0031-6997/82/3401-0051$02.00/0
PHARMACOLOGICAL REVIEWS

Vol. 34, No. 1
Printed in U.S.A.

Genetic Control of Cell-Cell Interactions

DAVID H. KATZ*

Department of Molecular Immunology, Scripps Clinic and Research Foundation, La Jolla, California

Introduction

SOMATIC cell differentiation has been a subject of extensive interest for many years, because a clearer understanding of the mechanisms governing such processes should unlock many of the unsolved problems concerning embryogenesis, ontogeny, and neoplastic transformation. Much information has accumulated about the correlations of cell surface membrane changes with various stages of differentiation. In terms of the consequences of translation of information from the genome as it pertains to control of phenotypic programming, this approach has been very informative and has opened an avenue for possible understanding of the manner by which alterations in the program may occur and thereby result in neoplastic changes.

Nonetheless, there is still a vast gap in our understanding of the various inductive and selective forces that govern the translational and/or transcriptional events at the genetic level that control the program(s) for differentiation. We will examine to what extent cell differentiation is influenced by cell surface molecules on the differentiating cells as well as those on neighboring cells and structures with which they may be interacting. The basis for this viewpoint stems from studies performed in our laboratory, and related observations from other laboratories, that have demonstrated the role of histocompatibility gene products in the control of cellular interactions between T lymphocytes and B lymphocytes and macrophages in the development of humoral immune responses. Since many reviews have already been written on this subject, the main emphasis of this discussion will be on recent studies from our own laboratory that bear directly on the relationships between receptors involved in intercellular communication and the phenotype of cell-cell interactions ultimately displayed by a given lymphoid cell population.

Genetic Restrictions on Immunocompetent Cell Interactions

The discovery that genetic restrictions on cell-cell interactions were linked with major histocompatibility complex (MHC) represented a significant advance in our understanding of the fine specificity of such intercellular communication events and has broadened our view of the biological significance of MHC genes and their products. The initial demonstrations of MHC restrictions on T cell-B cell interactions in the mouse (19, 20, 32) and on macrophage-T lymphocyte interactions in the guinea pig (39, 43) were followed by demonstrations of the involvement of MHC gene products in controlling the ability of cytotoxic T lymphocytes (CTL) to effectively lyse target cells (4, 7, 8, 33, 40, 42, 53). In fact, MHC-linked genetic restrictions have by now been identified in virtually every conceivable type of cell-cell interaction involving, directly or indirectly, cells of lymphohematopoietic origin. Although the principal MHC genetic loci involved may vary from one type of interaction to another (i.e., *I* region genes control lymphocyte-lymphocyte and macrophage-lymphocyte interactions, whereas *K/D* genes govern CTL-target cell interaction), the basic phenomenology is the same, namely that the most efficient cell-cell interactions are transacted when the two interacting partner cells share identical *I* or *K/D* region genes as the case may be. Essentially two bodies of thought have arisen as possible explanations for such genetic restrictions. One considers that genetic restrictions are manifestations of the preferable, or even necessary, perception by lymphocytes of antigen in some type of molecular association with MHC determinants on the surface membranes of partner cells with which they interact (i.e., altered-self, complex antigenic determinants) (1, 38, 53). The second considers genetic restriction as a reflection of a distinct cell-cell recognition system involving cell interactions (CI) molecules, at least some of which are encoded by MHC genes, that determine the specificity with which interacting partner cells can effectively communicate (16, 17, 19, 20). To date, both of these possibilities are still viable and will require much additional experimentation.

The interesting paradox regarding the original discovery of MHC restrictions is that the first concepts that linked immunocompetent cell communication events to self-recognition of MHC gene products evolved from a phenomenon that depended on recognition of "not-self"—namely, the allogeneic effect (12). The allogeneic effect described that phenomenon in which introduction of histoincompatible T cells to previously immunized recipients circumvented the normal requirement for antigen-specific helper T cells in secondary antibody responses; this resulted from the development of an active graft-vs.-host reaction in recipient lymphoid organs. The very fact that the allogeneic effect stimulated target T or B cells as a result of interaction at their cell surface MHC molecules prompted the consideration that perhaps precisely the same pathway was involved in syngeneic interactions, perhaps occurring by similar molecular mechanisms. Indeed, experiments designed to address this question demonstrated that physiological in vivo T-B cell

* Present address: Department of Immunology, Medical Biology Institute, 11077 North Torrey Pines Road, La Jolla, California 92037.

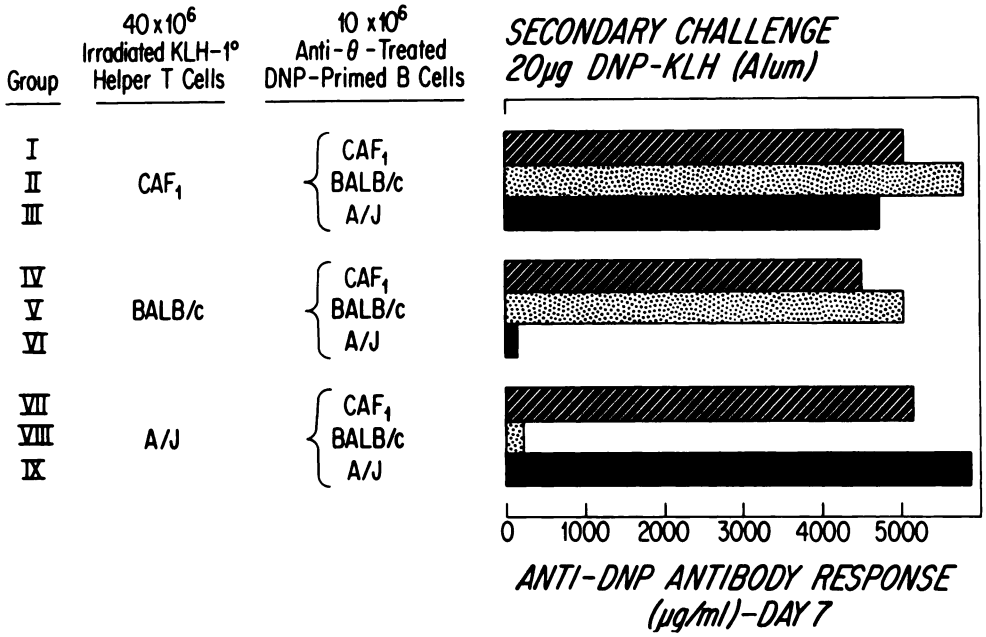

FIG. 1. Conventional parental, but not F_1, helper T cells are restricted in providing helper activity to partner B cells of isologous parental or F_1 type. Unirradiated CAF_1 recipient mice were treated by injection with 40×10^6 KLH primed spleen cells from CAF_1, BALB/c, or A/J donors. Twenty-four hours later, all recipients were irradiated with 650 rads and then given injections of T cell-depleted, DNP-primed B cells from either CAF_1, BALB/c, or A/J donors, as indicated. All cell transfers were performed by the i.v. route. Shortly after the transfer of B cells, all recipients were challenged with 20 μg of DNP-KLH adsorbed on alum. The data are presented as geometric mean levels of serum anti-DNP antibodies in individual mice (5 mice/group) bled on day 7 after secondary challenge (DNP, 2,4-dinitrophenyl; KLH, Keyhole limpet hemocyanin).

interactions in the mouse were genetically restricted by MHC-linked genes. As summarized in figure 1, the basic observation was that antigen-specific T cells, primed to keyhole limpet hemocyanin (KLH), were capable of providing specific helper function for B cells, primed to the 2,4-dinitrophenyl (DNP) hapten of semihistocompatible or histocompatible, but *not* histoincompatible, donor origin in secondary antibody responses of the IgG class (19, 20). At about the same time, others demonstrated a requirement of *H-2* identity for successful thymus reconstitution of nude mice (32) and the existence of MHC-linked genetic restrictions in macrophage-T cell interactions in in vitro proliferation assays (39, 43).

Genetic mapping studies established linkage of such genetic restrictions on T-B cell interactions to the *I* region of *H-2* (17, 23). Since such experiments had been designed to specifically circumvent potential defects in macrophage-lymphocyte interactions and specific or nonspecific suppressive effects (19–22), the original interpretation was that genetic identity between the T cell and the B cell was necessary for the relevant T cell surface molecules, distinct from antigen-specific receptors, to bind to the corresponding B cell molecule (termed "acceptor" sites) for effective interactions to occur (19, 20). The respective molecules were defined as CI molecules with the *I* region genes encoding them as *CI* genes (17).

Subsequently, the involvement of MHC gene products in controlling the ability of CTL to effectively lyse the virus-infected, chemically modified or minor H antigen-bearing target cells was found (4, 7, 8, 33, 40, 42, 53). These observations demonstrated that CTL are most efficient in lysing target cells derived from a similar MHC genotype, with the critical genetic loci involved mapping to the *K* and *D* regions of the MHC, thus differing from the *I* region location of the MHC genes involved in T cell-B cell-macrophage interaction.

In view of the substantial experimental and theoretical attention that has been accorded to this subject, one could validly question whether there is any evidence that such genetic restrictions that are, by necessity, identified and demonstrated under experimentally contrived circumstances, are physiologically relevant. There are at least four pieces of information that support the belief that MHC restrictions portray the actual physiology of cell-cell communication in the lymphohematopoietic system. First, the allogeneic effect demonstrates unequivocally that specific interaction at cell surface MHC molecules induces a discrete and measureable biological response by the target cell in such interactions (12), thus proving that MHC molecules can play a role in cell triggering. Second, the existence of MHC-linked *immune response* (*Ir*) genes, which map in precisely the same genetic locations as *CI* genes, determine the immune response phenotype of an individual to various specific antigens thus linking the MHC indisputably to functional responsiveness (2, 3, 36). Third, the fact that *CI* genes determine the effectiveness of cell-cell interactions necessary for nonlymphoid hematopoietic stem cell differentiation (34, 41) provides evidence for a biological significance for such restrictions that extends beyond the immune system. (Parenthetically, such genetic restric-

tions on cell-cell interactions that do not involve, in any obvious way, specific immunological responses provide evidence for a recognition system independent of that employed for recognition of the antigenic universe.) Finally, it is now established that the self-recognition repertoire by which interacting cells perceive themselves most efficiently is influenced significantly by elements in the environmental milieu to which developing cells are exposed during their early differentiation, i.e., the process of adaptive differentiation (13, 14, 18, 24).

Adaptive differentiation describes the process by which differentiating stem cells adapt their functionally expressed self-recognition repertoire, and hence their ultimate interacting phenotype, as a result of exposure to the MHC phenotype of the environment in which they differentiate (13, 14, 18, 24). This has been substantiated by experimentation with irradiation bone marrow chimeras, particularly the results obtained with chimeric lymphocytes of $F_1 \rightarrow$parent type (lethally irradiated parental hosts, of *A* or *B* type, repopulated with $[A \times B]F_1$ bone marrow stem cells) that no longer display the indiscriminate interacting phenotype for either parent typical of conventional F_1 lymphocytes, but rather interact preferentially with partner cells of host parental type, or F_1 type (5, 10, 11, 25, 44–46, 51, 52). Still to be determined are the ground rules of adaptive differentiation and the underlying mechanisms by which the self-recognition repertoire is sculptured by elements in the environment.

Studies on Adaptive Differentiation of Lymphocytes in Bone Marrow Chimeras

As an example of such studies (25), we tested the capacities of helper T lymphocytes and hapten-specific B lymphocytes primed in the environments of various combinations of bone marrow chimeras prepared between two parental strains (i.e., A/J and BALB/c) and their corresponding F_1 hybrid (CAF_1) to interact with primed B and T lymphocytes derived from conventional parent and F_1 donors in adoptive secondary transfer responses. While $F_1 \rightarrow F_1$ chimeric lymphocytes displayed no restrictions in terms of cooperative activity with all of the various partner cell combinations, as shown in figure 2, $F_1 \rightarrow$ parent chimeric lymphocytes displayed restricted haplotype preference in cooperating best with partner lymphocytes sharing the *H-2* haplotype, either entirely or codominantly, of the parental chimeric host. Suitable control studies ruled out the existence of either nonspecific or specific suppression mechanisms as possible explanations for the restricted partner cell preference of $F_1 \rightarrow$ parent chimeric lymphocytes as displayed in the adoptive transfer situation.

Since similar observations with bone marrow chimeras in the CTL systems were interpreted as evidence for a central role of the thymus in dictating the self-recognition repertoire to precursor T lymphocytes, we analyzed the cooperating preference of helper T cells originating from F_1 bone marrow, but differentiating in adult thymecto-

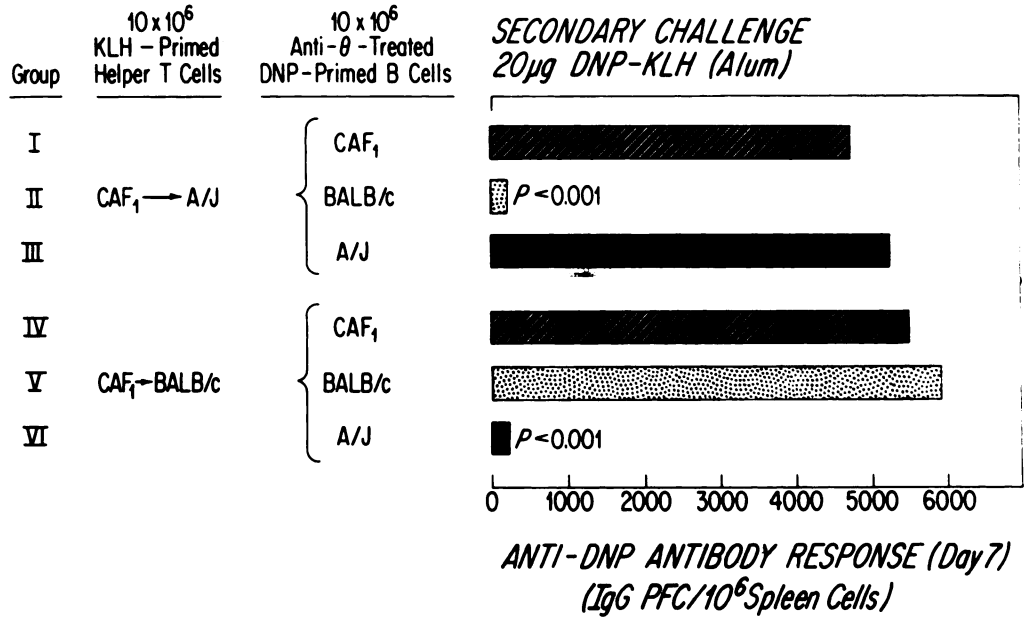

FIG. 2. Spleen cells from KLH-primed $CAF_1 \rightarrow$ A/J (groups I to III) and $CAF_1 \rightarrow$ BALB/c (groups IV to VI) were co-transferred with T cell-depleted B cells from DNP-*Ascaris*-primed conventional CAF_1, BALB/c, or A/J donors into 650 rad-irradiated CAF_1 recipients. All recipients were challenged with 20 μg of DNP-KLH in alum shortly after cell transfer. The data are presented as geometric mean levels of IgG plaque-forming cells/10^6 spleen cells of groups of four recipients each assayed on day 7 after cell transfer and challenge. Statistically significant differences, as measured by Student's *t* test are indicated adjacent to the pertinent horizontal bar (DNP, 2,4-dinitrophenyl; KLH, Keyhole limpet hemocyanin). [Adapted from Katz et al. (25).]

mized, lethally irradiated F_1 recipients reconstituted with either F_1 or homozygous parental thymus grafts (26). The results of these analyses revealed only a marginal tendency for helper T cells derived from parental thymic chimeras to provide better help for B cells of the same parental type corresponding to the origin of the thymus graft than for the opposite parent. Most importantly, in no instance was there any evidence of "restriction" in the classical sense of *presence* vs. *absence* of help as routinely observed in studies concerning genetic restrictions of T-B cell cooperative interactions by conventional lymphoid cell populations.

Thus, such studies demonstrated that the thymic microenvironment exerts relatively little influence on the cooperative phenotype of helper T cells generated in thymic chimeras. The next chimera study was conducted to analyze further the sites of dominant influence on lymphocyte maturation with regard to the self-recognition capabilities normally displayed by regulatory helper T cells (29). This was accomplished by utilizing lymphocytes obtained from: 1) $F_1 \rightarrow$ parent chimeras, and 2) intact parental mice rendered tolerant as neonates to the MHC determinants of a second parental strain. Lymphocytes were removed from these environments and *adoptively primed* to KLH in irradiated, thymectomized F_1 recipients. The resulting helper T cells were then analyzed for their partner cell preferences when mixed with conventional DNP-primed B lymphocytes of either parental or F_1 origin in adoptive secondary responses in irradiated F_1 recipients. As shown in figure 3, irrespective of their initial environmental origins, T cells of such types could be adoptively primed to develop totally unrestricted helper cell activity for B lymphocytes of both parental types as well as B cells of F_1 type. These results indicate that the dominant influence on cooperative capabilities of helper T cells is exerted by the extrathymic microenvironment in which such cells undergo their early differentiation. Moreover, they demonstrate that the haplotype restriction displayed by helper T cells primed in, and taken directly from, $F_1 \rightarrow$ single parent chimeras is actually a *pseudorestriction* since helper T cells with unrestricted cooperating phenotypes can be induced in such $F_1 \rightarrow$ single parent chimeric populations when adoptively primed in irradiated F_1 recipients. This pseudorestriction in cooperative capabilities was explained by a new concept termed *environmental restraint.*

Environmental restraint describes the process by which the environmental milieu can exert nonpermissive influences on the development of functional interacting partner cells corresponding to one of the possible (and actually existing) CI phenotypes inherent in a given lymphoid cell population. In other words, despite the fact

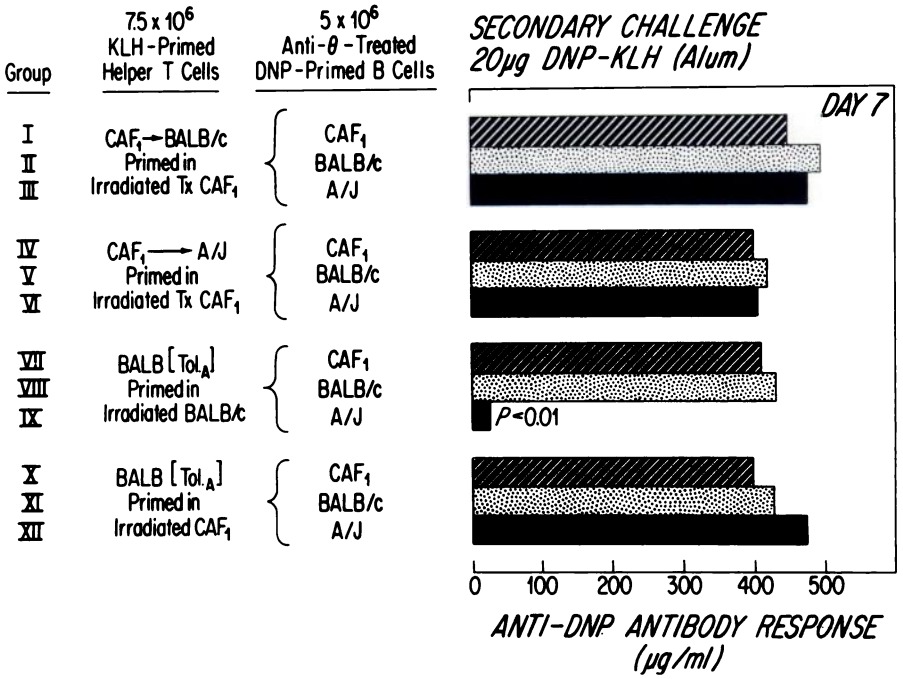

FIG. 3. Spleen cells from unprimed $F_1 \rightarrow$ parent chimeras (groups I to VI) were adoptively primed to KLH in irradiated thymectomized conventional CAF_1 recipients. Spleen cells from BALB/c mice, rendered tolerant to A/J MHC determinants as neonates (by injection of 50×10^6 irradiated CAF_1 spleen cells within the first 24 hours after birth) were adoptively primed to KLH in either irradiated BALB/c recipients (groups VII to IX) or irradiated CAF_1 recipients (groups X to XII). All adoptive priming consisted of injecting 50×10^6 donor spleen cells into irradiated recipients that were then immunized with 20 μg of KLH in CFA immediately after transfer. The adoptively primed KLH-specific helper cells were recovered seven days later and co-transferred with T cell-depleted B cells from DNP-*Ascaris*-primed conventional CAF_1, BALB/c, or A/J donors into 650 rad-irradiated CAF_1 recipients. All recipients were secondarily challenged with 20 μg of DNP-KLH in alum shortly after cell transfer. The data are presented as geometric mean levels of serum anti-DNP antibodies in groups of four recipients each. Statistically significant differences are indicated adjacent to the pertinent horizontal bar (KLH, Keyhole limpet hemocyanin; MHC, major histocompatibility complex; DNP, 2,4-dinitrophenyl; CFA, complete Freund's adjuvant). [Adapted from Katz et al. (29).]

that the F_1 lymphoid cells residing in an $F_1 \rightarrow$ parent chimera consist of self-recognizing subpopulations corresponding to each of the two inherited parental CI types, the parental host environment is only permissive for expression (in that environment) of that subpopulation corresponding to the CI phenotype of the parental host; that same environment is nonpermissive for emergence of the second parental type subpopulation for reasons that have yet to be delineated.

Thus, our current hypothesis is that adaptive differentiation is a dynamic rather than a static process and that the self-recognition repertoire within a given species enjoys a certain degree of plasticity. Moreover, we feel that the plasticity of the self-recognition repertoire is determined by the occurrence of responses against self-specific receptors for CI molecules (i.e. αCI) and these, in turn, determine the immune response phenotype for a given individual.

Orchestration of Cooperating Phenotypes of Conventional F_1 Lymphocytes

One very important lesson from the $F_1 \rightarrow$ parent chimera experiments has been the realization that the answers to all of the mysteries pertaining to self-recognition and adaptive differentiation are present in conventional heterozygous F_1 individuals. Consequently, experimental analysis of lymphoid cells from F_1 hybrids under various circumstances should allow us to unravel such mysteries. As shown in figure 4, it can be viewed that an ($A \times B$) F_1 individual contains a minimum of three subsets of self-specific interacting partner cells, one each corresponding to the two respective parental types (A and B) and the third corresponding to an F_1-specific subset (A/B). Each respective subset carries specific CI molecules (CI_A; CI_B, and $CI_{A/B}$), for which there are corresponding αCI receptors (αCI_A, αCI_B, $\alpha CI_{A/B}$). One need only envisage the possibility that responses can be generated against such αCI receptors (i.e., anti-αCI) under certain circumstances to realize that the cooperating phenotypes can display considerable plasticity.

The occurrence of such anti-αCI responses was first suggested by experiments demonstrating that the cooperating phenotypes of conventional F_1 lymphocytes could be orchestrated by certain experimental manipulations, including: 1) parental cell-induced allogeneic effects during priming of either T or B lymphocytes (27, 28); and 2) incorporation of lymphoid cells of parent B-type into cooperative interactions between F_1 hybrid T cells and B cells of parent A-type, and vice versa (30; see below). In both types of experiments, appropriate controls ruled out allosuppression phenomena, or blocks in effective macrophage-lymphocyte interactions. Most importantly, the effects observed were exquisitely haplotype-specific. The development of anti-αCI responses could explain the permissiveness of expression of one subpopulation of self-recognizing cells in the face of nonpermissiveness of expression of the second subpopulation of self-recognizing cells. Likewise, such anti-αCI responses provide a suitable explanation for manifestations of environmental restraint within an $F_1 \rightarrow$ parent chimera, as discussed above.

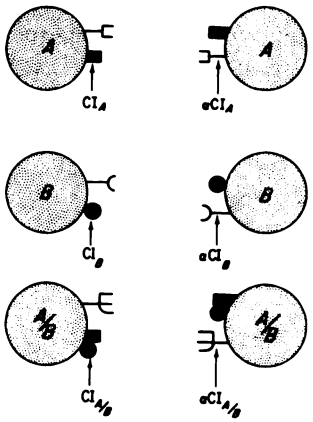

FIG. 4. Depicted are the three minimal subsets of potential self-specific interacting partner cells in heterozygous ($A \times B$) F_1 individuals. Subsets A and B correspond to the inherited cell interactions (CI) specificities of the respective parental A and B donor mice, while subset A/B represents a unique F_1 specific subset of interacting cells. The corresponding CI_A, CI_B, and $CI_{A/B}$ target molecules and the corresponding receptors for such molecules (αCI_A, αCI_B, and $\alpha CI_{A/B}$) are depicted.

A series of experiments were conducted to demonstrate means by which to maneuver the cooperating phenotypes of conventional F_1 hybrid lymphocytes. The first of such studies demonstrated circumstances in which restrictions in F_1-parent partner cell interactions determined by *Ir* genes could be willfully directed by induction of parental cell-mediated allogeneic effects during priming of the F_1 helper T cell population to the antigen governed by the relevant *Ir* genes (27). Responses to the synthetic terpolymer L-glutamic acid, L-lysine, L-tyrosine (GLT) in the mouse are controlled by *H-2*-linked *Ir-GLT* genes. (Responder × nonresponder) F_1 hybrid mice, themselves phenotypic responders, can be primed with GLT to develop specific helper cells capable of interacting with DNP-primed F_1 B cells in response to DNP-GLT. Unlike the indiscriminate ability of F_1 helper T cells for conventional antigens (i.e., not *Ir* gene-controlled) that can help B cells of either parental type (as well as F_1) equally well, GLT-primed F_1 T cells can provide help only under normal circumstances for B lymphocytes of responder parent origin (21); they are unable to communicate effectively with nonresponder parental B cells (figure 5). However, the induction of a parental cell-induced allogeneic effect during priming of F_1 mice to GLT actually dictates the direction of cooperating preference that will be displayed by such F_1 helper cells for B cells of one parental type or the other. Thus, as shown in figure 5, F_1 T cells primed to GLT under the influence of an allogeneic effect induced by parental BALB/c cells developed into effective helpers for nonresponder A/J B cells, but failed to develop effective helpers for responder BALB/c B cells, and vice versa. In contrast, F_1 T cells primed to GLT under the influence of an allogeneic effect induced

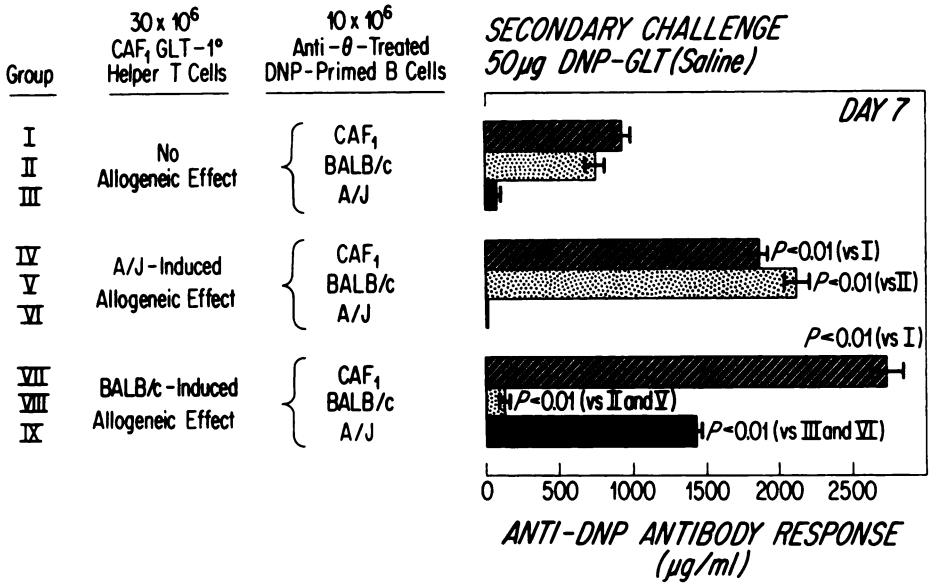

FIG. 5. Conventional CAF_1 mice were primed to GLT: 1) in the absence of an allogeneic effect, with 50 μg of GLT in CFA followed 10 days later by a second injection of 50 μg in saline (groups I to III); or 2) under the influence of an allogeneic effect induced by i.v. injection (on day 10 after initial immunization with 50 μg of GLT in CFA) of 25×10^6 spleen cells from either parental A/J (groups IV to VI) or BALB/c (groups VII to IX) donors just before the second injection of 50 μg of GLT in saline. All GLT-primed spleen cells were recovered seven days after the second injection to be used as helper cells. These cells were co-transferred with T cell-depleted DNP-*Ascaris*-primed B cells from conventional CAF_1, BALB/c, or A/J donors into 650 rad-irradiated CAF_1 recipients. All adoptive recipients were secondarily challenged with 50 μg of DNP-GLT in saline shortly after cell transfer. The data are presented as geometric mean levels of serum anti-DNP antibodies of individual mice in groups of five mice each bled on day 7 after cell transfer and secondary challenge. Horizontal lines represent the range of standard errors, and relevant statistically significant differences vs. corresponding control groups are indicated adjacent to the horizontal bars (GLT, L-glutamic acid, L-lysine, L-tyrosine; DNP, 2,4-dinitrophenol. [Adapted from Katz et al. (27).]

by either parental type displayed significantly enhanced levels of helper activity for B cells derived from F_1 donors (27).

These results were interpreted to reflect the existence of two interdependent events provoked by the allogeneic effect: One event augments the differentiation of GLT-specific helper T cells belonging to the subset corresponding to the opposite parental type; this would explain the development of increased helper activity provided to partner B cells of opposite parental type (as well as of F_1 origin). The second event, we postulated, involves the production of responses against the receptors that normally self-recognize native CI determinants; this form of anti-αCI response is restricted against self-recognizing receptors of the same parental type used for induction of the allogeneic effect, hence explaining diminished helper activity of such F_1 cells for partner B lymphocytes of corresponding parental type. The existence of haplotype-specific anti-αCI receptor responses was postulated to explain the permissiveness of the development of one subpopulation of self-recognizing cells (corresponding to one of the parental haplotypes) in the face of nonpermissiveness of the development of the subpopulation of self-recognizing cells corresponding to the second haplotype involved. Moreover, it is not difficult to envisage that the existence of such a mechanism might explain environmental restraint as described above.

The ability to orchestrate the cooperating phenotype of (responder × nonresponder) F_1 GLT-specific helper T cells, prompted us to investigate whether the success of such manipulations was unique to responses controlled by *H-2*-linked *Ir* genes, or whether priming F_1 lymphocytes to *any* antigen under the influence of a transient allogeneic effect would result in a similar deviation in cooperating preferences for partner cells of one or the other parent type. Additionally, it became important to ascertain whether F_1 B lymphocytes could be similarly directed in their cooperating partner cell preferences when primed under the influence of a parental cell-induced allogeneic effect. This ability to orchestrate the cooperating preferences of F_1 lymphocytes is not unique to antigen systems under *H-2*-linked *Ir* gene control, and is a property demonstrable in B lymphocytes as well as T lymphocytes (28).

Additional support for the idea pertaining to anti-αCI receptor responses came from experiments demonstrating that F_1-parent T-B cell cooperation in vivo is significantly diminished by the presence of lymphoid cells of opposite parental type (30). This inhibition phenomenon is not a straightforward allosuppression mechanism as it can be induced by parental lymphoid cells depleted of T cells, it does not operate on cooperative interactions between homologous T and B cells of opposite parental type, and absolutely requires the presence of F_1 cells as participants in the reactions generated. Since the presence of parental lymphoid cells only affected cooperative interactions between F_1 T cells and B lymphocytes of opposite parental type, but had no inhibitory effect on cooperative interactions between homologous F_1 T and B cells, this strongly argues for the existence of one or

more subsets of F_1 interacting partner cells that are uniquely specific for F_1, as distinct to either parental type, CI determinants. Moreover, it again appears that the most likely mechanism underlying such parental cell-induced inhibitory effects on F_1-parent partner cell interactions is the development of anti-self CI receptor responses by F_1 cells against the relevant self receptors of the parental partner cells involved.

Parallelisms between the Cell Interaction and Immune Response Phenotypes

Since the discovery of immune response (*Ir*) genes by Benacerraf and McDevitt and their colleagues (3), much effort has been directed toward delineating the nature of these genes and the mechanism by which they determine the ability of an individual to develop an immune response to a specific antigen. The discovery of MHC-linked genetic control of interactions between T cells and B cells (19, 20, 32) and between T cells and macrophages (39, 43) added additional complexities to these questions, particularly when the *CI* genes were mapped to the *I* region of the murine *H-2* complex (17, 23).

Even before the final mapping of *CI* genes to the *I* region had been accomplished, experimental evidence was obtained that strongly indicated a crucial functional linkage between *CI* and *Ir* genes. The first such evidence was the observation, described above, that T cells from (responder × nonresponder) F_1 hybrids primed to the synthetic terpolymer GLT, to which responses are governed by *Ir-GLT* genes, were restricted to providing GLT-specific help for DNP-primed B cells only from phenotypic responder parental and F_1 donors in response to DNP-GLT; the same F_1 T cell population was incapable of helping B cells obtained from nonresponder parental donors (21) (see fig. 5, groups I to III). Since F_1 T cells can indiscriminately interact effectively with partner B cells from either parent when the carrier antigen employed is not one to which responses are governed by a known *Ir* gene (19, 20), this restricted cooperating phenotype in the DNP-GLT experiment clearly signalled a role of *Ir* genes in determining the partner cell preferences in such cooperative interactions. For this and other reasons, we have concluded that *Ir* and *CI* genes are one and the same. If this is true, then one would predict that the immune response phenotype should exhibit comparable plasticity to that already demonstrated for *CI* gene-determined cooperative phenotypes based on the environment in which stem cells differentiate. Indeed, several reports have appeared that indicate that this is so in bone marrow chimeras (6, 9, 11, 35, 50).

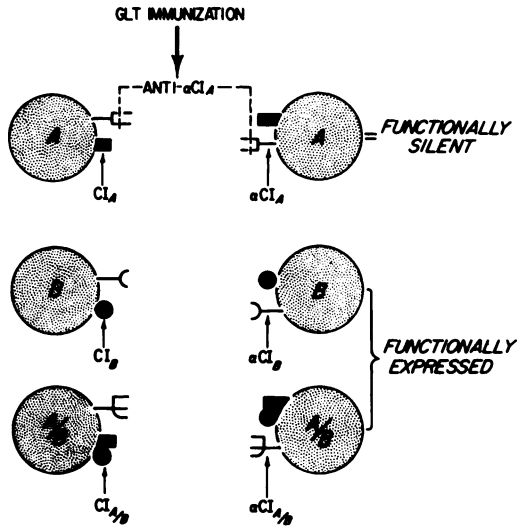

FIG. 6. As in figure 4, depicted are the minimal subsets of potential self-specific interacting partner cells in heterozygous ($A \times B$) F_1 individuals, with the corresponding CI and αCI molecules displayed on the surfaces of such cells. In response to a conventional antigen, such as KLH, all three subsets of interacting cells would presumably be activated thus explaining the indiscriminate cooperative phenotype of F_1 T cells with partner cells of either parental type or of F_1 type. In contrast, in response to GLT (to which the parent *A* strain is a nonresponder) the model proposes that there develops a rather immediate anti-αCI_A response that renders that particular subset functionally silent; the remaining *B* and *A/B* subsets are functionally expressed hence leading to the phenotype of effective cooperation by GLT-specific F_1 cells for partner cells of parent *B* and ($A \times B$) F_1 type, but no cooperative activity for partner cells of parent *A* type (KLH, Keyhole limpet hemocyanin; GLT, L-glutamic acid, L-lysine, L-tyrosine; CI, cell interactions).

The hypothesis that we are testing can thus be stated as follows: Returning to the model schematically illustrated in figure 4, which illustrates at least three minimal subsets of self-specific interacting partner cell subsets in a conventional heterozygous ($A \times B$) F_1 individual, it seems clear that when such an individual is immunized with an antigen to which there are no restrictions imposed on responses by *Ir* genes, all three subsets of interacting cells will be functionally expressed. Hence, the cooperating phenotype of the lymphocyte population from this F_1 individual will appear totally unrestricted in terms of cooperating with partner cells of both parents as well as of F_1 origin.

In contrast, when an F_1 individual is exposed to an antigen to which responses in one of the parental haplotypes is restricted by a specific *Ir* gene, the development of functionally interacting subsets follows a different course. Thus, as depicted schematically in figure 6, exposure of an ($A \times B$) F_1 hybrid to GLT, to which parent *A* is a nonresponder, results in development of functional expression of only the *B* and *A/B* responder subsets of interacting cells; the parental *A* subset is functionally silent, as evidenced by the restricted phenotype of F_1 cells described in the original DNP-GLT studies (21). The question that we have specifically addressed is whether the functional silence of the parent *A* subset under these circumstances might be a manifestation of the development of an anti-αCI_A response provoked by exposure of the lymphoid system to GLT.

Thus, thymic chimeras were constructed by reconstituting lethally irradiated, thymectomized recipients who were: 1) CAF_1, BALB/c, or A/J with CAF_1 bone marrow cells and CAF_1 thymus grafts; or 2) CAF_1 with both bone

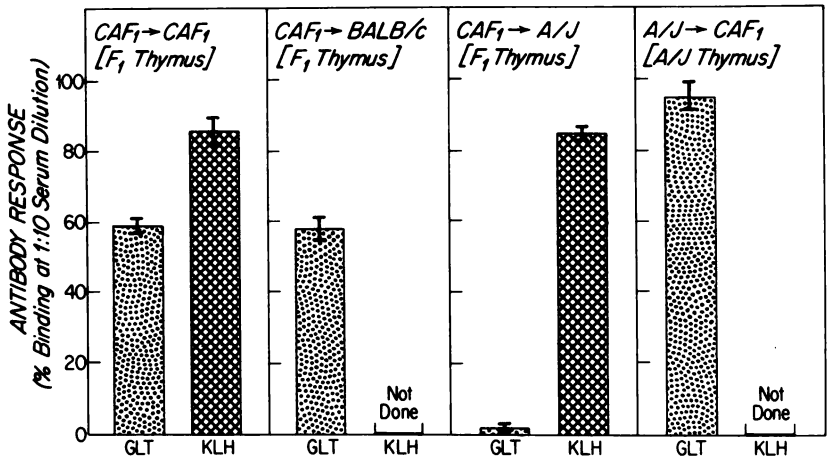

FIG. 7. Radiation bone marrow chimeras were constructed by transferring either CAF_1 bone marrow cells into thymectomized, lethally irradiated (950 rads) CAF_1, BALB/c, or A/J recipients (panels 1 to 3) or A/J bone marrow into thymectomized, lethally irradiated CAF_1 recipients (panel 4). Recipients were transplanted two weeks later with thymuses of the donor type indicated, under the kidney capsules. All mice were typed for *H-2* three to four months after reconstitution and were rested until nine months after reconstitution before immunization with GLT and/or KLH. All mice were immunized i.p. with 50 μg of GLT in CFA on day 0 and boosted with 50 μg of GLT in saline on day 14. The data presented are mean percent binding of [^{125}I]labeled GLT of 1:10 dilution of individual serum samples from bleedings of groups of four mice each on day 24 (10 days after boosting). Standard errors are indicated by the vertical line on each bar. Mice immunized with KLH (panels 1 and 3) were immunized i.p. on day 30 (after initiation of GLT immunizations) with 20 μg of KLH in CFA and boosted on day 40 with 10 μg of KLH in saline. The data presented are mean percent binding of [^{125}I]labeled KLH of 1:10 dilutions of individual serum samples from bleedings on day 47 (GLT, L-glutamic acid, L-lysine, L-tyrosine; KLH, Keyhole limpet hemocyanin; CFA, complete Freund's adjuvant). [Adapted from Katz et al. (31).]

marrow cells and thymus grafts obtained from nonresponder parental A/J donors. These chimeras were then immunized with unconjugated GLT and analyzed for their capacities to develop GLT-specific antibody responses (31).

As summarized in figure 7, $CAF_1 \rightarrow CAF_1$ and $CAF_1 \rightarrow$ BALB/c chimeras, both possessing CAF_1 thymus grafts, developed comparable GLT-specific antibody responses. In striking contrast, chimeras of $CAF_1 \rightarrow$ A/J type failed to produce detectable levels of anti-GLT antibody responses despite the fact that such chimeras possessed thymus grafts of CAF_1 origin. This did not reflect ineffective thymic reconstitution since such mice were able to develop KLH-specific antibody responses comparable to those displayed by corresponding $CAF_1 \rightarrow CAF_1$ controls. On the other hand, chimeras constructed with lymphoid stem cells and thymus grafts of nonresponder A/J parental origin, which had differentiated in the environment of CAF_1 hosts, developed excellent GLT-specific antibody responses.

This experiment may offer significant insight on the mechanism(s) by which *Ir* genes determine the immune response phenotype. The most pertinent findings, displayed by the $CAF_1 \rightarrow$ A/J and A/J $\rightarrow CAF_1$, indicate quite clearly that elements in the corporeal environment may determine the *Ir* phenotype of a given individual. This conclusion follows from the finding that stem cells from phenotypic responder F_1 donors that mature in an environment containing homologous F_1 thymus display the nonresponder phenotype characteristic of the remainder of the corporeal environment provided by the nonresponder parental host. Reciprocally, stem cells from phenotypic nonresponder parental donors differentiate in a corporeal environment provided largely by phenotypic responder F_1 elements, with the exception of the nonresponder parental thymus graft, to display phenotypic responsiveness to GLT. In other words, the *Ir* phenotypes in these circumstances reflect the permissiveness of the phenotypic responder F_1 environment, on the one hand, and the nonpermissiveness of the phenotypic nonresponder parental environment, on the other.

In order to ascertain to what extent lymphoid cells interact with other lymphoid as well as nonlymphoid elements in a chimeric environment, mixed parent chimeras were constructed by reconstituting lethally irradiated CAF_1 recipients with equivalent numbers of responder BALB/c and nonresponder A/J parental bone marrow cells. Six months after reconstitution, these double parent chimeras were primed with GLT in order to generate GLT-specific helper T cells. Spleens were removed from such mice, treated with BALB/c anti-A/J antibodies plus C to remove any cells of parental A/J type or of recipient F_1 type; the remaining "Chim.BALB/c" splenic cells were then tested for cooperative helper activity when co-transferred with DNP-primed B cells of CAF_1, BALB/c, or A/J origin in response to secondary challenge with DNP-GLT. The cooperative phenotype of "Chim.BALB/c" helper T cells was compared with that of GLT-primed helper T cells taken from conventional CAF_1 donors co-transferred with portions of the same populations of DNP-primed B cells.

As shown in figure 8, GLT-primed conventional CAF_1 helper T cells displayed the normal cooperative phenotype of providing good helper activity for B cells of

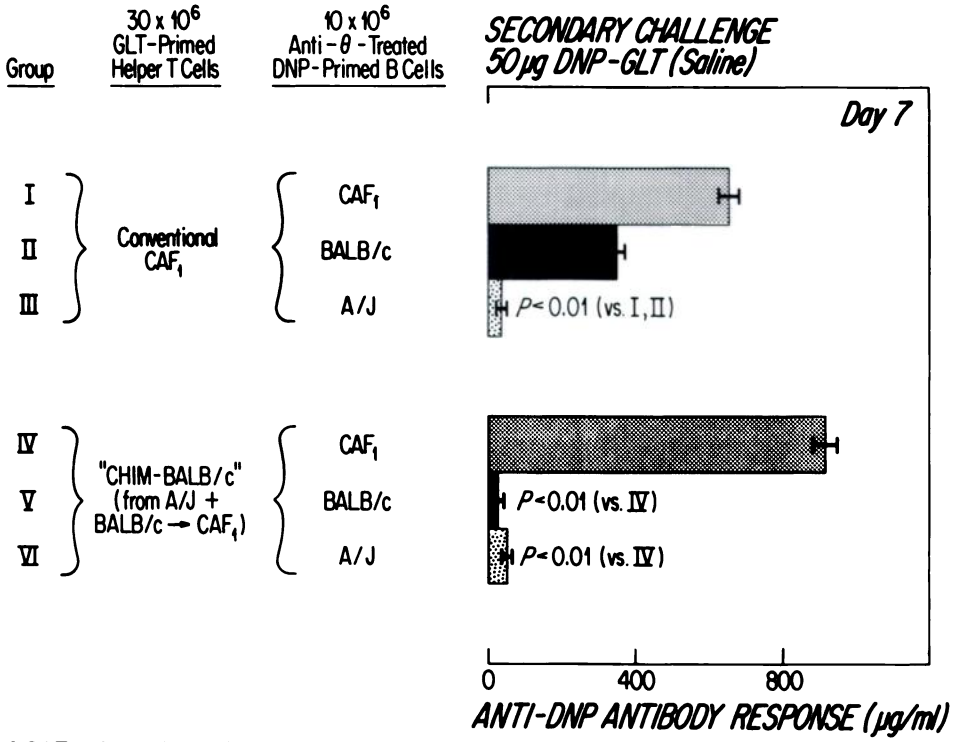

FIG. 8. Conventional CAF_1 mice and mixed parental A/J + BALB/c → CAF_1 chimeras were immunized with 50 μg of GLT in CFA followed by a single boost of GLT in saline three weeks thereafter. Spleen cells were obtained from such GLT-primed donor mice three to four weeks after the last saline boost to be used as helper cells. "Chim.BALB/c" spleen cells were obtained from such mixed parent → F_1 GLT-primed chimeras by treatment of the spleen cells in vitro with BALB/c anti-A/J antibodies + C. Then 30×10^6 GLT-primed conventional CAF_1 and "Chim.BALB/c" spleen cells were transferred together with T cell-depleted DNP-*Ascaris*-primed B cells from conventional CAF_1, BALB/c, or A/J donor mice into 650 rad-irradiated CAF_1 recipient. All recipients were secondarily challenged with 50 μg of DNP-GLT in saline shortly after cell transfer. The data are presented as geometric mean levels of individual serum anti-DNP antibodies of groups of five mice each assayed on day 7 after cell transfer and secondary challenge. Horizontal lines represent standard errors and relevant *P* values depicting statistically significant differences between experimental and control groups are indicated beside the corresponding horizontal bars (GLT, L-glutamic acid, L-lysine, L-tyrosine; DNP, 2,4-dinitrophenyl). [Adapted from Katz et al. (31).]

responder F_1 and parental BALB/c origins, but not for B cells of nonresponder A/J origin (groups I to III). The cooperative phenotype of GLT-primed "Chim.BALB/c" helper T cells (groups IV to VI) provides a striking contrast. Such cells displayed excellent helper activity for DNP-primed partner B cells of CAF_1 type, but failed to engage in effective interactions with either responder BALB/c or nonresponder A/J partner B cells.

The failure of "Chim.BALB/c" T cells to provide GLT-specific helper activity for either BALB/c or A/J partner B cells in response to DNP-GLT is not a reflection of some general abnormality existing in such mixed parental chimeras. Nor do these data reflect some unusual properties of the partner B cells employed in this experiment with respect to their ability to interact with mixed parental chimera T cells. Thus, "Chim.BALB/c" helper T cells obtained from the same group of mixed parental → F_1 chimeras, but primed to KLH rather than to GLT, provided adequate helper T cell activity for aliquots of the same B cells as those used in figure 8 in secondary adoptive responses to DNP-KLH, and such helper activity was comparable with the two parental-type partner B cells as well as with F_1 B cells.

The preceding experiments clearly demonstrate three critical points about the GLT system. First, the immune response phenotype of a given individual is not dictated by the nature of the thymic microenvironment; second, one or more elements in the extrathymic corporeal environment determine the permissiveness of immune response capability; and third, such elements are not derived primarily from the lymphoid stem cell pool, although lymphoid cells may interact with such corporeal elements in the determination of the immune response phenotype. It should be noted that no conclusion can be reached about the cellular locus at which the mechanism(s) determining *Ir* phenotype operates. For example, unresponsiveness to GLT displayed by CAF_1 → A/J chimeras could reflect a defect at the level of T cells, B cells, or macrophages, or any combination thereof, or at one or more of the requisite interactions between such cells. From the data in figure 8, it seems clear that nonpermissiveness can at least operate at the level of generation of a relevant subset of GLT-specific helper T cells, but again this could reflect a defect solely at the T cell level or at the level of T-macrophage and/or T-T cell interactions.

The interpretation we favor for such results is that responses against CI molecules can determine the ob-

served plasticity of the immune response phenotype. We further believe that such anti-αCI responses could readily explain the mechanism by which *Ir* genes function to determine the immune response phenotype; it is only necessary to assume that *Ir* genes encode CI molecules. If one considers that CI molecules are distinct entities from antigen-specific receptors, then the manner in which *Ir* genes exert such exquisite specificity for antigen in responses over which they display control depends on whether *Ir* genes encode molecules serving as: 1) αCI receptors alone (at least in part); 2) target CI molecules themselves; 3) or both αCI receptors and target CI molecules.

The above experiments are consistent with this notion. Thus, it is clear from these findings, as well as from our earlier studies in the *Ir-GLT* system (21) and from the work of others (6, 11, 35), that expression of *Ir* phenotype is not a reflection of whether or not a given *I* region gene or genes is absent from the genome of an individual. Nor, for that matter, is there any structural evidence to indicate whether *Ir* phenotype is associated with the expression of the relevant *Ir* gene product(s). Data pertinent to this point arises from the results obtained with GLT-primed responder BALB/c T cells that had differentiated in the same environment with nonresponder A/J parental cells (fig. 8). Such cells displayed a cooperating phenotype restricted for DNP-primed partner cells derived from conventional F_1 donors. The fact that differentiation and priming to GLT occurred in an environment where nonresponder parental lymphoid cells were also present obviously determined this unusual cooperating phenotype. We can think of no mechanism by which the presence of the cohabitating nonresponder A/J cells could have regulated expression of the relevant *I* region gene product by responder BALB/c cells that could account for functional deletion of the BALB/c-specific GLT-helper T cell subset.

On the other hand, one *can* explain this observation by a mechanism involving responses against self-specific CI molecules. As shown schematically in figure 6, if a nonresponder individual displays that phenotype because, for whatever reason, exposure to GLT evokes a very strong (and early) anti-αCI response, this would, in turn, blunt the development of any possible response to GLT. Exposure of an individual of a responder phenotype to GLT, conversely, would not elicit this type of anti-αCI response under normal circumstances, and hence the environment of such an individual would be permissive for responses to GLT.

Why, then, does cohabitation of responder cells with nonresponder cells result in nonpermissiveness for the population of responder self-specific cells? This could be explained by the fact that a state of mutual immunological tolerance exists between the cohabitating parental lymphoid cell populations in such chimeras (49). A consequence of such mutual tolerance is the emergence within each parental lymphoid cell population of interacting subsets specific (in terms of CI molecules expressed and recognized) for the CI phenotype of the other parental population (15). Indeed, this point has been experimentally verified (47). It follows from this, therefore, that, for whatever reason GLT evokes a self-specific anti-αCI response in the nonresponder individual, the state of mutual tolerance in the mixed parental chimeric environment would allow GLT to evoke a comparable response against the CI molecules displayed by the corresponding responder-specific subset reactive to GLT that originates from the responder stem cell pool.

The fact that GLT-specific responder helper T cells capable of interacting with B cells of conventional F_1 donor origin were induced in such chimeras implies the existence of: 1) an F_1-specific subset of T cells originating from the responder parental lymphoid population; and, likewise, 2) a subset of F_1-specific partner B cells (distinct from the subsets corresponding in cooperating specificity to each of the two parental CI types) within the conventional CAF_1 partner B cell population. Moreover, the presence of F_1-specific subsets of T and B cells within the mixed parental chimera explains why such chimeras produced circulating anti-GLT antibodies in situ (not shown) despite the absence of detectable GLT-specific helper T cells of BALB/c-specific cooperating potential. The existence of F_1-specific cooperating helper T cells has been found recently in studies performed by Sproviera et al. (48) and from our own laboratory (30).

Inherent in our thinking about CI molecules and their relationship to the immune response phenotype is the notion that in individual *A* there is heterogeneity among CI_A that we can denote $CI_{A1,\ A2,\ A3—An}$; for each CI_A specificity, there will be corresponding αCI_A receptors, i.e., αCI_{A1}, αCI_{A2}, αCI_{A3}, and so on (15). Moreover, one can further assume that within each CI_A subset are represented a given number of antigenic specificities in terms of distinct antigen-specific receptors. For example, let us assume that in a GLT nonresponder individual *A*, GLT-specific receptors may be affiliated on the same cells that belong to subset CI_{A1}. Anything that prevents the reaction $\alpha CI_{A1} \rightarrow CI_{A1}$ could be manifested as specific unresponsiveness to GLT; for example, something analogous to an anti-αCI_{A1} reaction, as suggested above.

If this is the case, then one might anticipate that after immunization of a nonresponder individual with GLT, which might provoke such an anti-αCI_{A1} response, competence of that individual to mount responses against other antigenic determinants for which specific receptors are also affiliated with subset CI_{A1} might be, at least transiently, compromised. This speculation is very difficult to test experimentally at the moment since the ability to detect such compromised responsiveness is hampered by the fact that a complex antigen, such as KLH, might display many major distinct antigenic determinants, receptors for each one of which could be affiliated with distinct CI_A subsets. Thus, temporary functional silence of subset CI_{A1} as a result of GLT

immunization could indeed compromise the response to one of the major determinants displayed by KLH, but since responses against the other major determinants would not be similarly compromised, one would hardly detect any defect in the response to KLH under these circumstances. The collective results presented in figures 7 and 8 are compatible with this interpretation, since where responses to GLT were absent, there was no compromise noticeable in the ability of such animals to respond to KLH.

Conclusions

The firmness of our grasp in understanding genetic control of lymphocyte recognition and differentiation processes has increased substantially over the past five years. Thus, concepts that were hardly imagined a decade ago concerning the role of the MHC in controlling cell-cell communication and certain aspects of recognition in the immune system have enabled us to view normal cell differentiation and its control with a quite different perspective. From these new perspectives have also developed new ideas in terms of the mechanisms by which immunocompetent cells transact their necessary and usually unmistakable communication processes that, we now know, determine the overall response pattern developed by the individual in both health and disease. It is probable that future studies will broaden our understanding of the genetic basis of self-recognition and cell-cell interactions that depend upon such self-recognition processes. Moreover, we should develop a clearer picture of the mechanisms underlying adaptive differentiation and the boundaries of the plasticity of phenotypic self-recognition. Finally, isolation and characterization of the CI molecules involved in such processes should clarify many ambiguities and questions with respect to the general issue of MHC restrictions. In the broad sense, we might also expect that information obtained in studies such as these will be pertinent to furthering our basic knowledge of cell differentiation, receptor expression, self-recognition, and other developmental processes involved in multicellular organisms.

Acknowledgments. Rebecca Mead, Lucy Gunnill, and Beverly Burgess have provided skilled assistance in the preparation of this manuscript. This is publication 2424 from the Immunology Departments, Research Institute of Scripps Clinic, La Jolla, CA. The author's work was supported by NIH grants AI 13781 and CA 25803, and March of Dimes-Birth Defects Foundation grant 1-540.

REFERENCES

1. Benacerraf, B.: A hypothesis to relate the specificity of T lymphocytes and the activity of I region-specific Ir genes in macrophages and B lymphocytes. J. Immunol. **120:** 1809–1813, 1978.
2. Benacerraf, B., and Katz, D. H.: The nature and function of histocompatibility-linked immune response genes. *In* Immunogenetics and Immunodeficiency, ed. by B. Benacerraf, pp. 117–129, Medical and Technical Publishing Co., Ltd., London, 1975.
3. Benacerraf, B., and McDevitt, H.O.: Histocompatibility-linked immune response genes. Science **175:** 273–275, 1972.
4. Bevan, M. J.: The major histocompatibility complex determines susceptibility to cytotoxic T cells directed against minor histocompatibility antigens. J. Exp. Med. **142:** 1349–1355, 1975.
5. Bevan, M. J.: In a radiation chimera, host H-2 antigens determine immune responsiveness of donor cytotoxic cells. Nature (Lond.) **269:** 417–420, 1977.
6. Billings, P., Burakoff, S. J., Dorf, M. E., and Benacerraf, B.: Genetic control of cytolytic T-lymphocyte responses. II. The role of the host genotype in parental → F_1 radiation chimeras in the control of the specificity of cytolytic T-lymphocytes responses to trinitrophenyl modified syngeneic cells. J. Exp. Med. **148:** 352–356, 1978.
7. Blanden, R. V., Doherty, P. C., Dunlop, M. B. C., Gardner, I. D., and Zinkernagel, R. M.: Genes required for cytotoxicity against virus-infected target cells in *K* and *D* regions of H-2 complex. Nature (Lond.) **254:** 269–274, 1975.
8. Gordon, R. D., Simpson, E., and Samelson, L. E.: *In vitro* cell-mediated immune responses to the male specific (H-Y) antigen in mice. J. Exp. Med. **142:** 1108–1111, 1975.
9. Hedrick, S. M., and Watson, J.: Genetic control of the immune response to collagen. II. Antibody responses produced in fetal liver restored radiation chimeras and thymus reconstituted F_1 hybrid nude mice. J. Exp. Med. **150:** 646–650, 1979.
10. Hodes, R. J., Hathcock, K. S., and Singer, A.: Cellular and genetic control of antibody responses. VII. Absence of detectable suppression maintaining the H-2 restricted recognition of F_1 → parent helper T cells. J. Immunol. **124:** 134–139, 1980.
11. Kappler, J. W., and Marrack, P.: The role of H-2 linked genes in helper T-cell function. IV. Importance of T-cell genotype and host environment in *I*-region and *Ir* gene expression. J. Exp. Med. **148:** 1510–1514, 1978.
12. Katz, D. H.: The allogeneic effect on immune responses. Model for regulatory influences on T lymphocytes on the immune system. Transplant. Rev. **12:** 141–146, 1972.
13. Katz, D. H.: The role of histocompatibility gene complex in lymphocyte differentiation. *In* Proceedings of the First International Symposium on the Immunobiology of Bone Marrow Transplantation. Transplant. Proc. **8:** 305–311, 1976.
14. Katz, D. H.: The role of the histocompatibility gene complex in lymphocyte differentiation. *In* Origins of Lymphocyte Diversity. Cold Spring Harbor Symp. Quant. Biol. **41:** 611–616, 1977.
15. Katz, D. H.: Adaptive differentiation of lymphocytes: Theoretical implications for mechanisms of cell-cell recognition and regulation of immune responses. Adv. Immunol. **29:** 137–149, 1980.
16. Katz, D. H., and Benacerraf, B.: The role of histocompatibility gene products in cooperative cell interactions between T and B lymphocytes. *In* The Immune System: Genes, Receptors, Signals. Proceedings of the 1974 I.C.N.-U.C.L.A. Symposium on Molecular Biology, ed. by E. E. Sercarz, A. R. Williamson, and C. Fred Fox, pp. 569–580, Academic Press, New York, 1974.
17. Katz, D. H., and Benacerraf, B.: The function and interrelationships of T cell receptors, Ir genes and other histocompatibility gene products. Transplant. Rev. **22:** 175–183, 1975.
18. Katz, D. H., and Benacerraf, B.: Genetic control of lymphocyte interactions and differentiation. *In* The Role of Products of the Histocompatibility Gene Complex in Immune Responses, ed. by D. H. Katz and B. Benacerraf, pp. 355–371, Academic Press, New York, 1976.
19. Katz, D. H., Hamaoka, T., and Benacerraf, B.: Cell interactions between histoincompatible T and B lymphocytes. II. Failure of physiologic cooperative interactions between T and B lymphocytes from allogeneic donor strains in humoral response to hapten-protein conjugates. J. Exp. Med. **137:** 1405–1412, 1973.
20. Katz, D. H., Hamaoka, T., Dorf, M. E., and Benacerraf, B.: Cell interactions between histoincompatible T and B lymphocytes. Demonstration that the H-2 gene complex determines successful physiologic lymphocyte interactions. Proc. Natl. Acad. Sci. U.S.A. **70:** 2624–2629, 1973.
21. Katz, D. H., Hamoaka, T., Dorf, M. E., Maurer, P. H., and Benacerraf, B.: Cell interactions between histoincompatible T and B lymphocytes. IV. Involvement of the immune response (Ir) gene in the control of lymphocyte interactions in responses controlled by the gene. J. Exp. Med. **138:** 734–740, 1973.
22. Katz, D. H., Hamaoka, T., Dorf, M. E., and Benacerraf, B.: Cell interactions between histoincompatible T and B lymphocytes. V. Failure of histoincompatible T cells to interfere with physiologic cooperation between T and B lymphocytes. J. Immunol. **112:** 855–863, 1974.
23. Katz, D. H., Graves, M., Dorf, M. E., DiMuzio, H., and Benacerraf, B.: Cell interactions between histoincompatible T and B lymphocytes. VII. Cooperative responses between lymphocytes are controlled by genes in the *I*-region of the *H-2* complex. J. Exp. Med. **141:** 263–269, 1975.
24. Katz, D. H., Chiorazzi, N., McDonald, J., and Katz, L. R.: Cell interactions between histoincompatible T and B lymphocytes. IX. The failure of histoincompatible cells is not due to suppression and cannot be circumvented by carrier-priming T cells with allogeneic macrophages. J. Immunol. **117:** 1853–1858, 1976.
25. Katz, D. H., Skidmore, B. J., Katz, L. R., and Bogowitz, C. A.: Adaptive differentiation of murine lymphocytes. I. Both T and B lymphocytes differentiating in F_1 → parental chimeras manifest preferential cooperative activity for partner lymphocytes derived from the same parental type corresponding to the chimeric host. J. Exp. Med. **148:** 727–732, 1978.

26. KATZ, D. H., KATZ, L. R., BOGOWITZ, C. A., AND SKIDMORE, B. J.: Adaptive differentiation of murine lymphocytes. II. The thymic microenvironment does not restrict the cooperative partner cell preference of helper T cells differentiating in $F_1 \rightarrow F_1$ thymic chimeras. J. Exp. Med. **149:** 1360–1366, 1979.
27. KATZ, D. H., KATZ, L. R., BOGOWITZ, C. A., AND MAURER, P. H.: Adaptive differentiation of murine lymphocytes. IV. (Responder × nonresponder) F_1 cells can be taught to preferentially help nonresponder, rather than responder, B cells. J. Exp. Med. **150:** 20–27, 1979.
28. KATZ, D. H., KATZ, L. R., AND BOGOWITZ, C. A.: Orchestration of partner cell preferences of cooperating T and B lymphocytes derived from primed conventional F_1 mice. J. Immunol. **125:** 1109–1113, 1980.
29. KATZ, D. H., KATZ, L. R., BOGOWITZ, C. A., AND BARGATZE, R. F.: The major influence on helper T cell cooperative partner cell preferences is exerted by the extrathymic environment. J. Immunol. **124:** 1750–1756, 1980.
30. KATZ, D. H., KATZ, L. R., AND BOGOWITZ, C. A.: Cell interaction (CI) molecules on immunocompetent lymphocytes: Development of anti-parent CI receptor reactions in F_1 hybrid mice and evidence for a unique F_1 hybrid subset of interacting cells. J. Exp. Med. **153:** 407–413, 1981.
31. KATZ, D. H., KATZ, L. R., BOGOWITZ, C. A., AND MAURER, P. H.: Plasticity of the immune response phenotype: Evidence that responses against cell interaction molecules may determine the immune response phenotype in a given host environment. J. Immunol. **127:** 1103, 1981.
32. KINDRED, B., AND SHREFFLER, D. C.: H-2 dependence of co-operation between T and B cells *in vitro*. J. Immunol. **109:** 940–945, 1972.
33. KOSZINOWSKI, U., AND ERTL, H.: Lysis mediated by T cells and restricted by H-2 antigen of target cells infected with vaccinia virus. Nature (Lond.) **255:** 552–557, 1975.
34. LENGEROVA, A., MATOUSEK, V., AND ZELENY, V.: Analysis of deficient colony-forming performance of bone marrow cells in non-syngeneic cell milieu—the impact of non-immune interactions on the behaviour of pluripotent stem cells and the role of H-2 gene products. Transplant. Rev. **15:** 89–95, 1973.
35. LONGO, D. L., AND SCHWARTZ, R. H.: Gene complementation. Neither *Ir-Gl* gene need be present in the proliferative T cell to generate an immune response to poly($Glu^{51}Lys^{36}Phe^{9}$)n. J. Exp. Med. **151:** 1452–1458, 1980.
36. MCDEVITT, H. O., DEAK, B. D., SHREFFLER, D. C., KLEIN, J., STIMPFLING, J. H., AND SNELL, G. D.: Genetic control of the immune response. Mapping of the *Ir-1* locus. J. Exp. Med. **135:** 1259–1264, 1972.
37. MILLER, J. F. A. P.: Restrictions imposed on T lymphocyte reactivities by the major histocompatibility complex: Implications for T cell repertoire selection. Immunol. Rev. **42:** 76–82, 1978.
38. ROSENTHAL, A. S.: Determinant selection and macrophage function in genetic control of the immune response. Immunol. Rev. **40:** 136–142, 1978.
39. ROSENTHAL, A. S., AND SHEVACH, E. M.: Function of macrophages in antigen recognition by guinea pig T lymphocytes. I. Requirement for histocompatible macrophages and lymphocytes. J. Exp. Med. **138:** 1194–1200, 1973.
40. SCHMITT-VERHULST, A.-M., AND SHEARER, G. M.: Bifunctional major histocompatibility-linked genetic regulation of cell-mediated lympholysis to trinitrophenyl-modified autologous lymphocytes. J. Exp. Med. **142:** 914–919, 1975.
41. SHARKIS, S. J., CAHILL, R., AHMED, A., JEDRZEJCZAK, W. W., AND SELL, K. W.: Genetic requirements for bone marrow transplantation for stem-cell-defective W/W^{v} mice. Transplant. Proc. **11:** 511–517, 1979.
42. SHEARER, G. M.: Cell-mediated cytotoxicity to trinitrophenyl-modified syngeneic lymphocytes. Eur. J. Immunol. **4:** 527–533, 1974.
43. SHEVACH, E. M., AND ROSENTHAL, A. S.: Function of macrophages in antigen recognition by guinea pig T lymphocytes. II. Role of the macrophage in the regulation of genetic control of the immune response. J. Exp. Med. **138:** 1213–1217, 1973.
44. SINGER, A., HATHCOCK, K. S., AND HODES, R. J.: Cellular and genetic control of antibody responses. V. Helper T-cell recognition of H-2 determinants on accessory cells but not B cells. J. Exp. Med. **149:** 1208–1219, 1979.
45. SPRENT, J.: Restricted helper function of $F_1 \rightarrow$ parent bone marrow chimeras controlled by K-end of H-2 complex. J. Exp. Med. **147:** 1838–1845, 1978.
46. SPRENT, J.: Role of H-2 gene products in the function of T helper cells from normal and chimeric mice measured *in vivo*. Immunol. Rev. **42:** 108–113, 1978.
47. SPRENT, J., AND VON BOEHMER, H.: T-helper function of parent $\rightarrow F_1$ chimeras. Presence of a separate T-cell subgroup able to stimulate allogeneic B cells but not syngeneic B cells. J. Exp. Med. **149:** 387–396, 1979.
48. SPROVIERO, J. F., IMPERIALE, M. J., AND ZAUDERER, M.: Clonal analysis of F_1 hybrid helper T cells restricted to parental or F_1 hybrid major histocompatibility determinants. J. Exp. Med. **152:** 920–928, 1980.
49. VON BOEHMER, H., SPRENT, J., AND NABHOLZ, M.: Tolerance to histocompatibility determinants in tetraparental bone marrow chimeras. J. Exp. Med. **136:** 455–470, 1975.
50. VON BOEHMER, H., HAAS, W., AND JERNE, N. K.: Major histocompatibility complex-linked immune-responsiveness is acquired by lymphocytes of low-responder mice differentiating in thymus of high-responder mice. Proc. Natl. Acad. Sci. U.S.A. **75:** 2439–2448, 1978.
51. WALDMANN, H.: The influence of the major histocompatibility complex on the function of T-helper cells in antibody formation. Immunol. Rev. **42:** 202–213, 1978.
52. WALDMANN, H., POPE, H., BRENT, L., AND BIGHOUSE, K.: Influence of the major histocompatibility complex on lymphocyte interactions in antibody formation. Nature (Lond.) **274:** 166–175, 1978.
53. ZINKERNAGEL, R. M., AND DOHERTY, P. C.: Immunological surveillance against altered self components by sensitised T lymphocytes in lymphocytic choriomeningitis. Nature (Lond.) **251:** 547–561, 1974.