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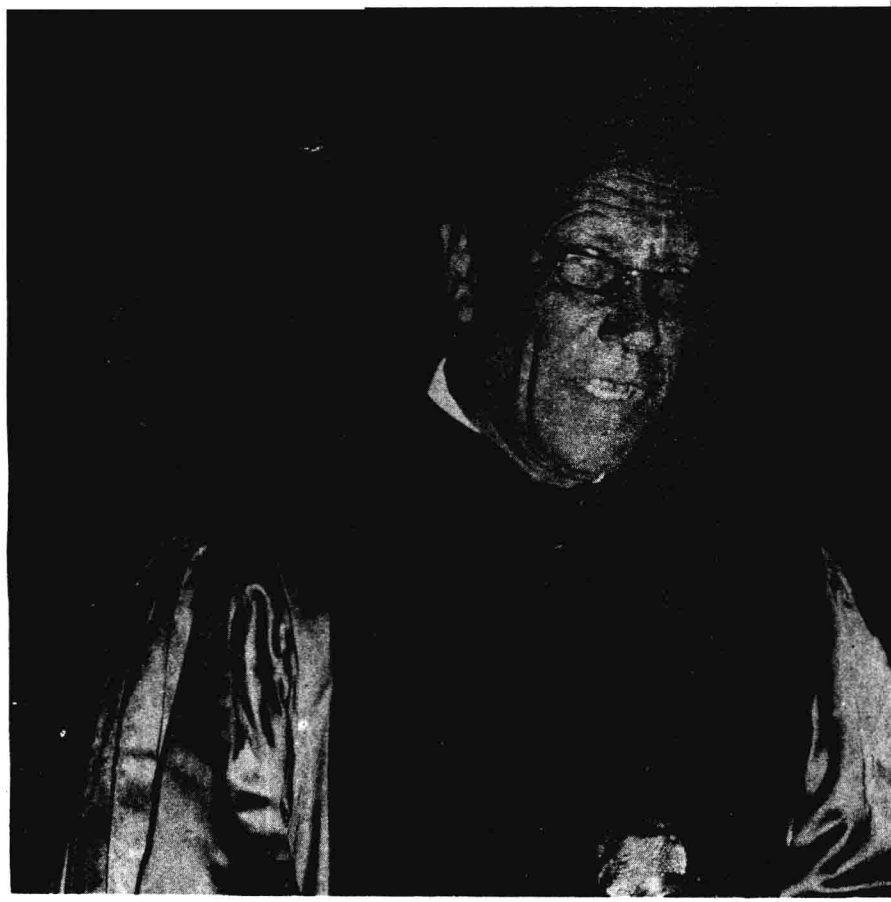
Lecture delivered at the Claude Bernard University by Dr J.J. van Rood who was appointed 'Doctor Honoris Causa'



BIOLOGICAL IMPORTANCE AND CLINICAL RELEVANCE OF THE HLA SYSTEM.

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> Dans la même aspece animale les races peuvent encore presenter un certain nombre de difference très interessantes pour l'expérimentateur Claude Bernard (1).

The HLA region is expanding. Until recently it was enclosed on the short arm of the 6th chromosome by the HLA-A locus at the centromeric side. The distance between the two being 1.7 centimorgans (cM) (Fig. 1).

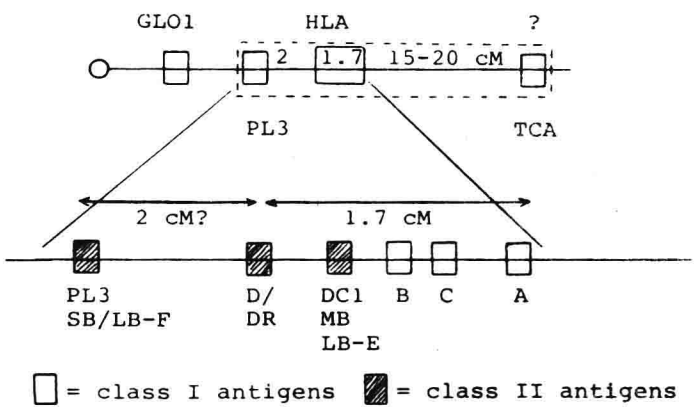

Figure 1. Schematic representation of the HLA supergene.

The HLA-A locus together with the HLA-B and -C locus code for class I antigens which are present on all nucleated cells. The class II antigens coded for by the HLA-D/DR locus are expressed on cells involved in the immune response such as the B lymphocytes, macrophages and activated T lymphocytes. Only recently two other

class II loci have been identified: DC (MB or LB-E) and PL3 (or SB). The HLA-DC locus is probably located between the HLA-B and HLA-DR locus. About 1 cM centromeric from the HLA-D/DR locus the PL3/SB locus is located. It was originally recognised by Termijtelen and independently discovered by Mawas and Shaw who called it SB (2).

The determinants of the PL3/SB locus were identified at first by the primed lymphocyte test. Recently it has been shown that antibodies exist which can recognize these determinants as well (3). It is probable that telomeric from HLA-A on a distance of 15 cM the TCA locus can be found, which codes for a diallelic system of antigens on T-gamma cells.

As far as the chemistry of the class I antigens is concerned, the following can be stated: it consists of 2 chains, a heavy chain with a molecular weight of 44.000 and a light chain with a molecular weight of 12.000. The class II molecules consist also of two chains α and β, with a molecular weight of 34.000 and 29.000 respectively. Amino acid sequencing studies and the three dimensional structures indicate that the genes coding for the class I and II antigens must have arisen in part from ancestral genes which also gave rise to the immunoglobulin genes (4-7). Fig. 2.

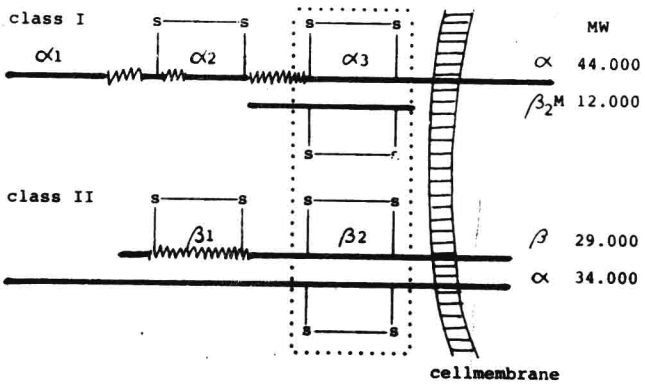

Figure 2. Homologies of class I and II molecules with immunoglobulins

These findings led to the speculation that if the HLA molecules resemble primitive immunoglobulins bound on the cell surface they might also have immunoglobulin-like functions such as the capacity to bind molecular foreign to the individual. If this is true it seems à priori most likely that this will happen at the variable part of the HLA molecule (epitope or HLA specificity). It follows that one would also expect a certain degree of specificity: some HLA antigens or epitopes would be able, certain foreign molecules and others would not. Penicillin might be such a molecule. For instance, if lymphocytes from individuals which are HLA-B14 and B15 positive are incubated with penicillin and thereafter with anti HLA-B14 and -B15 antibodies and complement, then only the HLA-B14 antibody will kill the cell (Table 1) (8). The most likely explanation for these findings is that the B14 epitope does not react with the penicillin which the B15 epitope does. Through steric hindrance the antibody cannot interact anymore with the epitope.

TABLE 1. Complement-dependent cytotoxicity of two HLA typing sera in the presence of penicillin

	Dead cells (%)	
Incubation before adding complement	Anti-B14	Anti-B15
Lymphocytes + penicillin, 15 min; then serum, 30 min	100	<5
Lymphocytes + penicillin + serum, 30 min	100	<5
Lymphocytes + serum, 15 min; then penicillin for another 15 min	100	40
Lymphocytes + serum, 25 min; then penicillin for another 5 min	100	85
Lymphocytes + serum, 30 min (without penicillin)	100	100

(Claas et al. 1982)

The next question is of course what happens if a complex between an HLA molecule and a foreign molecule is formed on the cell surface. Studies of Giphart indicate that this material is then endocytosed (9). Take together, these two findings (the blocking experiments and the endocytosis) lead to the hypothesis that the HLA molecules might have at least two functions: one is a transport and the other a presentation function.

When the number HLA foreign molecule complexes on the cell membrane is not too large, then the complexes will be cleared from the cell membrane by endocytosis and

broken down in the lysosomes. Clearance will take place without cell death. When the number of complexes becomes so large that they cannot be cleared completely by endocytosis, then the T helper cells are activated. This is thus the presentation function of the molecules. The activated T helper cells will provide factors which on their turn activate killer cells which will attack and kill the cells. Again clearance of the foreign molecules has taken place, but now with cell death (10). A good example in case is given in Table 2.

TABLE 2. The alloantigen recognised by CBA ($H\text{-}2^k$) derived. HSV-specific CTL's is $H\text{-}2D^d$

Target cells derived from					Percent specific lysis	
Mouse strain	H-2					
	K	I	D		50:1	10:1*
				HSV-infected	28	13
CBA**	k	k	k			
				noninfected	1	0
BALB/c**	d	d	d	noninfected	21	9
C3H.OH°	d	d	k	noninfected	1	-1
A/J**	k	k/d	d	noninfected	20	7
A.TL°	s	k	d	noninfected	12	6
A.TH**	s	s	d	noninfected	22	8
S.JL**	s	s	s	noninfected	0	0

* Effector: target cell ratio
** Macrophage target cells
° LPS-induced lymphoblast target cells

(Pfizenmaier et al. 1980)

Herpes simplex virus infected cells are killed by autologous cytotoxic lymphocytes (11). The experiment makes also another important point: the combination of autologous H-2 (the equivalent of HLA in the mouse) with herpes simplex virus resembles an H-2 alloantigen ($H\text{-}2D^d$). In other words, self-x (the virus) equals allo. This explains why so many T cells have receptors which can interact with alloantigens. It is clear from the above that also class I antigens play a role in the immune response and are thus Ir genes. Because there is specificity versus the foreign molecules (e.g. B15 "recognises" penicillin, but B14 does not), we will refer to these Ir genes as being antigen-specific.

However, it should not be forgotten that also non-specific Ir genes in the HLA region have been identified. These govern the efficacy of the Fc receptors, the

number of T-gamma lymphocytes and through them the immune response in general, independent of the structure of the antigen (12).

In some cases it can be difficult to decide whether one is confronted with a specific or non-specific Ir gene. For instance, HLA-DRw6 positive individuals are high responders in the sense that they reject mismatched renal allografts rapidly. On the other hand, HLA-DRw6 negative renal allograft recipients are low responders in this respect (Fig. 3a-b) (13).The unanswered question is whether this should be considered a specific Ir gene effect (the HLA alloantigens) or an aspecific Ir gene effect.

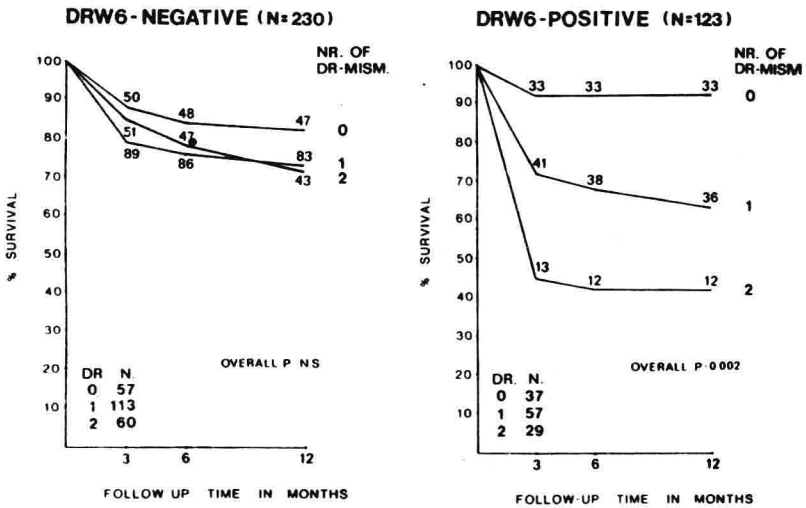

Figure 3a. Actuarial survival curve of 230 first renal allografts in DRw6 negative recipients in relation to number of HLA-DR mismatches. b. Actuarial survival curve of 123 first renal allografts in DRw6 positive recipients in relation to the number of HLA-DR mismatches (Hendriks et al. 1982)

The enormous complexity of the HLA system has not only made the unraveling of its genetics difficult but begs also the question whether it has a function in itself. This seems likely for the following reasons. In the mouse susceptibility to Gross leukemia virus is dependent on the H-2 type: H-2k are susceptible while

H-2b are resistant (Fig. 4) (14). In schistosomiasis infections the reverse is true. The conclusion is clear: a certain constellation of H-2 (or HLA) genes predisposes for infection A but protects for infection B and vice versa.

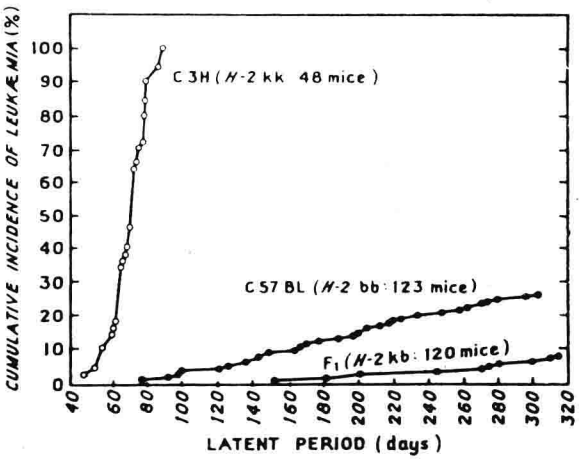

Figure 4. C3H (H-2K), C57 BL (H-2b) mice and their F-1's were infected with Gross leukaemia virus. Backcross studies proved that the high susceptibility of the C3H mouse was recessive and linked to the H-2k haplotype (Lilly et al. 1964)

That this applies also to the situation in man is suggested by the following "experiment of history". In the middle of the 19th century a large group of Dutch farmers emigrated to Suriname in South America. Shortly after their arrival they were decimated by epidemics of typhoid and yellow fever. The descendants of the survivors of these epidemics were typed for HLA and a large number of independent genetic systems (Fig. 5). It was found that the antigens HLA-Aw30, Bw38, Bw50 were more frequent in the descendants than in the present day population in The Netherlands. For HLA-B7 the reverse was true. In other words, HLA-B7 might predispose for a lethal course of a typhoid or yellow fever infection while the genes coded for the other antigens might be protective (15).

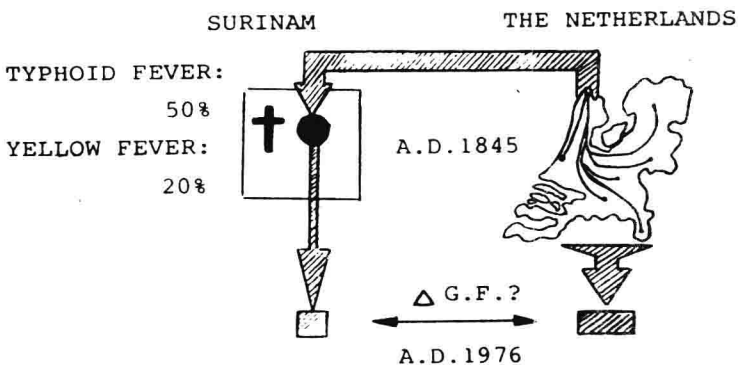

Figure 5. Protocol of our study on the effect of typhoid and yellow fever epidemics on the genetic make-up of Dutch settlers in Surinam (South-America) (De Vries and Van Rood 1982)

A similar situation might operate for HLA-DR2: it predisposes for multiple sclerosis but protects against juvenile onset diabetes (16-17). One could conclude from these observations that the polymorphism of the HLA system between individuals can be compared to the large variability of immuno- globulin idiotypes in a single individual. In both instances it serves a surveillance mechanism that is able to cope in the most effective manner with epidemics which either endanger the species (the polymorphism of the HLA system) or the individual (the large number of idiotypes).

Finally, the importance of the HLA system in the clinical situation should be mentioned. For diagnosis the HLA system is only of (limited) importance in ankylosing spondylitis, HLA-B27 being the predisposing gene. The situation is different if family members of patients suffering from HLA linked diseases seek medical advice. Table 3 indicates that siblings sharing two haplotypes with patients suffering from 21-dehydrogenase deficiency or haemochromatosis will virtually always become afflicted as well. (18,19). In ankylosing spondylitis and juvenile onset diabetes the situation is reversed