

Studies in Histocompatibility

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The major histocompatibility complex (MHC) is a group of closely linked loci present in remarkably similar form in all mammals and perhaps in all vertebrates. It plays a still imperfectly understood but clearly important role in immune phenomena. Because of the unusual concentration of similar genes, I referred to it in 1968 as a supergene (1). Bodmer (2) has gone me one better, calling it a super supergene. The term is not inappropriate because we now know that the MHC contains at least four gene clusters, each with its own type of end product and its own specific effects on the immune response.

The MHC was originally discovered because of its role in the rejection of transplants made between incompatible individuals. Genes competent to play this role in the appropriate experimental or surgical context are called histocompatibility or H genes. An influence on transplants probably is entirely irrelevant to the true function of such genes, but the influence does give the geneticist a handle by which to study them. It was by this route that, over a period of a good many years, I became involved first in immunogenetics and then in the new and fascinating area of cellular immunity.

Early Studies of the Major Histocompatibility Complex

That susceptibility and resistance to transplants is influenced by multiple genes showing Mendelian inheritance was demonstrated in the pioneering studies of Little and co-workers (3-5). Little became interested in this subject as a graduate student at Harvard because of experiments with tumor transplants in mice carried out by Tyzzer at the Harvard Medical School. Little (3) suggested a Mendelian interpretation of Tyzzer's data and worked jointly with him in experiments to test this hypothesis. After he founded the Jackson Laboratory, he and his associates returned again to an investigation of transplant genetics. While these studies revealed the existence of multiple histocompatibility

genes, they did not provide any means of identifying the individual loci. Any individuality was masked by the nondiscriminatory nature of a test based on only one variable—the success of transplant growth.

Methods of Locus Identification

Were there any methods by which the individuality of these genes could be revealed? A project in radiation genetics that I had pursued during my first few years at the Jackson Laboratory was winding down in the late 1930's, and in examining histocompatibility genetics as one of several potential new undertakings, I thought I saw possibilities for new openings. Two methods of locus identification appeared possible. The first was the use of visible marker genes to tag chromosome segments carrying a single or, at most, a few H genes. The second was the transfer, by appropriate crosses, of an H-bearing chromosome segment from one strain onto the inbred background of another. The result would be a new strain, appropriately referred to as congenic resistant or CR relative to its inbred partner. Arthur Cloudman, at the Jackson Laboratory, was at the time carrying a number of transplantable tumors, and he generously made these available for typing purposes. These plans were formulated in 1944, though not published until considerably later (6).

The linkage method promised faster results than the CR strain method and was the first undertaken. Starting in 1945, extensive crosses were set up involving a total of 18 marker genes (6, 7). These markers were assembled in six stocks which I had either produced or acquired (6). This grouping substantially simplified the testing process. One of the first crosses set up, utilizing the three dominant marker genes *Ca*, *Fu*, and *W*, revealed a linkage between a histocompatibility gene and *Fu* or fused tail.

Shortly after this linkage was established, Peter Gorer of Guy's Hospital, London, came to spend a year at the Jackson Laboratory. Gorer had previ-

ously identified a blood group locus in mice and shown that blood type segregated with susceptibility and resistance to a transplantable tumor (8). This was the first case of individual identification of a histocompatibility locus. During Gorer's stay in Bar Harbor, he tested our backcross animals segregating for the *Fu* gene and transplant resistance and found that his blood group antigen also segregated with *Fu* (Fig. 1). His locus and mine were one and the same. Because Gorer was using an antiserum reactive with what he had called antigen II, the locus was called H-2. The existence of three alleles was indicated by the serological data (9).

Marker genes, in appropriate circumstances, can be powerful genetic tools. By using the linkage of *Fu* and H-2, it was possible to show whether a previously untested inbred strain carried a previously known or a new H-2 allele. With this method, the number of known alleles was raised to seven (10).

One by-product of the linkage study was the finding that the first filial (F_1) generation from any cross giving an $H-2^d/H-2^k$ heterozygote was susceptible to tumors from $H-2^a/H-2^a$ donors (11). Some sort of complementation was taking place. This suggested that the $H-2^a$ genotype carried two "components" present separately in $H-2^d$ and $H-2^k$. In recognition of this, $H-2^a$ at the time was called $H-2^{dk}$ (11). The suggestion that there were actually two H-2 loci was not made at the time, but evidence was soon forthcoming that this indeed was the case.

In independent studies, crossing over was shown to occur within H-2. Amos *et al.* (12) used red cell typing and Allen (13) used the linked marker method with tumor transplants as a typing tool. Each study yielded one intra-H-2 recombinant. Additional recombinants were soon added, including seven in a study at the Jackson Laboratory (14, 15). A recent review (16) lists a total of 90 recombinants identified by 1980.

The occurrence of crossing over proved that there are no less than two loci within H-2. The symbols assigned

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were H-2K and H-2D (sometimes abbreviated K and D). The loci are listed in this order because H-2K is proximal to the centromere. The crossover percentage between K and D has varied in different studies, influenced certainly by the sex of the heterozygous parent and perhaps other factors, but is usually given as 0.5 percent or less.

The newly found complexity required a change of nomenclature. What had been called an H-2 allele was actually a linked pair or cluster of alleles. Because the linkage was close, the alleles tended to be inherited as a unit, and a name for this unit was necessary. This problem ultimately was solved by borrowing the term "haplotype" from the HLA terminology (Fig. 2).

The second method for the identification of H loci, the production of CR lines, was by its nature a much longer project than the linkage study. The series of crosses initially used is shown in Fig. 3. An absolute minimum of 14 generations was necessary. The crosses were first set up in 1946 about the time that Gorer came to Bar Harbor. This group was lost in the Bar Harbor fire of 1947 but replaced with new crosses in 1948. In 1953, an entirely new group was set up with some refinements in method (17). All told, the first set of crosses led to the establishment of 32 CR lines, the second to 22.

Once a CR line was established, all that was known about it was that it carried a gene (or possibly a group of closely linked genes) that made it resist transplants from its inbred partner strain. Some method was still necessary to tell whether the introduced locus was the same as or different from the introduced locus of any other CR strain. Two methods were available. The first required a substantial element of luck. If a visible marker gene happened to be present on the introduced segment, and if this marker had been placed on the linkage map, the accompanying H gene was thereby given an individual identity. The second was a complementation test, involving a cross between a known and an unknown. This was more laborious and in some ways less informative, but it was much more widely applicable (18).

By good luck, three of the congenic strains developed in the first set of crosses carried introduced visible markers. Tests confirmed that these were linked with the introduced H gene. The three strains are shown in Fig. 4. The marker introduced into the first strain in the figure was albinism in chromosome 1. The accompanying histocompatibility lo-

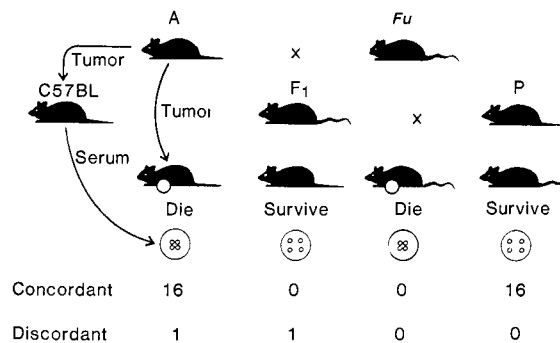


Fig. 1. Association of normal tail, tumor susceptibility, and the H-2 antigen of strain A as indicated by red cell agglutination, in the cross $(A \times Fu) \times P$. A and P are inbred strains, and Fu is a strain carrying the dominant marker gene Fu which produces kinks in the tail. Death from the strain A tumor and agglutination of red cells with the C57BL antiserum to A are tests for the H-2 allele of strain A, whereas survival and nonagglutination are tests for the allele from strain Fu. Both tests were concordant for all except two of the 34 tested backcross mice. The two discordant mice are listed according to their blood type, presumably the more reliable indicator for H-2. The discordant mouse showing nonagglutination but dying from the tumor was a probable recombinant. All other 33 mice were nonrecombinants. [From Snell (9), courtesy of the *Journal of the National Cancer Institute*]

cus was called H-1. The marker in the second strain was Fu or fused in chromosome 17. This suggested that the accompanying locus was H-2, and this was confirmed by appropriate tests. Strain three was marked by agouti on chromosome 5. The accompanying H locus was called H-3.

Application of the complementation test ultimately led to the identification of eight more loci. In two cases, the loci were in loosely linked pairs that had to be separated by crossing over. Subsequent studies by other investigators have raised the number of known non-H-2 loci to at least 50 (19). By far the largest contribution has been made by Bailey (20) through the use of an extensive group of congenic lines started at the University of California and completed and tested in Bar Harbor. Bailey used skin grafts instead of tumor transplants, and a variety of other refinements.

As the CR lines became available and

new histocompatibility loci were identified, certain properties of the loci became apparent. A test of the survival of skin grafts made across H-1, H-2, and H-3 barriers showed that an H-2 difference caused a much more rapid rejection than differences at the other loci. H-2 seemed to be a particularly "strong" locus (21). This result has been confirmed and extended in many subsequent studies (22, 23). Some representative data are shown in Table 1. The uniqueness of H-2 became further apparent as the analysis of the first group of CR lines neared completion. Of the 32 completed and tested lines in this group, 26 differed from their inbred partner at H-2 (7, 24).

Besides the first two groups of congenic lines, two other groups of lines of a more specialized nature were produced in collaboration with Ralph Graff and Marianna Cherry. All told, 206 lines were started and 92 carried through to completion and tested. Sixty-one of

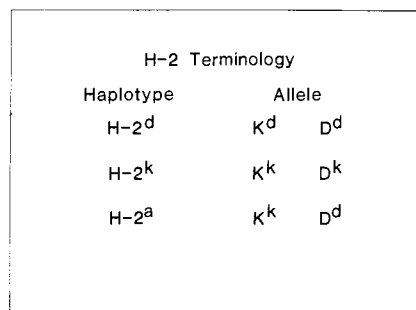
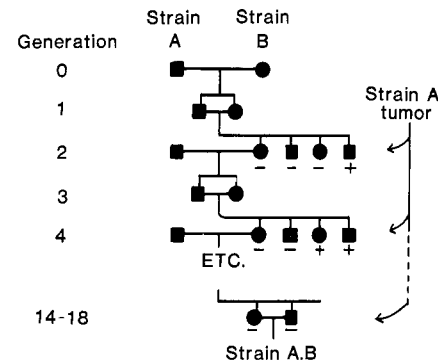


Fig. 2 (left). The relations between the terms "haplotype" and "allele" and their symbols.

The H-2 allelic symbols may be written either H-2K^d or, where appropriate, abbreviated to K^d. Fig. 3 (right). The cross-intercross system for the production of congenic-resistant (CR) strains. Mice of every even numbered generation are challenged with a tumor from A, a highly inbred strain, and a survivor (indicated by a -) mated back to strain A. Each mating to strain A increases the proportion of strain A and reduces the proportion of strain B genes. However, the tumor challenge ensures that the mouse selected for mating is homozygous for a histocompatibility gene inherited from B and foreign to A. At generation 14 or later, two resistant mice are mated, giving the CR strain A.B. [From Snell (17), courtesy of the *Journal of the National Cancer Institute*]



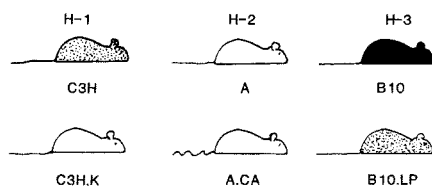


Fig. 4. The identification of histocompatibility loci through the introduction into CR lines of chromosome segments bearing marker genes producing visible effects as well as histocompatibility genes. [Snell *et al.* (18), courtesy of Academic Press]

these are still maintained. In addition, Jack Stimpfling, when at the Jackson Laboratory, produced seven widely used H-2 lines (15) and Bailey 25 non-H-2 lines (20). Many lines have been produced in other laboratories (25).

I shall mention later some of the uses to which the CR strains have been and are being put. It is sufficient to note here that in a 1-year period ending in 1980, 87,000 of the ten most widely used congenic strains and 31,000 of their three inbred partner strains (C57BL/10Sn, A/WySn, and C3H/DiSn) were supplied by the Jackson Laboratory to other laboratories. This includes mice of four strains developed by Stimpfling. The number of congenic mice sent out has increased every year.

Serological Studies of H-2

While the linkage testing and production and analysis of CR lines were going on at the Jackson Laboratory, there was also a growing use by Gorer and his students of the serological approach. While this was limited to H-2, it was a powerful tool for the study of this complex. Two basic methods were used, red cell agglutination (26) and the cytotoxic action of isoantibody plus complement on lymphocytes (27). As time went on, more and more researchers entered this field, and the methods were refined and diversified (18, 28).

One of the first uses to which the CR lines were put was in the production of antisera which, because donor and recipient differed only at H-2, could contain only H-2 antibodies. Hoecker, a student of Gorer's, spent a year at the Jackson Laboratory developing and applying these simplified antisera (29). This study by Hoecker and co-workers will serve to illustrate some of the serological findings.

As in the case with virtually all aspects of H-2, the antisera revealed an extraordinary complexity. The antisera, even if made in CR lines, could usually

be simplified by absorption *in vivo* with mice of appropriate H-2 type. Each antiserum so prepared showed a characteristic strain distribution in its reactions. Table 2 presents the reaction patterns known at the time of Hoecker's 1954 paper. Each reaction pattern defined a "specificity" to which a number could be assigned. It will be seen that four specificities in Table 2—2, 16, 17, and 19—are confined to a single haplotype. These are "private specificities." The specificities with a wider distribution are referred to as "public," though with the qualification that a private specificity may appear in two haplotypes if one is derived by recombination from the other. H-2.4 (Table 2) is a case in point. The number of identified H-2 specificities has grown steadily since these observations and now stands at 113 (16).

Along with the growth in known specificities there has been a growth in known haplotypes and alleles. Thirty-seven haplotypes have been described in inbred strains and 34 more have been added in extensive analyses by Klein of mice caught in the wild (16, 30). Klein estimates that there are not less than 200 alleles at the K locus and a similar number at D. This extraordinary polymorphism is further emphasized by a high mutation rate at H-2 revealed in studies by Bailey, Egorov, and Kohn and their co-workers [(31, 32); see also reviews in (18, 33)]. Curiously, there seems to be much less MHC polymorphism in the rat and hamster (19).

Serological methods were used in all the H-2 recombination studies except that of Allen. The crossovers that were found made it possible to assign specificities to particular regions or loci. Thus, specificity 11 was identified with the K region and specificity 2 with the D region of H-2. As data accumulated, it appeared to be necessary to postulate additional loci or regions, and the number ultimately grew to five (12, 34). However, problems began to appear with this interpretation of H-2 structure. These centered around the discovery that there are specificities that map at both ends of H-2 (34–36). It finally became clear that return to a two locus model of H-2 would resolve the problems and provide an interpretation entirely consistent with the facts (37).

Prior to the onset of this debate, Démant, Cherry, and I had turned to serotyping, using the quantitatively precise chromium label method of lymphocyte cytotoxicity as well as red cell typing. One of the findings from these studies was that the private H-2 specificities can be arranged in two mutually exclusive

Table 1. Differences in "strength" of histocompatibility loci. Data from Graff *et al.* (22).

Locus	Median survival time of skin grafts (days)	
	♀ → ♀ B10 donor	♀ → ♂ B10 recipient
H-2	12	12
H-1	25	NR*
H-4	120	25
H-11	78	164

*NR, no rejections.

series, one mapping at the K and one at the D end of H-2 (Table 3) (38). The existence of two allelic series had already been established for the human lymphocyte antigens (HLA) (39). This is one of the few cases in which mouse studies of the MHC lagged behind those of other species.

One of the most interesting results of the serological studies of Démant, Cherry, and myself was the finding of a third but unique series of allelic specificities determined by the H-2 complex. Whereas the original K and D series were composed of clearly distinct private specificities, the new series was composed of two families of related specificities, the 1 family and the 28 family (40–42). Members of each family showed similar but not identical strain distributions. In the original studies, it was not suggested that the new series identified a new locus, but Démant and co-workers, in further investigations, found that this was indeed the case (43, 44). The new locus, called H-2L, is close to and so far has not been separated by crossing over the H-2D. The existence of H-2L has been confirmed in numerous tests. One of the most interesting confirmations was the discovery of a mutant of H-2^d in which H-2L is lost but H-2D remains (45). Specificities 27, 28, 29, all members of the 28 family characteristic of the D end of H-2^d (41, 46), are all lost in the mutant. There remain several puzzling aspects of the 1 and 28 families—for example, some form of 1 or 28 has been found on the K and D as well as the L molecules—but this does not invalidate the evidence for a separate H-2L product.

Démant (47) has recently identified two additional H-2 products, one determined by a locus close to K, the other by a locus, in addition to L, close to D.

Studies of the murine H-2K, D, and L loci played a seminal role in the growth of our conception of the major histocompatibility complex, but the conception in its current form is the result of an explosion of information that followed the

initial discoveries of Dausset and Benacerraf. Dausset's recognition that HLA is similar to H-2 (48) was the first hint that a gene or genes with especially strong histocompatibility effect may be common to all mammals. H-2-like complexes have now been identified in at least eight other mammals and in poultry (49). The demonstration by Benacerraf and co-workers (50) of an association in guinea pigs between a major histocompatibility locus and immune capability and by McDevitt and co-workers (51) of a similar association in mice, and the further demonstration that the murine immune response genes were in a distinct (I) region (52), was the beginning of our conception of the true complexity of this remarkable system. The expression "major histocompatibility complex" became fully justified.

This is not the place for anything approaching a full description of the complex, but a brief summary is necessary. Some of the essential facts are set forth in Fig. 5. The complex consists of five main regions, K, I, S, D, and *Tla* (or *Qa*), producing four classes of antigens, class I associated with the K and D regions, class II associated with the I region, class III associated with the S region, and class IV associated with the *Tla* region. Present evidence points to a total of 22 loci, but this number is likely to grow. The principal bases of the classification are the tissue distribution and the chemical properties of the end products. Information is much more complete concerning some products than others, and some changes in the classification may be necessary, but the general outline seems likely to stand. The tissue distribution is summarized in Fig. 5. The chemical properties of the class I and the class IV products seem to be similar [for a review, see (53)], but the two classes are clearly differentiated by the wide distribution of the K, D, L antigens and the restriction to lymphocytes of *Tla* and its relatives. With this exception, each class shows distinct chemical characteristics. The growing evidence that all the products play fundamental roles in the immune response is a common bond that unites them and justifies the conception of all 22 loci as part of a complex or system.

Immunological Influences of MHC

A major reason for the current interest in the MHC is the extraordinary range of processes, both immunological and non-immunological, on which it has an influence (18, 54). Ivanyi (54) lists 35 quanti-

The T and H-2 complexes				
Map distance	Region	Class of loci	No. of loci	Tissue distribution
17	T		6?	Early embryo
0.2	K	I	2	Most or all cells except early embryo
	I	II	8	Each antigen on specific classes of lymphocytes and macrophages or macrophage-related cells
0.3	S	III	2	Serum
1.5	D	I	3	Same as K
	<i>Tla</i>	IV	6	Specific lymphocyte classes

Fig. 5. A summary of the genetics of the T and H-2 complexes and the tissue distribution of the antigens that they determine. The principal sources of data on the genetics are map distance (16, 18), T complex (95, 96), K and D region loci (18, 47, 97), I region loci (98, 99), S region loci (98, 100), and *Tla* region loci (101, 102). The principal sources of information on the tissue distribution are T complex products (72, 103, 104), K and D region products (18), I region products (98, 105-107), S region products (98, 100), and *Tla* region products (101, 102).

tative traits affected by it. Particularly important from the medical point of view is its influence on immune processes. I cannot begin to cover this subject thoroughly. The few examples I select reflect my judgment of importance or interest or some degree of personal involvement. I start with immunological areas and move to those apparently without immunological connection.

The first reports suggesting a possible role for H-2 in immune processes concerned the phenomenon of hybrid resistance. I came across this phenomenon in the course of producing and analyzing the first two groups of congenic resistant lines (17, 55). The phenomenon consists

of a resistance of F_1 hybrids to tumors indigenous to the parental strains, a resistance which, according to the accepted laws of transplantation, should not occur. It was noted that major resistance required heterozygosity at H-2, but that non-H-2 heterozygosity could have some effect. The major role of H-2 with, however, a minor role for one or more non-H-2 loci, was established in much greater detail by Cudkowicz and co-workers, using marrow transplants, and the added observation was made that the D end of H-2 was the active region (56, 57). A recent study in vitro suggests a possible role for natural killer cells in the phenomenon (58), but this may not be

Table 2. A chart of H-2 specificities based on 1954 data of Hoecker *et al.* (29). Minus signs indicate a negative reaction.

H-2 haplotype	2	3	4	5	11	16	17	19
a	-	3	4	5	11	-	-	-
b	2	-	-	5	-	-	-	-
d	-	3	4	-	-	-	-	-
k	-	3	-	5	11	-	-	-
p	-	3	-	5	-	16	-	-
q	-	3	-	5	-	-	17	-
s	-	3	-	5	-	-	-	19

Table 3. The initial assignment of most H-2 private specificities to either the K or the D regions. Based on Snell *et al.* (41). In current charts, the K specificity 23 is replaced by 11, and the unlocated private specificities have been located.

Haplotype	Located		Unlocated	
	K specificity	D specificity	Haplotype	Specificity
b	33	2	f	9
j	15	2	p	16
d	31	4	r	18
u	20	4	v	21
k	23	32		
m	23	30		
q	17	30		
qp	17	12		
s	19	12		

Table 4. The H-2 type and percentage of virus-induced leukemia as seen in congenic strains differing at H-2. From Tennant and Snell (65).

Strain	Haplotype	Percentage with leukemia	Significance of difference from	
			B10.D2	B10
BALB/c*	d	100		
B10.D2	d	83		< .001
B10.A	a	73	> .05	< .001
B10.BR	k	62	< .05	< .01
B10	b	39	< .001	
A	a	100		
A.BY	b	75		

*Strain of origin of inducing virus.

the only mechanism of hybrid killing (59).

Another group of early studies suggesting a role for H-2 in immune processes concerned viral leukemogenesis. In 1954–1956, Gross reported that cell-free filtrates from AKR or C58 leukemias caused early leukemia development when injected into newborn C3H/BI or C57BR/cd mice (60, 61). All these mice are H-2^k, a fact probably noticed by most or all of the H-2 students of that time. Could H-2 be involved? Lilly *et al.* (62) answered this question in the affirmative by inoculating leukemic extracts into H-2-typed mice from segregating generations.

In a study started independently but published somewhat later, Tennant (63) and Tennant and Snell (64, 65), using CR mice and an agent prepared by Tennant from BALB/c (H-2^d) leukemias, showed preferential leukemia induction in other H-2^d mice and also a difference in the degree of resistance engendered by other haplotypes. Table 4 shows some of the results. These data demonstrate very nicely the power of congenic strains. Definitive results could be obtained without the production of segregating generations. The data (including some not in the table) also show that non-H-2 loci play a significant role.

While these results suggested an immunological role for H-2, the real breakthrough came with the demonstration, already mentioned, that the H-2 complex contains immune response (Ir) genes. Since this discovery, an ever expanding effort has gone into the unraveling of the processes involved. I shall mention only two of the major findings.

The H-2 linked Ir genes in the mouse were originally mapped in the I region of the H-2 complex (52), and it was assumed for some years that all such genes were confined to this region. It now appears that this was an oversimplification occasioned by the use of tests in which the active cells were T helper cells. Most of the early studies involved antibody pro-

duction to pauci-determinant antigens, and in this context the T lymphocytes are T_H or helpers. When studies turned to cell-mediated lysis (CML) *in vitro*, new complexities appeared; the K and D antigens as well as I region products seemed to be influencing the response [(66, 67); for a review, see (53)]. Further studies tended to confirm this (68–71). From this and other evidence it appears that I region products regulate helper lymphocyte activity, including Ir activity, whereas K and D region products, including the K and D antigens themselves, play the corresponding role for effector lymphocytes.

Another link between H-2 and immune capability is the phenomena of H-2 restriction. The response of T lymphocytes to antigens other than H-2 requires a simultaneous response to H-2. Apparently the recognition structures of these cells are so constructed that they react not only with a specific antigen on the surface of a foreign or altered cell, but also and simultaneously with an H-2 antigen on that cell. The H-2 antigen typically “seen” by helper cells is apparently an Ia (class II) antigen; the antigen “seen” by effector cells is a K, D, or class I antigen. Whether there are two receptors on the T cell to account for this dual capability, or one receptor with two reactive sites, or a single receptor reacting with a fusion product is still debated, but the phenomenon itself is firmly established [reviews in (18, 72)]. A corollary of H-2 restriction is that T cells, when confronted with any of a number of cultured cell lines that have no H-2 products on their surface, not only are barred from reacting with H-2 but also with any non-H-2 products on the cell surface (73–75).

A curious and, from the point of view of basic mechanisms, certainly important exception to the phenomenon of H-2 restriction is the reaction of T cells with the products of H-2 itself. Cell-mediated attack against an I region target, for example, does not require concomitant

recognition of a K or D target on the same target cell (76). Similar results have been reported with *Qa* (class IV) antigens (77, 78).

Nonimmunological Manifestations of H-2

The H-2 complex, or a gene closely linked with it, can influence mating preference in mice. This was demonstrated by Boyse and co-workers using congenic strains, one carrying H-2^b, the other H-2^k. If males of one genotype were presented with estrous females of both genotypes, a statistically significant proportion of the males preferred females of the opposite type (79). The active agent maps at the right (D-*Tla*) end of H-2 (80, 81). This surprising finding presumably reflects an ability of mice to smell an H-2 product or products.

Another manifestation of H-2 demonstrated with congenic strains is the degree of susceptibility to cortisone-induced cleft palate. When B10.A (H-2^a) and B10 (H-2^b) pregnant females were treated with cortisone, the incidence of cleft palate in the offspring were 81 and 21 percent, respectively (82). Strain A mice with the H-2^a genotype that favors cortisone-induced cleft palate also show a relatively high spontaneous rate of the defect.

It is interesting that Reed and Snell in 1931, using crosses with the A strain as one parent, found evidence for one locus with a major role in determining cleft palate susceptibility (83). Could this have been the first identification of H-2?

The two nonimmunological manifestations of H-2 which I have described seem largely irrelevant to any basic function of this complex. Are there any nonimmunological manifestations that do suggest a basic function? The answer is yes. There is a growing body of experimental data that suggests a role for H-2 in cell interactions.

I cannot begin to summarize the literature here. Reviews will be found in Snell (72) and Dausset and Contu (84). Perhaps the best clue as to a possible role of the MHC in cell interactions comes from some recent studies by Curtis and co-workers (85, 86).

In one experiment (85), mouse kidney tubule epithelium was grown in cultures so designed that there would be confrontation between outgrowths either matched or mismatched at H-2. Contact inhibition, as measured by lack of overlapping growth, was increased in mismatched cultures. In other studies, low molecular weight diffusible glycoproteins were demonstrated which, in a va-

riety of mixed cultures, would reduce adhesion among cells of the type to which they were foreign. The active molecules were called "interaction modulation factors" or IMF's. They were demonstrated in mixtures of cells ranging from those of unrelated sponges to mouse T cells. The important finding in the present context is that T cell IMF's were active in H-2 disparate cultures. The active region of H-2 appeared to be H-2D.

Since the T cell IMF's act only on H-2 disparate cells, they must have a degree of H-2 specificity. It is interesting that McKenzie and co-workers (87, 88) have reported the presence in mouse serum of low molecular weight glycoproteins with Ia specificity. They appear to be of T cell origin. The nature of the interaction between IMF's and the disparate cells whose capacity to adhere they inhibit is obviously a problem of great importance which only future studies can clarify.

I find attractive for a number of reasons the concept that the ancestral function of MHC products is the regulation of cell interactions. It seems to me that the early appearance and wide tissue distribution of the K and D (class I) antigens is difficult to reconcile with a purely immunological role, whereas it is quite in keeping with a developmental one. The association on the cell surface of H-2 and other alloantigens in specific configurations demonstrated by Boyse *et al.* (89) and Flaherty and Zimmerman (90) also seems to me to fit best with this role. Finally, the Ia (class II) antigens seem clearly to be involved in cell interactions, though, in keeping with their presence only or primarily on lymphocytes and macrophages, interactions restricted to these cells. Perhaps the class II genes evolved from the class I genes along with the evolution of the immune system.

A cell interaction role for the MHC has been suggested by a number of authors [for example, see (91-94)]. The major problem in this thesis is its reconciliation with the proven role of apparently all MHC products, including the class I antigens, in immune phenomena. I have proposed a possible route that such an evolution could take (72). The proposal is admittedly speculative; only time and much more research will provide firm answers. Whatever the ultimate conclusion, the fascination of H-2 is unlikely to diminish.

Science is like a web, growing by interactions that reach out in time and space. My own small place in this web was made possible by strands from the past and the help of contemporaries. To them, my deep appreciation. Dr. Clar-

ence Little provided the background for my studies of histocompatibility and, as founder of the Jackson Laboratory, the environment that made them possible. Dr. Peter Gorer was the original discoverer of H-2 and, although my own identification of the complex was independent, our studies, once united, reinforced each other. Dr. Gorer's untimely death was a tragic loss to his many friends and to this field of science. I was aided in the work by many wonderful associates. It is unfair to single out a few but I feel I must note the contributions of Jack Stimpfling, Bill Hildemann, Ralph Graff, Marianna Cherry, Peter Démant, and Ian McKenzie. One of the great satisfactions of the work has been to see it develop in directions I could not possibly have foreseen. In these developments, the contributions of Jean Dausset and Baruj Benacerraf have been outstanding. Finally, on behalf of my family, I thank the members of the Nobel Foundation and Mrs. Ingela Johansson of the Royal Ministry for Foreign Affairs for their kind and helpful hospitality during our visit to Sweden.

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The Agriculture Grants Program

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The Competitive Research Grants Office (CRGO) was established in 1978 to implement a section of the Food and Agriculture Act of 1977 (1). Its purpose is to make grants to support basic research in areas of science that underlie

been directed largely at the more applied aspects of plant science and has been confined mainly to scientists in the state Agricultural Experiment Stations and the federal laboratories operated by the USDA. A substantial number of scien-

Summary. The Competitive Research Grants Office was established in 1978 by the federal government to encourage and support basic research related to agriculture. The effort has been enfeebled by controversy and continues to teeter on the edge of congressional extinction. The origins of the Competitive Research Grants Office and its first 3 years of operation make an interesting portrait of the problems of science and government in these times.

agricultural productivity and human nutrition. The origins of the office are numerous, and its creation by Congress was the result of a convergence of many forces.

Researchers interested in basic aspects of plant biology have often felt like "poor relations" in the scientific community. Support for such research has come from the National Science Foundation (NSF), the National Institutes of Health (NIH), the Department of Energy (DOE), and the Department of Agriculture (USDA). The USDA support has

tists outside the traditional agriculture community received support from the NIH to do research on fundamental aspects of photosynthesis, nitrogen fixation, and other processes which occur in plants, but which are fundamental to the understanding of life and may contribute to understanding processes directly affecting human health. In 1968 a refinement of NIH mission goals led to withdrawal of grant support for most of these projects in plant science. Although the NSF and DOE maintained and even increased their support of plant science research, practitioners in this area felt that their potential for accomplishing important science was sadly limited, especially by comparison to the generous support from the NIH for work on animal and bacterial processes. There was a

sense that great scientific opportunities were within reach as a result of breakthroughs in other areas of biological research.

A more powerful impetus to foster plant science research was to come from the world at large. In the 1970's world grain reserves were drawn down, and world population continued to grow at a frightening rate. Sunday newspapers often described the grim realities of starvation in the Third World and the grimmer prospects of famines to come. At the same time, U.S. food exports were soaring and were identified as a major economic success in world markets. The U.S. grain surpluses were reduced, and it seemed time to focus on ways to improve agricultural productivity and help balance oil imports with food exports.

Finally, it was realized that agricultural productivity, which had grown mightily during the postwar decades, might be leveling off. The great gains in productivity achieved during the Green Revolution had come from traditional techniques of plant breeding, from high energy inputs in the mechanization of farm practices, and from high chemical inputs in the use of fertilizers, pesticides, and plant growth regulators. There was concern that too little new knowledge was being generated which could provide for future gains. The economic and environmental costs of the energy and chemical inputs were rising astronomically. New, fundamental knowledge about plants seemed to be needed to help solve these practical problems.

In the middle 1970's, a conference at Boyne Highlands, Michigan, sponsored by the Michigan State University Agricultural Experiment Station and the Charles F. Kettering Foundation, signaled that some important steps had been taken (2). The combination of sponsors of this conference showed a new alliance of a traditional USDA- and

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