	0	0	0	0	0	•	•	0.87
0	•	•	•	•	0	0	0	0	0.33

Fig. 2. Homing in lymph nodes according to identities (•) or differences (0) Labeled lymphocytes were injected intravenously into mice under different genetic conditions: allogenic (first line), syngenic (second line), congenic where the difference involves only one or several genes of the H-2 complex (all other lines). The average value of r (percentage of homing from which the control value has been deducted) is high wherever there is identity (•) with H-2D or H-2K; H-2I identity has no influence (66).

We are thus faced with a very general phenomenon with such a consistent record that it is difficult to escape the conclusion that the two types of molecules have a common function. They could serve as a recognition signal (recognizers) among cells of the same organism; a signal necessary but probably insufficient to permit effective cooperation between the two subpopulations of cells because it would be the same, at least at class I, for all cells of the organism (2-5).

The passive or negative discrimination of self implies that the cells "ignore" one another. This seems improbable in view of the cohesion of tissues and of their interaction. Without self-recognition, each specialized cell and each tissue would be isolated and incapable of surviving. These considerations thus suggest that self-recognition is an active phenomenon.

The subjacent mechanism of self-recognition is still unknown. At least three possibilities come to mind. The most orthodox is the complementarity between two different molecules. But one cannot exclude recognition by identity, whether that recognition takes place between two identical molecules or through a ligand. This fascinating problem has been discussed in detail elsewhere (67). Suffice it to mention here just two remarks in relation to complementarity:

- If a second molecule (receptor) existed with the same immunogenicity as the HLA determinant, a second allelic system as complex as the former would have been found. To date no such system has been found. However, one should remain aware of the weak immunogenicity of the idiotypes which could represent these receptors.

- If the receptor and the determinant were coded by two different genes, any mutation and selection of one should correspond to the mutation and selection of the other. This is unlikely. Here again, however, one might envisage, according to Jerne's theory, that each individual has all possible receptors, the appropriate receptor being selected in early life, perhaps in the thymus. This is probably what occurs, for example, in the growth of allophenic mice in which cells carrying different H-2 antigens coexist.

Whatever the mechanism, the fact remains that self-recognition is a general and active phenomenon of any cell that is at least partially, linked to the MHC. We suggest that class I products are responsible for individuality, for integrity, and perhaps for the general cohesion of the being and that class II products are an example of cellular cooperation, thanks to self-recognition at the level of the differentiated cells of the immune system, allowing the immune system to function harmoniously.

### **Future Prospects**

Thus the increasingly deep understanding of the MHC in man opens up exhilarating prospects both in public health and in basic science.

With regard to organ transplantation, we do not feel that the choice of the most compatible donor will be the last word. On the contrary, our aim must be to provoke in the recipient a specific tolerance to incompatible donor antigens without at the same time diminishing his or her immunological defenses. It seems that with preoperative transfusions the way has been opened to this type of preparation. We must now attempt to unravel its detailed mechanism so that the method can be used more generally. This will be the objective of the years to come, and we have no doubt that it will be achieved.

Although organ and bone marrow transplantations mark a milestone and have already brought help to numerous patients, they should not be considered an end

in themselves. Etiological treatment should progressively replace them.

The discovery of more than 50 diseases associated with or linked to HLA is perhaps still more promising, and although the diagnostic or prognostic benefits to practising physicians are still limited, physicians recognize the validity of this approach. They know that correction of the abnormality which provokes a disease is close at hand when the gene responsible has been located and its function defined. Thanks to the astounding possibilities offered by genetic engineering it will henceforth be possible to know the exact DNA sequence in the vicinity of the HLA genes. The latter will serve as markers and will make it possible to discern anomalies of susceptibility genes. We must emphasize the possibility that in some cases no anomaly will be found because a gene (or combination of genes) may be perfectly active in the defense against certain antigens but totally inactive in the defense against others. Thus an inventory of the immunological capacities of each individual will need to be drawn up. This inventory will show the weaknesses (susceptibility), the excesses (autoimmunization), and the good capacities (protection) afforded by each type of gene combination. In this way, preventive medicine of high precision will be possible; a personalized medicine that will be more efficient and less burdensome for the community than the present mass system.

At the same time, researchers now have the means with which to approach the crucial problem represented by the subtle organization of man's immune system. The cascade of interrelationships, and the language, between different immunocompetent cells will be clarified; the place of the "specific" and the "nonspecific" will be recognized; the role of HLA products in messages between well-defined cells will be determined. This deeper understanding of man's immune response will quickly have major repercussions in pathology. It will perhaps provide the key to the irritating problem of the treatment of cancer, and may also provide a simple means of inducing graft tolerance at will. It will also perhaps lead to an immunological treatment of the major parasitic diseases that still afflict such a large part of mankind.

Finally, the discovery of the primary function of the molecules of the MHC found at the surface of all, or almost all cells of the organism will be a decisive step in our understanding of the differentiation and social organization of cells.

The way already trod is but a simple introduction. They are still many marvellous pages to be written. . .

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