Histocompatibility-Linked Immune Response Genes

A new class of genes that controls the formation of specific immune responses has been identified.

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The most sophisticated defense mechnism to find expression in vertebrate organisms is the immune response: that is, the capacity, after foreign macromolecules or allogeneic cells are introduced, to produce specifically sensitized lymphocytes and to synthesize and secrete specific antibodies capable of reacting with these foreign substances (antigens). This function is extremely versatile, and yet it is characterized by great specificity as shown by (i) the considerable discriminatory power of the immune mechanism, (ii) the extremely wide range of antigenic determinants against which antibodies are synthesized, and (iii) the remarkable heterogeneity of antibody molecules, both as to class and affinity, produced against a single determinant.

The genetic control of such varied responses must be very complex, involving many structural and regulatory genes, even if only the genes concerned with the structure and synthesis of specific immunoglobulins are considered. The use of allotype markers has permitted the identification of structural genes for the constant (C) regions of the various immunoglobulin chains in man and several animal species. These genes constitute identifiable linkage groups (*1*). It is also becoming increasingly clear, primarily as a result of evidence derived from the study of allotype markers on the variable (V) region of rabbit immunoglobulin heavy (H) chains, that there are distinct V genes coding for this region, and that these are linked with C genes, and that together they control the sequence of immunoglobulin heavy chains (*2*). However, the number of such V genes is not known, nor have accurate estimates been made (*3*). Nor is there agreement on the issue of whether somatic mechanisms are, in some measure, responsible for the generation of diversity in V genes (*4*).

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Identification of Specific Immune Response Genes

In spite of the complexity of immune phenomena and of the numerous specificities against which specific responses can be formed, and therefore contrary to expectation, the ability to form specific immune responses has been shown to be under genetic control. Several autosomal dominant genes, each concerned with the ability to form specific immune responses to distinct antigens, have been identified (*5*). An animal possessing such a gene can form a vigorous immune response against the corresponding antigen, a response characterized both by cellular immunity and sustained antibody synthesis. Animals lacking the gene do not display cellular immunity and are either totally or partially deficient in their antibody response to the antigen.

The discovery of specific immune response genes has depended on experiments in which the immunological system is presented with a challenge of highly restricted heterogeneity and specificity. Three types of antigens have been used: (i) synthetic polypeptides with limited numbers of different L-amino acids, and their hapten conjugates, to present the immunological mechanism with molecules of limited structural diversity; (ii) weak native antigens—that is, molecules that differ but slightly from the corresponding host proteins, and (iii) strong native protein antigens, injected, however, in limiting doses—that is, in a dose range that is immunogenic for only some individuals or certain inbred strains in a given species. This device limits the possibilities of specific interaction between the antigen and cells of the immune system, so that presumably only the thermodynamically most efficient pathway is functional.

These three methods have permitted the identification, within a relatively short time, of many distinct specific immune response genes in the two species most intensively investigated, guinea pigs and mice. They have, in addition, allowed some conclusions to be drawn concerning the relationships of these genes among themselves and with genes controlling major histocompatibility specificities. Attempts have also been made to ascertain the cell type in which these genes are expressed and the possible function which they subserve. The specific immune response genes identified up to now by the various techniques are listed in Table 1.

1) We shall first consider specific immune response genes controlling reponsiveness to synthetic polypeptide antigens. In guinea pigs there are two inbred strains, 2 and 13—developed by Sewall Wright from a small closed colony (*6*)—as well as random-bred lines, that have been used to study the genetic control of specific immune responsiveness. The PLL (*7*) gene was the first specific immune response gene identified (*8*). It controls responsiveness to poly-L-lysine (PLL), to poly-L-arginine (PLA), to copolymers of L-glutamic acid and L-lysine (GL) and to hapten conjugates of these polypeptides such as dinitrophenyl (DNP)-PLL. The PLL gene is found in all guinea pigs of strain 2 and is lacking in animals of strain 13. Another gene designated as the "GA gene" and identified in all strain-2 guinea pigs controls responsiveness to the linear random copolymer of L-glutamic acid and L-alanine ($Glu_{60}Ala_{40}$). Like the PLL gene, the GA gene is not found in strain-13 guinea pigs (*9*). A third gene, the GT gene, has also been identified in inbred guinea pigs. It is concerned with responsiveness to a linear random copolymer of L-glutamic acid and L-tyrosine ($Glu_{50}Tyr_{50}$). This trait is a property of strain-13 guinea pigs and is not found in strain-2 guinea pigs, in con-

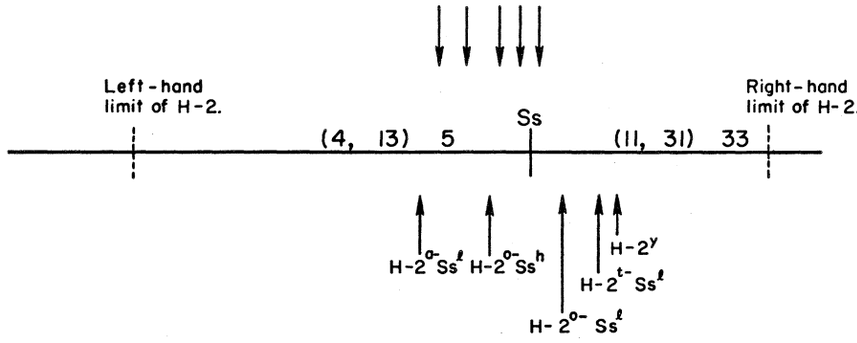

Fig. 1. Diagram of the organization of the H-2 locus, with arrows indicating the approximate position of crossovers resulting in recombinant H-2 alleles. The top arrows indicate a set of five reciprocal crossovers between H-2^a and H-2^b to give rise to H-2^h and H-2^i recombinant alleles. All five of these recombinant alleles localize Ir-1 to the right of the crossover event. The three bottom arrows indicate a set of three reciprocal crossovers between H-2^d and H-2^k, giving rise to H-2^a-Ss^l, H-2^o-Ss^l, and H-2^o-Ss^h. Once again, Ir-1 is located to the right of these crossovers. H-2^t-Ss^l was derived from a crossover between H-2^a-Ss^l and H-2^s, and Ir-1 is located to the left of this crossover. H-2^y is derived from a crossover between H-2^a and H-2^q, and in this crossover event there was an outside marker (brachyury, T) which established that the crossover was a single crossover event. Ir-1 was also localized to the left of this crossover. Since Ir-1 is to the left of the last two crossovers, and the crossovers are known to be to the right of the serum substance (Ss) locus, these results definitely localize Ir-1 between the Ss locus and the K region H-2 antigenic specificities.

trast with the distribution of the GA and PLL genes (*9*).

The immune response of guinea pigs to the antigens, the recognition of which is under the control of the PLL, GA, and GT genes, is characterized by cellular immunity and the synthesis of significant levels of specific antibody. Animals lacking the genes never develop cellular immunity and do not produce significant levels of antibodies under usual conditions of immunization. The activity of these immune response genes is therefore responsible for clear-cut qualitative differences between responder and nonresponder animals, particularly as concerns cellular immunity and carrier function.

A signal experimental advantage that the genetic systems discovered in guinea pigs have over the ones identified in mice is the fact that the same genes detected in inbred strains are also found in a significant proportion of random-bred Hartley guinea pigs (*8*, *9*). The genes controlling immune responsiveness to GA, GT, and PLL are not inherited independently. As would be expected, the GA gene and the PLL gene are linked in strain-2 guinea pigs. Responsiveness to GA and PLL are also linked in most Hartley responder guinea pigs. However, there is a small proportion of Hartley guinea pigs that respond to GA but not to PLL or that respond to PLL but not to GA. The very existence of these animals that may result from a crossover between the PLL gene and the GA gene may be considered as evidence for the nonidentity of these two genes. The ability of random-bred Hartley animals to respond to GT is also not independent of the PLL or GA responder status. But in this case, responsiveness to GT tends to segregate away from PLL and GA responsiveness, an indication of allelism or pseudoallelism between the GT gene on the one part and the PLL and GA genes on the other in random-bred animals.

Homopolymers and linear copolymers of two amino acids are not immunogenic for mice (*10*). The most thoroughly studied immunogenic polypeptides in mice are a set of branched multichain synthetic copolymers with a restricted range of amino acids: L-glutamic acid with L-tyrosine, or with either L-histidine or L-phenylalanine (Phe) on a backbone of L-lysine (L) and D,L-alanine (A) side chains. These are (T,G)-A--L, (H,G)-A--L, (Phe,G)-A--L (*7*). The ability of inbred mice to make antibodies in response to each of these antigens is a *quantitative* genetic trait controlled by autosomal dominant genes at a locus designated Ir-1 (*11*).

These polypeptides are not immunogenic in random-bred Swiss mice. It is not yet known whether the Ir-1 locus is a single gene with multiple alleles or whether this locus has three closely linked genes, although the available evidence is most compatible with the latter interpretation.

The immunogenicity of two other copolymers has been found to be under dominant unigenic control. A random terpolymer of L-glutamic acid and L-lysine with 5 percent alanine (GLA_5) was shown by Pinchuck and Maurer to be antigenic in 47 percent of random-bred Swiss mice. The pattern of transmission of this trait showed the response to this antigen to be governed by an autosomal dominant gene (*12*). More recently, responsiveness to another terpolymer containing L-glutamic acid, L-alanine, and 10 percent L-tyrosine (GAT_{10}) was found to be also controlled in inbred mouse strains by a dominant gene, distinct from those previously identified at the Ir-1 locus (*13*). In contrast to the quantitative differences in antibody response to the branched copolymers, this gene apparently determines responsiveness to GAT_{10} in an all-or-none fashion.

2) We will now discuss specific immune response genes controlling responsiveness to weak allogeneic antigens. Several dominant Ir genes have been identified in inbred mice controlling respectively: (i) the ability of inbred mouse strains to form antibodies against the Ea-1^a antigen on erythrocytes of wild mice (*14*); (ii) the ability of female recipients in some inbred mouse strains to reject male syngeneic skin grafts and therefore to recognize a histocompatibility antigen controlled by the Y chromosome (*15*); (iii) the ability to form an immune response against the H-2.2 specificity (*16*); (iv) the ability to recognize H-13 specificities (*17*); (v) the capacity to form antibodies against allotypic determinants on immunoglobulin A (IgA) myelomas (*18*); and (vi) the rejection of allogeneic bone marrow by irradiated recipients (*19*).

3) Last we must consider the specific immune response genes controlling responsiveness to limiting doses of strong native antigens. Limiting immunizing doses of strong protein antigens, such as human or bovine serum albumin (BSA) in inbred guinea pigs (*20*) or bovine gamma globulin and hen ovalbumin in inbred mice (*21*), stimulate vigorous antibody responses only in some inbred strains. The low dose responsiveness to BSA, which has been best studied, is a property of strain-2 but not of strain-13 guinea pigs and was demonstrated to be under the control of a dominant autosomal Ir gene, BSA-1, linked to the PLL and GA genes (*20*).

Size of the Specific Immune Response Gene Pool

As will be discussed, most Ir genes described in both guinea pigs and mice are intimately linked with the major histocompatibility locus of the species and may possibly determine histocompatibility specificities. We must consider, therefore, whether the specific Ir genes identified are distinct genes or whether a single gene may control responsiveness to several structurally unrelated antigens that are not cross reactive. The data on the Ir-1 locus in mice and the studies in guinea pigs, where Ir genes are expressed in both inbred and random-bred strains, indicate that immune response genes controlling responsiveness to different polypeptides are distinct. Thus, whereas the PLL and GA genes are linked in strain-2 guinea pigs and are often also linked in random-bred Hartley animals, many random-bred guinea pigs may be found that respond to one and not another of these antigens. The size of the gene pool in a given species should be considered. A relatively large number of specific Ir genes has been identified in a relatively short time. The ease with which they have been discovered and the necessity to use antigens with limited structural diversity or to use limiting immunizing doses to identify individual Ir genes suggest that there are a relatively large number of these genes. Indeed, when uniformly immunogenic larger immunizing doses of more complex antigens are used, several pathways controlled by different Ir genes must operate. On the other hand, the number of specific immune response genes is certainly much smaller than that of antibody specificities or of individual immunoglobulins which may be produced, since responses controlled by an individual Ir gene always result in the synthesis of a highly heterogeneous population of antibodies both as to specificity and affinity (*5*).

Linkage to Genes Controlling Histocompatibility Antigens

A high proportion of specific Ir genes is extremely closely linked with genes controlling histocompatibility antigens in mice and guinea pigs. The Ir-1 locus has indeed been localized in mice within the H-2 region itself. Although the biological significance of this remarkable relation between these two highly polymorphic specificity systems is not understood, such a close association between genes concerned with individual specificities and a class of Ir genes could not be fortuitous. All of these associations have been described in the past 3 years since the original observation of the linkage between the Ir-1 locus and H-2 (*22*); and, while some of them were the result of a chance observation of close association between immune response and histocompatibility type, the majority were discovered by a deliberate search for linkage to histocompatibility antigens.

On the basis of the experience of the past few years, it would seem reasonable to make the additional postulate that not only are dominant, autosomal, specific immune response genes likely to be common phenomena, but that a large proportion of them will be shown to be closely linked with genes controlling histocompatibility antigens, frequently the species' major histocompatibility antigen complex. Some types of genetic control of the immune response, however, do not appear to be associated with genes controlling histocompatibility antigens; for example, the genetic control of the ability to respond to (T,G)-Pro--L (*23*). This system presumably reflects genetic control over some different aspect of the immune response.

Most of the associations between immune response genes and histocompatibility antigens have been detected in inbred strains of mice (*13, 18, 22*) and guinea pigs (*20, 24, 25*). Histocompatibility-linked immune response genes have also been found in random-bred guinea pig populations (*26*), although they have not so far been identified in random-bred domestic mice or in wild-type mice. This is primarily because only a small number of random-bred mice and wild-type mice have been tested for response to antigens known to be under the control of histocompatibility-linked response genes.

During the past 3 years, an extensive series of studies of the immune response of mice bearing known recombinant H-2 alleles to the three branched synthetic polypeptide antigens, (T,G)-A--L, (H,G)-A--L, and (Phe,G)-A--L (*7*), all of which are under the control of the Ir-1 gene or genes, has shown that the Ir-1 locus has been identified in the middle of the H-2 chromosome region, lying just to the right of the serum substance locus and just to the left of the "K" region antigenic specificities in the right-hand part of the H-2 locus. This is shown diagrammatically in Fig.

Table 1. Histocompatibility-linked specific immune response genes.

Antigens	Species	Linkage	Reference
		Guinea pig	
		Strain 2	
PLL	(Probably same gene)	H specificity	(*7, 24*)
PLA	(Probably same gene)	H specificity	(*7, 24*)
GL	(Probably same gene)	H specificity	(*7, 24*)
DNP-PLL	(Probably same gene)	H specificity	(*7, 24*)
		Strain 2	
GA		H specificity	(*25*)
		Strain 13	
GT		H specificity	(*25*)
		Strain 2	
BSA (low dose)	(Probably same gene)	H specificity	(*20*)
DNP-BSA (low dose)	(Probably same gene)	H specificity	(*20*)
HSA (low dose)	(Probably same gene)	H specificity	(*20*)
		Mouse	
(T,G)-A--L		$H\text{-}2^{b,t}$	(*11, 22*)
(H,G)-A--L		$H\text{-}2^{a,k,h}$	(*11, 22*)
(Phe, G)-A--L		$H\text{-}2^{a,b,d,i,k,q}$	(*11, 22*)
GAT_{10}		$H\text{-}2^{a,b,d,k}$	(*13*)
GAL_{10}		$H\text{-}2^{a,b,d,k,s}$	(*47*)
GLA_5		H-2	(*47*)
GLΦ		H-2	(*47*)
(T,G)-Pro--L		Not H-2 linked	(*23*)
Ovomucoid (low dose)		$H\text{-}2^{a,k}$	(*21*)
Ovalbumin (low dose)		$H\text{-}2^{b,d,q}$	(*21*)
Bovine gamma globulin (low dose)		$H\text{-}2^{a,k}$	(*21*)
Trinitrophenyl-hapten		$H\text{-}2^{b}$	(*44*)
Mouse erythrocyte antigen $Ea\text{-}1^{a,b}$		H-3 or H-6	(*14*)
Mouse male (Y) transplantation antigen		$H\text{-}2^{b,t}$	(*15*)
H-2.2 specificity		Not known	(*16*)
Mouse IgA myeloma		H-2	(*18*)
H-13 specificity		$H\text{-}3^{a}$	(*17*)
Autoimmune murine thyroiditis		H-2	(*48*)
		Rat	
Porcine lactate dehydrogenase		Not known	(*45*)
GLT		Not known	(*46*)

1. This localization was achieved by studying the immune response of animals bearing known recombinant H-2 alleles derived from known crossover events between H-2^a and H-2^b or H-2^d and H-2^k, or H-2^a and H-2^s, or H-2^a and H-2^q. The results of these findings were also confirmed by a four-point mapping study which showed that the only identifiable recombinants between the H-2 chromosome region and the Ir-1 gene were actually crossovers within the H-2 locus involving crossovers between the "D" or left-hand and "K" or right-hand parts of the H-2 locus. All of this evidence is thus consistent in localizing the Ir-1 gene or genes in the middle of the H-2 locus in the position described above and shown in Fig. 1 (*27*). These data, however, do not establish or rule out the possibility that Ir-1 may code for distinct histocompatibility specificities.

Identical results were obtained in guinea pigs. The PLL, GA, and BSA-1 genes were shown to be linked to the locus controlling the major histocompatibility specificities of strain-2 guinea pigs (*20, 24, 25*). The GT gene was found to be similarly linked to a major strain-13 histocompatibility specificity (*25*). The closeness of the relationship between guinea pig Ir genes and histocompatibility genotype is illustrated in random-bred guinea pigs by the inability to dissociate the PLL gene from strain 2 specificities in these animals (*26, 28*). Thus among 94 random-bred guinea pigs tested, only those animals with the PLL gene were found to possess histocompatibility specificities detected by isologous antiserums to strain 2. Similar studies are being made in random-bred guinea pigs with the GA and GT genes; but because the knowledge of the major histocompatibility antigens in the guinea pig is still fragmentary, it is not known whether the segregation of ability to respond to PLL and GA represents a situation analogous to the recombinant H-2 alleles in mice. Thus, all of the evidence in both mice and guinea pigs is compatible with the concept that the histocompatibility-linked immune response genes map within the H-2 locus in the mouse and are probably equally closely associated with the major histocompatibility locus in the guinea pig. Precise mapping studies have not yet been carried out for the other histocompatibility-linked immune response genes listed in Table 1, but initial evidence (*15*) indicates that the genetic control of the ability to respond to the male Y transplantation antigen is a function of the right-hand part of the H-2 locus (or to the right of the H-2 locus), and this finding is completely analogous to the earlier findings for the Ir-1 gene or genes.

The existence of genetic controls of specific immune responses to a wide variety of antigens, all of which are linked to genes controlling major histocompatibility antigens, raises the possibility that this genetic control is, in fact, a manifestation of immunologic cross reactivity between histocompatibility antigens and the foreign antigenic determinants under study. For example, an H-2$^{k/k}$ mouse may fail to respond to (T,G)-A--L because some part of the H-2^k antigenic complex is cross-reactive with (T,G)-A--L, and the animal is therefore tolerant of this type of antigenic determinant. There is a great deal of experimental evidence against this possibility, and up to now there is none in support of it. The observation that the first generation (F_1) between a responder and nonresponder is a responder, although it possesses all the histocompatibility antigens of both parental strains, argues against this postulate. The objection may be raised that some histocompatibility antigenic configurations are recessive, although there is no clear-cut evidence of this as yet.

There are, however, several other experiments which fail to support the tolerance hypothesis. (i) It has so far not been possible to demonstrate any cross reactivity between (T,G)-A--L and (H,G)-A--L and antiserums to H-2^k and H-2^b, or between H-2^k and H-2^b cells and antiserums to (T,G)-A--L and (H,G)-A--L. (ii) H-2^k and H-2^b spleen cells fail to sensitize H-2^b or H-2^k animals for an immune response to (T,G)-A--L or (H,G)-A--L, respectively. (iii) Neither H-2^k spleen cells nor H-2^k thymocytes will absorb antibody to (T,G)-A--L. (iv) H-2^k thymocytes fail to sensitize H-2^b mice for immune response to (T,G)-A--L. (v) Responder antibody to (T,G)-A--L transferred to normal H-2^b or H-2^k mice disappears from their serum at the same rate, and roughly at the normal rate for catabolism of mouse immunoglobulin G (IgG). (vi) In radiation chimeras induced by the injection of responder fetal liver into irradiated nonresponder recipients, approximately half of the responder chimeras can be shown to have no graft-versus-host reactivity against the nonresponder's recipient H-2 type. (vii) Tetraparental mice, produced by the fusion of C3H (H-2^k) and C57 (H-2^b) embryos at the eight-cell cleavage stage and demonstrated to be mosaics for coat color, hemoglobin type, and immunoglobulin allotype, are high responders to (T,G)-A--L in approximately half of the 15 cases tested so far (*29*). Within the limits of our understanding of the nature of tolerance in tetraparental mice, this experiment would tend to completely exclude cross tolerance as the mechanism of genetic unresponsiveness.

Identity of the Cell Type Where Ir Genes Are Expressed

In the two systems most extensively studied, the PLL gene in guinea pigs (*30*) and genes at the Ir-1 locus in mice (*31*), responsiveness can be passively transferred to irradiated, nonresponder recipient strains with immunocompetent cells from animals possessing the Ir genes; this transfer demonstrates that the genes are indeed expressed in cells that participate in the immune response. However, to identify the cell type involved, we must consider that the genetic complexities of the immune system have been magnified by the recent recognition of two pathways for the differentiation of antigen-reactive cells. It is generally accepted that a class of lymphocytes from the bone marrow migrates to the thymus where the cells develop new surface antigens (*32*) and immunocompetence (*33*). These "thymus derived" cells, capable now of reacting specifically with antigen, migrate to the peripheral lymphoid tissues and recirculate in search of antigen through "thymus dependent" anatomical sites (*33*). These cells are responsible for the various phenomena of cell-mediated immunity, such as delayed sensitivity, homograft, and graft-versus-host reactions—a major function of thymus derived lymphocytes being the recognition of and reaction with histocompatibility antigens (*32*).

Thymus derived lymphocytes are also concerned with the enhancement and regulation of the response to antigen by the other line of antigen sensitive cells, the precursors of cells that secrete antibody (*34*). This second lymphocyte cell line originates also in the bone marrow and settles directly in distinct anatomical sites in lymphoid tissues. These cells are usually referred to as "bone marrow derived." Thus, while phenomena of cellular immunity appear to depend exclusively on thymus derived cells, specific antibody synthesis

results, in large part, from the interaction of two specific cell types with antigen. The cooperation between thymus derived cells and bone marrow derived cells in antibody responses explains the fundamental observations of Landsteiner (*35*) that antibodies may be produced against any structure or "hapten" provided that it is bound to an immunogenic "carrier." In terms of the two-cell concept, now generally accepted, the thymus derived cell is the initial reactive cell that binds the carrier molecule (carrier function). As a result of this interaction bone marrow derived cells bearing immunoglobulin receptors against the various determinants or "hapten" on the antigen are efficiently stimulated by the antigen (*36*). We may therefore conclude that the specificity of the two cell types need not be identical and that, whereas the specificity of the antibody secreting cell precursor and the immunoglobulin nature of its receptors are easily identified from the product, the specificity of the thymus derived cell has only been estimated indirectly from its reactivity to antigen. Moreover, it is still not known whether thymus derived cells have immunoglobulin receptors and whether these postulated receptors explain exclusively the reactivity of these cells to antigen. Both these issues are extremely pertinent when considering the function of Ir genes, which, as will be shown below, appear to be essentially concerned with immune phenomena attributed to thymus derived cells.

This last statement is based on evidence from the mouse Ir genes at the Ir-1 locus and from the guinea pig Ir genes. Each of these groups of genes display identical properties to the other in every respect. It is reasonable to conclude that these Ir genes control the same process in the two species and that they may be considered models for other Ir genes similarly linked to histocompatibility genotype.

In guinea pigs, such functions that are attributed essentially to the activity of thymus derived cells—for example, cellular immunity and carrier function—depend exclusively on the presence of the relevant Ir gene.

1) The reactions of cellular immunity to PLL, dinitrophenyl-PLL, GA, and GT are totally under the control of the corresponding specific immune response genes. They are not observed in animals lacking the genes (*8, 9*).

2) Responsiveness to antigens under control of specific immune response genes is accompanied by antibody responses to the haptens they bear, thus illustrating that the carrier function is controlled by the gene (*8, 20*).

3) Conversely, dinitrophenyl-PLL can stimulate marked antibody synthesis in the absence of cellular immunity in guinea pigs lacking the PLL gene if this molecule is administered as a complex with an immunogenic carrier. Thus, dinitrophenyl-PLL may behave as a hapten in a nonresponder animal (*37*). This experiment demonstrates the ability of genetically nonresponder guinea pigs to form antibodies to determinants on a nonimmunogenic molecule provided that appropriate carrier cells, presumably thymus derived, are stimulated. Similar strong responses by 7*S* antibody have also been induced with (T,G)-A--L bound to methylated BSA in mice of a low responder strain.

In the (T,G)-A--L system the Ir-1 locus controls primarily the amounts of 7*S* antibody produced against this antigen, particularly in the secondary response (*5*). As recently reported, both high and low responder strains immunized with this antigen in saline form identical 19*S* responses (*38*). The animals lacking the corresponding Ir gene are therefore capable of forming specific antibodies to this antigen. They must possess precursors to antibody secreting cells capable of binding (T,G)-A--L. An even stronger argument in favor of the expression in mice of these Ir genes in thymus derived cells is the finding that the genetically controlled difference in the 7*S* antibody responses between high and low responder strains immunized with (T,G)-A--L is lost in irradiated thymectomized mice restored with syngeneic bone marrow. Both such groups form only 19*S* antibody responses identical with that seen in the normal, nonthymectomized low responder strain (*38*).

Convincing, although admittedly indirect, evidence has thus been obtained from experiments with both guinea pigs and mice of the necessary expression of this class of Ir genes in thymus derived cells where they must perform a specific and essential function in the immune response. However, among the many unanswered questions regarding the activity of these genes, two essential ones deserve further comment. (i) Are these Ir genes clonally expressed in antigen reactive cells? (ii) Is this class of Ir genes also expressed in antibody secreting cells and their precursors?

If this is the case, Ir genes would be expected to control the specificity of immunoglobulin molecules themselves, either directly as structural V genes, or indirectly by a mechanism such as the one proposed recently by Jerne (*39*). There is as yet no clear evidence that this class of Ir genes is also expressed in antibody secreting cells as they appear to be in thymus derived cells, but such a possibility has not yet been ruled out.

The possibility that Ir genes may affect in some way the differentiation or selection by antigen of antibody secreting cells and their precursors must indeed be considered very seriously in order that we explain the challenging findings in several systems, both in mice and guinea pigs, that Ir genes do affect to some extent the specificity of the antibody populations produced (*5, 40*). The data in this respect is unequivocal, but they are difficult to explain at the present time, particularly when the heterogeneous aspect of the antibody populations produced in these unigenic systems is considered. The effect of Ir genes on antibody specificity could result either from a direct or indirect control of the variable segment of the immunoglobulin chain as discussed above, or, in our opinion, preferably from the manner in which individual determinants can select from the available population of precursors of antibody producing cells after interaction of the antigen with thymus derived cells.

If, indeed, the class of Ir genes considered is only expressed in thymus derived cells, these genes may be concerned with the structure of the antigen receptors themselves or with molecules affecting, secondarily, the manner in which these cells bind or react with the antigen. In any case, this last hypothesis, the exclusive expression of the Ir genes in thymus derived cells would explain why, although the number of Ir genes is not small, they are far less numerous than the different specific immunoglobulin molecules synthesized in immune responses controlled by single genes.

Nature of the Ir Gene Product

The data already presented offer a picture of a large number of histocompatibility-linked genes that control the specific immune response. These genes appear to affect the specificity of antigen recognition by thymus derived and possibly by bone marrow derived immunocompetent lymphocytes. This raises the question of the nature of the

product of this class of Ir genes and of its relation to histocompatibility antigens. All the available evidence would tend to exclude cross tolerance as the mechanism of Ir gene function; furthermore, Ir-1 maps in the center of the H-2 locus and is not linked to the heavy chain linkage group in mice. It is more reasonable to propose, therefore, either (i) that the Ir genes and genes coding for histocompatibility specificities are identical and their function in the immune response reflects directly or indirectly the properties of individual histocompatibility antigens or (ii) that the Ir genes represent a separate and distinct set of antigen receptors, presumably present only on the surface of thymus derived lymphocytes.

The first of these postulates suggests that individual histocompatibility antigenic determinants on the surface of immunocompetent cells modify the function of classical immunoglobulin receptors on the surface of these cells and either facilitate or obstruct the binding of antigen to specific immunoglobulin receptors, possibly by their close relationship to these receptors. If this postulate is correct, then we could predict that Ir gene effects for different antigens would be associated with most of the individual histocompatibility antigenic specificities that can be mapped linearly within the H-2 chromosome region, at least for the H-2 locus in the mouse, and presumably for the HL-A locus in man. A corollary of this prediction is that precise mapping of the location of particular Ir genes within the H-2 chromosome region would result in different Ir genes being distributed throughout the left-hand, center, and right-hand parts of the H-2 complex. A further corollary of this prediction is that particular H-2 antigenic specificities should be found to be regularly associated with certain Ir-1 alleles. Attempts to establish such associations have so far been negative (*41*), but negative results are inconclusive because all specificities are not precisely identified and it is probable that a number of antigenic specificities within the H-2 region do not elicit humoral antibodies that can be used in typing. An alternative explanation consistent with this first postulate is the recent hypothesis by Jerne (*39*) whereby histocompatibility specificities would affect indirectly the generation of diversity in immunoglobulins.

The second postulate, that the Ir genes represent a separate and distinct type of antigen receptor on thymus derived lymphocytes, is compatible with, but does not require, the prediction that all the Ir genes should map in a narrow region in the center of the H-2 locus in the mouse or in the center of the HL-A locus in man. Since thymus derived lymphocytes appear to possess both antigenic specificity (*33*) and "memory," it must be provisionally concluded that the antigen receptors on individual thymus derived lymphocytes differ, and that the Ir gene region in the center of the H-2 locus must either comprise a large number of such genes with differential expression in individual thymus derived lymphocytes, or there must be some type of somatic differentiation of a single or small number of Ir gene loci during the course of development and differentiation.

If subsequent experiments should demonstrate that all the Ir genes map in a narrow region in the center of the H-2 locus, this will be suggestive evidence that the Ir genes are a separate set of antigen receptors. However, the question of the nature of the Ir gene products remains open. The Ir gene products could either represent primordial V regions expressed on thymus derived lymphocytes, presumably entirely cell bound and noncirculating, or alternatively they could be a series of cell surface antigens analogous to transplantation antigens except that they have acquired during the course of evolution or of differentiation the function of binding or of reacting with certain classes of antigenic determinants on foreign antigens, such as the carrier antigenic determinants. The answer to this question will be difficult to obtain without isolating the actual Ir gene product, either chemically or through the use of specific antiserums against this type of antigen receptor. The great technical difficulty of isolating Ir gene products chemically or through specific antiserums should be obvious.

Significance

The significance of the immune response genes depends only in part on the nature of the Ir gene product. Whether the function of the Ir gene product represents merely a property of known histocompatibility antigenic specificities, or whether it represents a new class of antigenic receptors on the surface of thymus derived lymphocytes, there is considerable reason to believe that this type of genetic control of specific immune responses may play an important role in susceptibility to a variety of diseases in both animals and man. The best example of this is the demonstration by Lilly that one of two major genes controlling susceptibility to Gross murine virus leukemogenesis is linked to the right-hand part of the H-2 locus (*42*). Susceptibility to several other viral neoplasms in mice is also associated with H-2 type (*43*), and it is likely that the mechanism of at least some of these associations, particularly that for Gross murine virus leukemogenesis, will be via the mechanism of immune response genes.

In addition to affecting susceptibility to disease, the Ir genes may have an additional and more general function. Whether these genes represent individual H antigenic specificites or a separate type of antigen receptor, they appear to function as an independent control of the amount and specificity of antibody produced by antibody producing, bone marrow derived, plasma cells. In view of the very wide diversity of the humoral antibody response and the frequency of autoantibodies in a number of clinical diseases, such as rheumatoid arthritis, systemic lupus erythematosus, thyroiditis, and other autoimmune diseases, such an additional level of control on the immunogenicity of foreign antigens may have evolved prior to or in parallel with the evolution of the immunoglobulin system as a means of controlling the specificity of immune responses, preventing the development of autoimmunity, and facilitating the development of specific immunologic memory.

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NEWS AND COMMENT

Technology Initiatives: Hints on the Magruder Effort

In coming weeks President Nixon is expected to announce the new technology opportunities program designed to lift the $28-billion U.S. research establishment from its current trough of fund cuts, scientific unemployment, and charges that science and technology are producing little of relevance to national problems. The plan will be based on the efforts of the Office of Science and Technology and William M. Magruder, special consultant to the President, who was appointed, with much fanfare on 13 September 1971.

The Magruder appointment and accompanying rumors that the President personally prized the advice of Magruder, the former director of the supersonic transport (SST) fight, over that of his science adviser, Edward E. David, Jr. (*Science*, 22 October 1971), created conflicting waves in the scientific community. Among them was stirred the inevitable hope—perhaps now a pipe dream—that Nixon's concern for U.S. leadership in technology would prompt him to overhaul policy on R & D.

As of now, however, some hints can be gleaned as to what the program may contain. The technology opportunities program is expected to receive some mention in the State of the Union address which President Nixon will give on 20 January. The program is expected to be announced in detail in February according to the current schedule.

Financially the program appears at present to fall far short of the scientists' dreams of billions. While overall national R & D funding is expected to rise a bit in fiscal 1973 to approximately $18 billion, only a small portion of this total—perhaps no more than a couple hundred million dollars, will go specifically to Magruder's program. Unless the President culls other money from other federal projects and asks Congress for supplemental appropriations (as he did with his energy program announced in June 1971), the technology program will be a very modest one in the coming fiscal year.

It is too early for the exact shape of the program to be known, and White House sources say that they expect the plan to remain in a state of flux up until the time it is announced. Also, last minute decisions could change all previous plans. However, through conversations with a number of nongovernment scientists who have contributed inputs to the Magruder study, *Science* was able to draw up a list of some of the front-running proposals.

It is not known whether the President will announce a broad package of "initiatives" in several different problem areas, from natural disasters to transportation, or whether he will concentrate on one or two.

Magruder apparently has sorted out eight main problem areas where government support might aid some high-risk, but socially and economically useful "initiatives" in getting off the ground. Unknown, at the present time, is exactly how any of these initiatives would be implemented—whether by loans, subsidies, tax exemptions, or new administrative arrangements.

► *Productivity.* Certain industries may be selected where further automation