SUPPRESSOR CELLS IN TOLERANCE TO CONTACT SENSITIVITY ACTIVE AGAINST HAPTEN-SYNGENEIC AND HAPTEN-ALLOGENEIC DETERMINANTS

BY HENRY N. CLAMAN, STEPHEN D. MILLER, AND MAN-SUN SY

(From the Departments of Medicine and Microbiology and Immunology, University of Colorado Medical School, Denver, Colorado 80262)

A growing number of immunological responses have been shown to be under genetic control. In general, these responses have been linked to the major histocompatibility complex (MHC), and it appears that it is the gene products of the MHC which are critical for the recognition of self and not-self (1). Such MHC-linked responses include the generation and expression of cytotoxic T lymphocytes directed against viral-infected (2), chemical-modified (3), or closely related (4) syngeneic cells, the antibody response to certain antigens (1), the recognition of antigen on macrophages (5), the collaboration between T and B lymphocytes (6), and the transfer of delayed hypersensitivity (7, 8). A considerable amount of work is being done to define the number and location of the MHC loci responsible for these genetic restrictions.

A new regulatory phenomenon has recently been explored, i.e., that of suppressor cells (9, 10). The exact nature and mode of action of these cells is not known, but they appear to be important in the regulation of antibody and cell-mediated responses.

Following the lead of Asherson and Zembala (11), we have shown that the induction of tolerance to contact sensitivity to 1-fluoro, 2,4-dinitrobenzene (DNFB) by injection of 2,4-dinitrobenzene sulfonate (DNBSO₃) involves the production of antigen-specific T suppressor cells. These cells are capable of adoptively transferring this tolerance to naive syngeneic recipients, which are thereby rendered relatively unresponsive to sensitization by the specific contactant, DNFB, but which are normally sensitized by unrelated contactants (12). There are recent data suggesting that these T suppressors (Ts) carry hapten 2,4-dinitrophenol (DNP) on their surfaces (13). We have also shown that there is another pathway of tolerance in these mice which is longer lasting, also hapten specific, and not transferable by cells which we have called clone inhibition (14).

We have recently investigated the production of tolerance to contact sensitivity by injection of DNP-modified spleen cells (DNP-SC). These experiments also show that the same two pathways of tolerance are involved, that of clone inhibition and of development of TS (15, 16).

We are now exploring the genetic requirements for the generation and expression of suppressors induced by haptenated spleen cells (17). We have shown that there is a
genetic restriction in this model. DNP-syngeneic or DNP-H-2 compatible SC injected into BALB/c mice make those animals tolerant to DNFB and also induce the production of suppressor cells able to transfer tolerance to other BALB/c mice. In contrast, DNP-allogeneic SC injected into BALB/c mice also make those animals tolerant to DNFB but do not induce the production of suppressor cells able to transfer tolerance to other BALB/c mice.

The experiments reported here explore these genetic requirements further and show that DNP-SC can induce hapten-specific suppressors which have MHC-restricted expression or non-MHC-restricted expression, depending on the relation between the strain of origin of (a) the haptenated SC (tolerogen), (b) the animal used to generate suppressors (donor of suppressors), and (c) the recipient of transferred populations containing suppressors. The results show that (a) hapten-SC injected into an allogeneic strain cause the production of suppressor cells which are active only in the strain of origin of the tolerogen (not in the suppressor cell donor strain) but (b) hapten-SC injected into syngeneic mice cause the production of suppressors which are active both in syngeneic and in unrelated allogeneic recipients. The results are discussed in terms of a recent model of T-cell recognition and suppression (18).

Materials and Methods

Mice. BABL/c mice were obtained from Simonsen Labs, Gilroy, Calif. CBA, C3H/HeJ, and DBA/2 mice were obtained from The Jackson Laboratory, Bar Harbor, Maine.

Antigens and Tolerogens. DNB was obtained from Sigma Chemical Company, St. Louis, Mo. Picryl chloride (1-chloro-2,4,6-trinitrobenzene, TNCB) and picryl sulfonic acid were obtained from Matheson, Coleman & Bell, Matheson Scientific, Inc., Rutherford, N. J.

Preparation of Hapten-Modified Lymphoid Cells. Erythrocyte-free spleen cell suspensions were prepared in Hank's balanced salt solution (HBSS) as described previously (15). Spleen cells were dinitrophenylated exactly as previously described (15) and are termed DNP-SC. Spleen cells were trinitrophenylated by incubation with 10 mM picryl sulfonic acid (in HBSS) for 30 min as previously described (15) and are termed TNP-SC.

Induction of Tolerance. Mice were injected intravenously with 5 x 10^7 DNP-SC or trinitrophenol (TNP)-SC in HBSS 7 days before contact sensitization or transfer of tolerance.

Sensitization and Elicitation of Contact Sensitivity. Mice were contact sensitized with DNFB or TNCB and the degree of sensitization determined by an ear thickness assay exactly as previously described (15). The increment in ear thickness is called ear swelling and is expressed in units of 10^-4 inches. Positive controls were sensitized and ear challenged; negative controls were ear challenged only. Percent tolerance was calculated according to the following formula:

\[
\text{Percent tolerance} = \left[ \frac{\text{positive control} - \text{experimental}}{\text{positive control} - \text{negative control}} \right] \times 100
\]

Transfer of Tolerance. Peripheral and mesenteric lymph nodes were collected 7 days after tolerization with 5 x 10^7 DNP- or TNP-modified lymphoid cells. Single cell suspensions were prepared in HBSS and 100 x 10^6 donor lymphocytes were injected intravenously into lightly irradiated (250 R 60Co) recipients. Control mice received either no cells or cells from normal donors. The recipient and control mice were contact sensitized 1-2 h after transfer. The degree of tolerance in recipient mice was expressed as percent tolerance transferred as described above.

Results

Previously, we have shown that mice injected with syngeneic DNP-SC become tolerant to DNFB contact sensitization and can transfer hapten-specific suppression to other naive syngeneic mice. These recipients are thereby prevented from developing full contact sensitivity to DNFB. In contrast, mice injected with
TABLE I
Suppressors Generated by Allogeneic Tolerogen Transfer Suppression Only to Those Allogeneic Mice

| Tolerogen   | Donors of suppressors | Recipients | Ear swelling* | Tolerance transferred |
|-------------|------------------------|------------|---------------|----------------------|
| (H-2 haplotype) | (H-2 haplotype) | (H-2 haplotype) | Strain | Negative | Positive | + Suppressors | % |
| DNP-CBA     | BALB/c (H-2\(^d\)) | CBA (H-2\(^a\)) | 5 ± 1 | 84 ± 2 | 28 ± 2 | 70.9 |
| DNP-CBA     | BALB/c (H-2\(^d\)) | BALB/c (H-2\(^d\)) | 3 ± 1 | 62 ± 3 | 63 ± 2 | 0.0 |
|             | C₅₇B1 (H-2\(^b\))   | C₅₇B1 (H-2\(^b\)) | 14 ± 1 | 89 ± 2 | 81 ± 2 | 10.7 |

* Units of 10⁻⁴ inches ± standard error.

allogeneic DNP-SC also become tolerant to DNFB themselves but cannot transfer suppression to recipients (17). This latter situation is shown in group (B) of Table I. Here, BALB/c mice receiving DNP-CBA SC (and tolerant to DNFB, data not shown) were unable to transfer suppression to BALB/c recipients. On the other hand, group (A) shows that BALB/c mice receiving DNP-CBA SC were able to transfer significant tolerance to CBA recipients, i.e., to the same strain used to prepare haptenated SC as tolerogen. Group (C) shows that such tolerance could not be transferred to C₅₇B1 mice which are MHC incompatible with both the DNP-SC tolerogen and the BALB/c animals in which suppressors were generated.

These results are not surprising. One would expect, in analogy with the development of delayed-type hypersensitivity, that BALB/c mice would develop suppressors directed against the hapten-modified antigens of the CBA tolerogen. When these suppressor cells are transferred into a naive BALB/c mouse (group [B]), and this mouse is sensitized with DNFB, the antigenic complexes created by DNFB painting are DNP-BALB/c, and suppressors directed against DNP-CBA would not be expected to be effective. On the contrary, such suppressors are effective when transferred into CBA recipients (group [A]) as DNFB painting of these mice will create DNP-CBA determinants which are the determinants on the tolerogen used to generate the suppressors. Such suppressors will obviously not be effective in C₅₇B1 mice (group [C]).

We further explored the range of specificity of suppressors generated by syngeneic tolerogen, i.e., by DNP-BALB SC injected into BALB/c animals. We were surprised to find that such animals were able to serve as donors of suppressor cells active in allogeneic recipients, e.g., CBA mice. Group (A) of Table II shows such a transfer of suppression. The failure of transfer from BALB/c donors tolerized with sham-haptenated BALB/c SC (group [B]) shows that the tolerogen must be haptenated. Group [C] again shows the generation of DNP-CBA-specific suppressors in BALB/c mice, able to transfer tolerance to CBA recipients, and group (D) shows that allogeneic effects are not responsible for the transfer of tolerance.
### Table II

**Suppressors Generated By Syngeneic Tolerogen Transfer Suppression into Allogeneic Mice**

| Tolerogen Donors of suppressors | Strain | Ear swelling | Tolerance transferred |
|---------------------------------|--------|--------------|----------------------|
| (H-2 haplotype) (H-2 haplotype) | (H-2 haplotype) | CBA | 45 ± 4 | 56.4 |
| (H-2 haplotype) (H-2 haplotype) (H-2 haplotype) | | CBA | 85 ± 2 | 13.8 |
| (H-2 haplotype) (H-2 haplotype) (H-2 haplotype) | | CBA | 35 ± 3 | 67.0 |
| (H-2 haplotype) (H-2 haplotype) (H-2 haplotype) | | CBA | 89 ± 3 | 9.6 |
| (H-2 haplotype) (H-2 haplotype) (H-2 haplotype) | CBA (positive) | 98 ± 3 | - |
| (H-2 haplotype) (H-2 haplotype) (H-2 haplotype) | CBA (negative) | 4 ± 1 | - |

### Table III

**Suppressors Generated By Tolerogen Compatible Only Within the MHC Transfer Suppression to Allogeneic Mice**

| Tolerogen Donors of suppressors | Strain | Ear swelling | Tolerance transferred |
|---------------------------------|--------|--------------|----------------------|
| DBA/2 (H-2 haplotype) | BALB/c (H-2 haplotype) | DBA/2 (H-2 haplotype) | 6 ± 1 | 61 ± 3 | 15 ± 1 | 83.6 |
| BALB/c (H-2 haplotype) | BALB/c (H-2 haplotype) | BALB/c (H-2 haplotype) | 8 ± 1 | 63 ± 2 | 28 ± 3 | 63.6 |
| CBA (H-2 haplotype) | CBA (H-2 haplotype) | CBA (H-2 haplotype) | 6 ± 1 | 100 ± 2 | 40 ± 2 | 63.8 |

In Table III we explored some of the MHC requirements for the development of suppressors. In this experiment, DNP-DBA/2 SC (H-2 haplotype) were used as tolerogen in BALB/c mice which are also H-2 haplotype but which differ from DBA/2 mice at non-MHC loci. As can be seen, BALB/c mice injected with DNP-DBA/2 SC generate suppressors which are effective in transferring tolerance to DBA/2 recipients, to BALB/c recipients, and to non-H-2 haplotype mice, i.e., CBA recipients.

Our final experiment was to confirm the previous findings and to demonstrate the exquisite hapten sensitivity of the suppressor cells. To do this, BALB/c mice were doubly tolerized with DNP-BALB/c SC (syngeneic) and with TNP-CBA SC (allogeneic). After 1 wk, 10⁸ lymphoid cells were transferred into BALB/c and into CBA recipients which were sensitized with either DNFB or TNCB. Table IV shows that, when the haptenated SC are syngeneic with the animal used to
Simultaneous Generation of Hapten-Specific Suppressors Demonstrating MHC Restriction and Non-MHC-Restriction of Transfer of Suppression

| Tolerogen | Donors of suppressors | Strain | Sensitization of recipients | Ear swelling | Tolerance transferred |
|-----------|-----------------------|--------|-----------------------------|--------------|----------------------|
|           |                       |        |                             |              |                      |
| DNFB      | BALB (H-2^d)          | BALB/c (H-2^d) | DNFB | 4 ± 1 | 93 ± 3 | 52 ± 2 | 46.1 |
|           | CBA (H-2^k)           | CBA    | DNFB | 5 ± 1 | 85 ± 3 | 40 ± 4 | 56.3 |
| TNCB      | BALB (H-2^d)          | BALB/c (H-2^d) | TNCB | 9 ± 2 | 65 ± 2 | 61 ± 2 | 7.1 |
|           | CBA (H-2^k)           | CBA    | TNCB | 11 ± 1 | 60 ± 1 | 31 ± 2 | 59.2 |

generate suppressors (DNP-BALB/c SC into BALB/c donors), then tolerance to that hapten can be transferred into syngeneic recipients (BALB/c, group [A]) and into allogeneic recipients (CBA, group [B]). However, when the haptenated SC are allogeneic with the animal used to generate suppressors (TNP-CBA SC into BALB/c donors), then tolerance to that hapten can be transferred into the strain of the tolerogen (CBA, group [D]) but not into the strain of the donor of suppressors (BALB/c, group [C]). The reasons for this are given in the explanation for the results in Table I.

Discussion

Understanding the regulation of the immune response requires knowledge of the genetic restrictions of such regulation. The contact sensitivity model is highly appropriate because it is simple to induce a hapten-specific, T-cell-mediated hypersensitivity reaction merely by painting DNFB on the skin. The converse of this reaction, a hapten-specific T-cell-mediated tolerance, is induced by injecting the same material, DNFB (or a congener, DNBSO₃). This tolerance involves (in part) the activation of hapten-specific suppressor T cells (12). The ability to generate suppressor cells by injecting hapten-modified spleen cells, instead of free hapten, allowed us to study the genetic requirements for the development of tolerance (15, 17).

Induction of Alloreactive Suppressor Cells. We previously reported that the injection of DNP-syngeneic or DNP-H-2-compatible SC into BALB/c mice made those mice tolerant to DNFB and generated suppressor cells able to transfer such tolerance into normal BALB/c mice. However, the injection of DNP-allogeneic SC into BALB/c mice, although rendering those mice tolerant to DNFB, did not produce suppressor cells active in BALB/c recipients (17).

This report shows that tolerization with DNP-allogeneic SC will generate suppressor cells, which are active only in the strain which provided the tolerogen. For example, BALB/c mice tolerized with CBA DNP-SC will transfer
suppression only to CBA recipients. As explained in the results, this is not a surprising finding. It indicates that BALB/c mice recognize both DNP and CBA determinants on the DNP-CBA SC tolerogen and raise suppressors directed against those antigens. Since painting CBA recipients with DNFB creates DNP-CBA antigens (and not DNP-BALB/c antigens), it is clear why those cells suppress CBA and not BALB/c or third party recipients.

Induction of Synreactive Suppressors Cross Reactive with Allogeneic Recipients. Suppressors generated in a syngeneic or H-2 compatible combination, i.e., DNP-BALB/c SC tolerogen injected into BALB/c donors, will transfer suppression not only to BALB/c mice (as expected) but also to CBA mice, which are H-2 incompatible. In accordance with the above explanation, one would say that BALB/c mice recognize DNP-BALB/c antigens and raise suppressors which are able to suppress the development of contact sensitivity to DNP-CBA antigens, since those are the ones created by painting CBA recipients with DNFB. Before proceeding to a discussion of this finding, we should point out that, while suppressors induced in BALB/c donors by DNP-DBA/2 were effective in transferring tolerance to both BALB/c and to CBA recipients, they were more effective in transferring tolerance into DBA/2 recipients (Table III, group [A]). These results may indicate that, although both DBA/2 and BALB/c are H-2d mice, the fit of suppressors generated against DNP-DBA/2 is better when tested against DBA/2 than against BALB/c. This kind of result suggests that minor degrees of heterogeneity exist between the two strains, but the experiment does not make it possible to decide whether the differences important in this suppressor system exist within or outside of the MHC.

Hypotheses Able to Explain These Results. In attempting to explain these results, we believe that the generation of restricted alloreactive suppressors by injection of, e.g., DNP-CBA SC tolerogen into BALB/c mice, is best explained according to the accepted paradigms of T-cell recognition in delayed hypersensitivity. What requires explanation is how the suppressors produced by DNP-BALB/c SC injected into BALB/c mice (synreactive suppressors) are also able to suppress allogeneic mice. At least three models may be made.

A first possibility is that there is a mouse-specific non-MHC antigen which is present in the haptenated tolerogen and that synreactive suppressors generated against this DNP-mouse antigen in BALB/c mice by DNP-BALB/c SC are effective in suppressing DNFB sensitization in many other strains. One finding appears to contradict this model; namely, the failure of DNP-CBA SC (presumably carrying the DNP-mouse antigen) to produce suppressors in BALB/c mice able to suppress BALB/c recipients. One could fit this finding to the model, however, by postulating that the DNP-CBA determinants are immunodominant over DNP-mouse antigens as DNP-CBA is allogeneic to BALB/c while DNP-mouse antigen would be weakly antigenic. Thus, DNP-mouse antigen would not be very stimulatory to suppressor precursors in allogeneic mice but would be the main stimulus in syngeneic mice, i.e., DNP-BALB/c SC injected into BALB/c animals. A final difficulty with this model is that it would postulate that non-MHC restricted hapten-specific suppressor generation is quite different from hapten-specific sensitization and expression of delayed hypersensitivity where MHC participation has been shown to be crucial (7, 8).

A second explanation (suggested by Dr. Sally Fairchild) is based on the idea
that efficient activation of suppressor precursors requires two low affinity
signals or one high affinity signal. When DNP-CBA SC are injected into BALB/c
mice, precursors able to recognize allogeneic DNP-CBA determinants with high
affinity are efficiently activated to produce suppressors which are specifically
able to suppress DNFB-painted CBA recipients. In contrast, when DNP-BALB/c
SC are injected into BALB/c mice, the recognition of DNP-BALB/c determinants
is weak, but is increased by interactions between Ia products associated with the
DNP-BALB/c determinants (perhaps on BALB/c macrophages) and Ia products
on BALB/c suppressor precursors. This dual recognition will efficiently stimu-
late suppressors for DNP-BALB/c. If DNP is immunodominant, DNP-BALB/c
SC will also have some affinity for suppressor precursors actually programmed
for DNP-allogeneic determinants. In addition, however, there will be increased
affinity between these cells and DNP-BALB/c afforded by the above-mentioned
Ia product recognition and the combined dual recognition will cause the genera-
tion of suppressors able to suppress CBA or other allogeneic mice. This idea
would be strengthened by the determination of Ia on the suppressor cells and is
presently being explored. Although we have no data to refute this hypothesis,
we favor a third explanation which also involves dual receptor recognition.

Recently, Janeway et al. published a hypothesis concerning the nature of the
T-cell receptor (18). We believe that our results support this hypothesis and may
be explained by it. In this hypothesis, the T cell possesses two receptors, each
coded for by V_H genes. Receptor no. 1 recognizes foreign non-MHC antigens.
Receptor no. 2 recognizes self MHC antigens with low affinity, but certain
receptor no. 2 V_H gene products fortuitously cross react with high affinity with
foreign MHC determinants, leading to an apparent high incidence of alloreac-
tive T cells (19). Both recognitions are crucial for the development and expres-
sion of the various immunological reactions mentioned in the introduction. A
similar model has also been outlined by Doherty et al. (20).

We believe that the development and activity of suppressors also requires
dual recognition, and we have tried to outline this schema in Table V. We
indicate that BALB/c mice have suppressor precursor clones which will recog-
nize DNP-self MHC. These are designated α-DNP-A, α-DNP-B, etc. The various
designations indicate that different but related clones of suppressors recognize
hapten and H-2ª self with low affinity. Receptor no. 1 is directed toward DNP.
The self-receptors (no. 2) designated d_1, d_2, etc. react with self with various
degrees of fit. Nevertheless, one of these clones has a receptor no. 2 which
fortuitously cross reacts with a certain allogeneic MHC with high affinity; e.g.,
clone α-DNP-C has a low affinity receptor (d_b) for self but receptor d_b has high
affinity for H-2ª which is the property of CBA cells. In terms of the development
of suppressors in BALB/c mice generated by DNP-CBA-SC and able to suppress
contact sensitization only in CBA recipients, we believe that the DNP-CBA-SC
tolerogen activates suppressors of clone α-DNP-C which have receptor no. 1
directed to DNP determinants (e.g., DNP-0-tyrosyl, etc. [21]) and which have
receptor no. 2 with high affinity for CBA determinants. Therefore, these cells
are highly efficient in suppressing the CBA recipient's response to DNFB. This
clonal also should have low affinity for self MHC determinants but alone is not
sufficient to suppress BALB/c recipients (see below).

The model also explains why DNP-BALB/c SC generate suppressors in BALB/
Table V

| Tolerogen       | Donors | Suppressor precursor clones | Affinity of suppressor receptors for H-2 | Clone activated | DNFB-painted recipients |
|-----------------|--------|-----------------------------|-----------------------------------------|----------------|-------------------------|
| DNP-CBA (H-2<sup>x</sup>) | BALB/c (H-2<sup>y</sup>) | α-DNP-A d<sub>i</sub>, x | Low | BALB/c | DNP-H-2<sup>y</sup> |
|                 |        | α-DNP-B d<sub>i</sub>, y | High | CBA   | DNP-H-2<sup>y</sup> |
|                 |        | α-DNP-C d<sub>i</sub>, k |       | C57Bl/6 | DNP-H-2<sup>y</sup> |
|                 |        | α-DNP-D d<sub>i</sub>, b |       | BALB/c | DNP-H-2<sup>y</sup> |
| DNP-BALB/c (H-2<sup>x</sup>) | BALB/c (H-2<sup>y</sup>) | α-DNP-A d<sub>i</sub>, x | Low | BALB/c | DNP-H-2<sup>y</sup> |
|                 |        | α-DNP-B d<sub>i</sub>, y | High | CBA   | DNP-H-2<sup>y</sup> |
|                 |        | α-DNP-C d<sub>i</sub>, k |       | C57Bl/6 | DNP-H-2<sup>y</sup> |
|                 |        | α-DNP-D d<sub>i</sub>, b |       | BALB/c | DNP-H-2<sup>y</sup> |

---

- Suppression by a library of low-affinity α-DNP-self clones.
- Suppression by a limited number of low-affinity α-DNP-self clones which cross react with high affinity with foreign non-self MHC.
- No suppression.

*The designations α-DNP-A, α-DNP-B, etc., refer to clones of suppressor precursors in BALB/c mice with low affinity for self-MHC antigens and cross reactive with high affinity with allogeneic MHC.

...
share H-2\textsuperscript{a} or H-2\textsuperscript{d} regions with the stimulators (2, 3). This may indicate that the production and effectiveness of suppressors cells in vivo is distinctly different from the activation and expression of cytotoxic cells.

**Summary**

Genetic restrictions in generation and expression of hapten-specific suppressor cells for contact sensitivity were found. Dinitrophenol- (DNP) or trinitrophenol-modified mouse spleen cells (SC) induced suppressors in donors able to transfer suppression to normal recipients.

When allogeneic DNP-SC were injected into BALB/c mice, cells were generated which were suppressive only in the allogeneic strain providing the DNP-SC. In contrast, when DNP-BALB/c-SC were injected into BALB/c mice, suppressors were generated which were active both in BALB/c and in allogeneic mice (e.g., CBA). This apparent absence of syngeneic major histocompatibility complex restriction may be explained by cross reactive T-cell receptors which are V\textsubscript{H} gene products.

We are grateful for the excellent technical assistance of Miss Helen Kowach and the excellent secretarial assistance of Miss Susan Patterson. We thank Doctors Sally Fairchild, J. John Cohen, and John W. Moorhead for helpful discussions of the data and their interpretations.

*Received for publication 28 February 1977.*

**References**

1. Benacerraf, B., and D. H. Katz. 1975. The histocompatibility linked immune response genes. *Adv. Cancer Res.* 21:121.
2. Doherty, P. C., R. V. Blanden, and R. M. Zinkernagel. 1976. Specificity of virus-immune effector T cells for H-2K or H-2D compatible interactions: implications for H-antigen diversity. *Transplant. Rev.* 29:89.
3. Shearer, G. M., T. G. Rehn, and A-M Schmitt-Verhulst. 1976. Role of the murine major histocompatibility complex in the specificity of in vitro T cell-mediated lymphyolysis against chemically modified autologous lymphocytes. *Transplant. Rev.* 29:222.
4. Gordon, R. D., E. Simpson, and L. E. Samuelson. 1975. In vitro cell-mediated immune responses in the male specific (H-Y) antigen in mice. *J. Exp. Med.* 142:1108.
5. Shevach, E. M., and A. S. Rosenthal. 1973. The function of macrophages in antigen recognition by guinea pig T lymphocytes. II. Role of the macrophages in the regulation of genetic control of the immune response. *J. Exp. Med.* 138:1213.
6. Katz, D. H., and B. Benacerraf. 1975. The function and inter-relationships of T-cell receptors, Ir genes, and other histocompatibility gene products. *Transplant. Rev.* 22:175.
7. Miller, J. F. A. P., M. A. Vadas, A. Whitelaw, and J. Gamble. 1975. H-2 gene complex restricts transfer of delayed-type hypersensitivity in mice. *Proc. Natl. Acad. Sci. U.S.A.* 72:5095.
8. Miller, J. F. A. P., M. A. Vadas, A. Whitelaw, and J. Gamble. 1976. Role of major histocompatibility complex gene products in delayed-type hypersensitivity. *Proc. Natl. Acad. Sci. U. S. A.* 73:2486.
9. Gershon, R. K. 1974. T cell control of antibody production. *Contemp. Top. Immunobiol.* 3:1.
10. Pierce, C. W., and J. A. Kapp. 1976. Regulation of immune responses by suppressor T cells. *Contemp. Top. Immunobiol.* 5:91.
11. Asherson, G. L., and M. Zembala. 1976. Suppressor T cells in cell-mediated immunity. *Br. Med. Bull.* 32:158.
12. Phanuphak, P., J. W. Moorhead, and H. N. Claman. 1974. Tolerance and contact sensitivity. III. Transfer of tolerance with "suppressor T cells." *J. Immunol.* 113:1230.
13. Moorhead, J. W., and D. W. Scott. 1977. Tolerance and contact sensitivity to DNFB in mice. VII. Functional demonstration of cell-associated tolerogen in lymph node cell populations containing specific suppressor cells. *Cell. Immunol.* 28:443.
14. Claman, H. N., S. D. Miller, and J. W. Moorhead. 1977. Tolerance—two pathways of negative immunoregulation in contact sensitivity to DNFB. *Cold Spring Harbor Symp. Quant. Biol.* XLI: In press.
15. Miller, S. D., and H. N. Claman. 1976. The induction of hapten-specific T cell tolerance using hapten-modified lymphoid cells. I. Characteristics of tolerance induction. *J. Immunol.* 117:1519.
16. Miller, S. D., M. S. Sy, and H. N. Claman. 1977. The induction of hapten-specific T cell tolerance using hapten-modified lymphoid cells. II. Relative roles of suppressor T cells and clone inhibition in the tolerant state. *Eur. J. Immunol.* In press.
17. Miller, S. D., M. S. Sy, and H. N. Claman. 1977. H-2 restriction of suppressor T-cell induction by hapten-modified lymphoid cells in tolerance to 1-fluoro-2,4-dinitrobenzene contact sensitization. *J. Exp. Med.* 145:1071.
18. Janeway, C. A., Jr., H. Wigzell, and H. Binz. 1976. Two different V_{H} gene products make up the T cell receptors. *Scand. J. Immunol.* 5:993.
19. Wilson, D. B. 1974. Immunologic reactivity to major histocompatibility alloantigens. HAC, effector cells, and the problem of memory. *In Progress in Immunology II.* Brent, L. and J. Holborow, editors. North-Holland Publishing Company. Amsterdam. 2:145.
20. Doherty, P. C., D. Götze, G. Trinchieri, and R. M. Zinkernagel. 1976. Models for recognition of virally modified cells by immune thymus-derived lymphocytes. *Immunogenetics.* 3:517.
21. Janeway, C. A., Jr. 1976. The specificity of T lymphocyte responses to chemically defined antigens. *Transplant. Rev.* 29:164.