Langerhans Cell Function Dictates Induction of Contact Hypersensitivity or Unresponsiveness to DNFB in Syrian Hamsters

J. WAYNE STREILEIN, M.D., AND PAUL R. BERGSTRESSER, M.D.

Department of Cell Biology and Division of Dermatology, Department of Internal Medicine, Southwestern Medical School, Dallas, Texas, U.S.A.

The relationship between distribution and function of Langerhans cells within the epidermis and the capacity of cutaneous surfaces to promote the induction of contact hypersensitivity to DNFB have been examined in inbred Syrian hamsters. In a manner very similar to previous findings in mice, the results indicate that hamster cutaneous surfaces deficient in normally functioning Langerhans cells, naturally (check pouch epithelium) or artificially (after perturbation with ultraviolet light), are inefficient at promoting DNFB sensitization. Instead, DNFB applied to these regions of skin results in the induction of a state of specific unresponsiveness. Viable lymphoid cells from unresponsive hamsters can transfer the unresponsiveness to naive hamsters suggesting that active suppression is at least partly responsible, probably mediated by T lymphocytes.

Langerhans cells, a minor but distinct population of epidermal cells [1], are now regarded as macrophage-equivalents in the skin and have been assigned a functional role in the processing and presentation of exogenous antigen applied to the skin. The evidence in favor of this statement is largely circumstantial, albeit extremely strong: there seems little doubt that even in adult animals, Langerhans cells derive from a precursor stem cell residing within the bone marrow [2,3]. The phenotype of Langerhans cell surface molecules includes Fc and C3b receptors [4] and class II (Ia, D/DR) alloantigens [5,6], and strongly resembles a macrophage-like cell. The capacity of these cells to present antigen to primed T cells (evoking a proliferative response among the latter) and to stimulate mixed lymphocyte-type reactions is strongly corroboratory [7,8]. Studies from this laboratory, conducted chiefily in mice, have determined that cutaneous surfaces, naturally deficient in normal Langerhans cells, or in which the density or function of Langerhans cells is perturbed with ultraviolet light (UVL), fail to promote and sustain the induction of contact hypersensitivity to simple haptens [9]. Specifically, it has been shown that ultraviolet light (UVL) treated murine body wall skin (resulting in a profound reduction in ATPase positive Langerhans cells in the epidermis) does not serve efficiently as a medium through which contact sensitivity can be attained. Similarly, tail skin of C57BL/6 mice, which has a reduced number of Langerhans cells arranged such that the scalea areas are devoid of these dendritic cells, fails to promote the induction of contact hypersensitivity. These findings provide circumstantial evidence in favor of the thesis that Langerhans cells may be the only important cells within the epidermis capable of presenting hapten in an immunogenic form.

A similar line of investigation has now been conducted in Syrian hamsters. This species has recently been shown to display contact hypersensitivity to simple chemicals in a manner similar to mice [10,11]. In addition, it was previously shown that the cheek pouch of hamsters, an immunologically privileged site [12], is relatively deficient in surface Langerhans cells [13]. The availability of this specialized cutaneous tissue (resembling the murine tail in its Langerhans cell constitution) affords an opportunity to re-examine in another species the relationship thought to exist between the density of Langerhans cells within an integumentary surface, and the capacity of that surface to promote contact hypersensitivity. The results of these studies form the basis of this report and further substantiate the claim that normally functioning Langerhans cells within the epidermis are required for optimal induction of contact hypersensitivity. As in the mouse, chemical contactants applied to special hamster cutaneous surfaces induce a state of specific unresponsiveness which is actively maintained by lymphoid cells.

MATERIALS AND METHODS

Animals

Hamsters of the isogenic LSH strain, obtained from our domestic colony, were between 3 and 5 mo of age for these studies. Experimental and control animals were matched for age and sex.

Cheek Pouch Grafts

Excised cheek pouch was grafted heterotopically to prepared beds on the thoracic wall of syngeneic recipients as described previously [14]. Large (25 x 25 mm) grafts were sutured in place with chromic catgut and wrapped in plaster of Paris bandages. Casts were removed at 8 days and the graft sites used for hapten application after 30 days. Control body wall skin grafts of comparable size were prepared by a method previously described [15].

DNFB Sensitization

The immunization protocol for 2,4-dinitro-1-fluorobenzene (DNFB) used in these experiments was identical to that described recently for hamsters [10]. Briefly, two 25 ul applications of 0.5% DNFB in acetone: sweet oil (4:1) were placed on shaved abdominal wall skin of hamsters on days 0 and 1. Comparable applications were placed on intact cheek pouches that were everted for this purpose.

Ear Swelling Response

Ears were challenged (on day 5) with 20 ul of 0.2% DNFB and the amount of swelling measured by a micrometer at 24, 48, and 72 hr as described previously [10]. The maximum difference between experimental and control ears of each animal was used as the measure of specific reactivity. In most instances, peak ear swelling occurred 48 hr after ear painting.

Positive controls consisted of hamsters that were sensitized in the conventional fashion through normal abdominal wall skin. For negative controls, unsensitized hamsters' ears were similarly challenged with DNFB.

Lymphoid Cell Suspensions

In adoptive transfer studies, lymph node, and spleen cell suspensions were prepared as described previously [10]. Cells were adjusted to appropriate final concentration in Hanks' balanced salt solution.
Adoptive Transfer

Unresponsiveness was transferred by the protocol described previously [16]. Briefly, one donor equivalent of pooled lymph node and spleen cells was suspended in a final volume of 0.5 cc and inoculated intravenously into recipients that had received 250R whole body gamma irradiation 24 hr previously. Within the subsequent 2 hr, each recipient was subjected to the conventional sensitization protocol with 2 sequential applications of 0.5% DNFB to shaved abdominal wall skin. Ears were challenged at the usual time thereafter.

Ultraviolet Light Irradiation

Ultraviolet light (UVL) was administered to a 2.5 cm square area of shaved abdominal wall skin with FS-20 fluorescent tubes (Westinghouse, Pittsburgh, PA) as described previously for mice [13]. Exposure parameters were identical except that the time of exposure was increased to 8 min for each day (40 mJ/cm² daily). After the last of 4 consecutive daily exposures, the UVL-exposed abdominal skin was subjected to the conventional sensitizing protocol with DNFB.

Langerhans Cell Identification

Cheek pouch, normal body wall skin sites, and body wall skin following UVL irradiation were assayed for the surface density and morphology of ATPase positive Langerhans cells as described elsewhere [13]. In each specimen 10 randomly chosen interfollicular areas in epidermal whole mounts were counted by light microscopy with a superimposed optical grid, and the surface densities reported as ATPase positive cells per mm² skin. Although UVL depletes Langerhans cell ATPase activity in both hamsters and mice, loss of such activity from the epidermis does not necessarily imply that cell destruction has occurred. Since this issue was not addressed in these studies, we refer to this UVL-induced effect as a loss or depletion of ATPase positive Langerhans cells, as we have claimed previously [9].

RESULTS

Capacity of Hamster Cheek Pouch to Promote Induction of DNFB Contact Hypersensitivity

The hamster cheek pouch is an evable, epidermal sac which extends from the buccal mucosa posteriorly onto the shoulder of the animal. In anesthetized animals, the pouch can be easily everted with aid of a toothed forceps. In light of the experiments to be described, a preliminary study was conducted to determine the density and distribution of Langerhans cells in various LSH hamster cutaneous sites, including the intact cheek pouch. Using the ATPase assay to identify these cells, numbers comparable to those found in other species were found in skin of the back and abdomen (see the Table). Cheek pouch epithelium, however, possessed markedly reduced numbers of Langerhans cells and these cells were distributed in a randomly uneven pattern. As described previously, the dendritic processes of cheek pouch Langerhans cells were somewhat longer than those found in other skin sites [13]. In addition, the cheek pouch possesses no lymphatic drainage. In order to test the capacity of this natural epithelial site with both reduced number of Langerhans cells and an absent lymphatic drainage to promote contact hypersensitivity, the following experiments were conducted. One everted cheek pouch per LSH hamster was held in place with a gauze pad; a solution of 0.5% DNFB (25 μl) was applied to the glistening surface and allowed to air dry. The pouch was then pushed back into its anatomical position. Twenty-four hr later the same pouch was re-everted for a second application. In every instance, an intense inflammatory reaction had developed within the pouch epidermis during this interval and at least one large blister was found at or near the site of the previous application. The second dose of 0.5% DNFB was applied to this inflamed surface, allowed to air dry, and the pouch was returned to the anatomical position. External palpation during the subsequent 2 days revealed a cord-like swelling in the region of the pouch. Four days after the second application of DNFB to intact cheek pouch, the animals' ears were challenged with 20 μl of a 0.2% DNFB solution. The amount of ear swelling, as measured by micrometer, was determined during the subsequent 24, 48, and 72 hr intervals. Results of a typical experiment are presented in Fig 1. Peak specific swelling responses indicative of contact hypersensitivity were usually achieved in positive control animals at the 48 hr reading. The amount of ear swelling elicited in hamsters whose sensitizing regimen of DNFB were applied to the cheek pouch rather than shaved body wall skin was significantly less when compared to positive controls (35%). Thus the hamster cheek pouch is less efficient than normal body wall skin at promoting the induction of contact hypersensitivity. In this regard, the cheek pouch resembles murine tail skin which also supports hypersensitivity induction less well than does murine body wall skin [9].

Cheek Pouch Painting with DNFB Interferes with Subsequent Sensitization through Body Wall Skin

It was previously found that mice that received their first exposure to DNFB through tail skin were rendered unresponsive by that maneuver; that is, when an immunizing regimen of DNFB was applied to shaved body wall skin 2 weeks after initial tail painting, mice failed to develop the anticipated magnitude of ear swelling response [9]. These data were interpreted to mean that DNFB painted initially on the tail somehow perturbs the immune system and establishes a dominant state of specific suppression. Since the hamster cheek pouch has been shown to be devoid of a draining lymphatic network [12], one might expect that DNFB painted thereon would not gain access to the systemic immune system. It was thus of considerable interest to determine whether hamsters that were painted first with DNFB on intact cheek pouch epithelium and found to be poorly responsive to ear challenge with DNFB could be immunized subsequently by painting their abdominal skin with this material. Panels of LSH hamsters received two daily applications of 0.5% DNFB to an intact cheek pouch. Two

---

**Table: Morphology and surface densities of ATPase positive Langerhans cells in LSH hamster epidermis**

<table>
<thead>
<tr>
<th>Site</th>
<th>Morphology</th>
<th>Cells/mm² (Mean ± 1 SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back</td>
<td>Normal</td>
<td>950 ± 210</td>
</tr>
<tr>
<td>Abdomen (UVL treated)</td>
<td>Abnormal</td>
<td>28 ± 30</td>
</tr>
<tr>
<td>Cheek pouch</td>
<td>Normal</td>
<td>140 ± 50</td>
</tr>
</tbody>
</table>


---

**Table: Site of DNFB Application and Ear Challenge With DNFB**

<table>
<thead>
<tr>
<th>Site of DNFB Application</th>
<th>Ear Challenge With DNFB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Skin (Positive Control)</td>
<td>Ear Swelling Response x 10⁻⁴ Inches ± SEM</td>
</tr>
<tr>
<td>Cheek Pouch (9)</td>
<td>(35%)</td>
</tr>
<tr>
<td>None (Control) (4)</td>
<td>0</td>
</tr>
</tbody>
</table>

---

**Fig. 1.** Relative capacities of abdominal skin and cheek pouch epithelium to promote induction of 2,4-dinitro-1-fluorobenzene (DNFB) contact hypersensitivity. LSH hamsters received 2 paintings of 25 ul of 0.5% DNFB, days 0 and 1, on application sites. They were ear challenged on day 5 and ear swelling was measured on days 6, 7, and 8. Negative controls received no skin painting, but were ear challenged. Bars represent mean swelling ± 1 standard error of the mean. (N%) indicates percent of experimental response compared to positive control which is defined as 100%.
weeks later, their abdominal skin was shaved and 2 daily applications of 0.5% DNFB made. Four days later their ears were challenged with 0.2% DNFB as described above. Ear swelling responses of these animals are presented in Fig 2. In 2 different experiments (one of which is summarized in Fig 2) a modest, but significant, diminution in ear swelling was found in the cheek pouch painted animals. Ear swelling responses of 69% (Fig 2) and 61% (data not shown) of the response found in conventionally sensitized positive control animals were seen. While these differences are statistically significant ($p < 0.05$), they are not as impressive as had been achieved following tail skin painting in mice [9]. Moreover, while we were attracted to the idea that reduced responsiveness could be correlated with reduced concentration of Langerhans cells in cheek pouch epidermis, (see the Table) we were mindful of the possibility that a chemical contacant placed on mucous membranes of the oral cavity could be swallowed by the animal, leading to induction of unresponsiveness as originally described in guinea pigs by Chase and Battisto [17]. The next series of experiments was designed to examine this possibility.

**Capacity of Heterotopic Grafts of Hamster Cheek Pouch to Promote Induction of DNFB Contact Hypersensitivity**

The hamster cheek pouch, when excised from its buccal attachments and cleaned of loose areolar tissue, can be grafted easily to heterotopic sites such as the thoracic wall of syngeneic recipients. Large grafts of this type were prepared. When allowed to heal in place for upwards of 30 days, the grafts retain their rugose appearance, consistent with cheek pouch epidermis, and afford an ideal surface for the application of a chemical contacant without fear of the material being swallowed. It has been shown by others that heterotopic cheek pouch grafts such as these retain their quality of immunologic privilege, and presumably lack an effective efferent lymphatic drainage route [14]. Thus, panels of LSH hamsters, bearing syngeneic cheek pouch grafts on their thoracic cages for more than 30 days, received 2 daily applications of 0.5% DNFB to the graft. For control, a panel of LSH hamsters, bearing syngeneic body wall skin grafts for more than 30 days, was similarly painted on the grafts with DNFB. The results of ear challenge of these animals 4 days later are presented in Fig 3. Animals immunized through body wall skin grafts sensitized as well as did the positive control animals sensitized in the conventional manner through intact abdominal skin. By contrast, hamsters whose DNFB applications were made on heterotopic cheek pouch grafts displayed much less intense ear swelling responses—37% of positive control. The reduced responses attained in hamsters painted on heterotopic cheek pouch grafts with immunogenic doses of DNFB identifies the cause as being inherent within the cheek pouch tissue itself. The relative failure of animals painted on intact cheek pouch epithelium to develop optimal contact hypersensitivity is probably not due to postulated ingestion of the contacant.

Moreover, when cheek-pouch grafted and DNFB painted animals were subsequently subjected to the standard DNFB regimen through abdominal body wall skin, they responded quite poorly—virtually no ear swelling was seen (Fig 4). We conclude that the hamster cheek pouch is deficient in the capacity to promote induction of contact hypersensitivity and we suggest that the deficiency relates to the concomitant deficiency of Langerhans cells in this curious buccal structure, although the absence of an afferent lymphatic drainage is also clearly important.

It was not expected that cheek pouch painted hamsters would prove to be unresponsive to DNFB even after a subsequent immunizing regimen. One might have predicted that the lack of a lymphatic drainage of the cheek pouch would have precluded the development of a systemic unresponsive state. The data imply that antigen applied to the cheek pouch may gain access to the systemic circulation, apparently by a nonlymphatic route.
analogous to the systemic (vascular) dissemination of antigen placed in the anterior chamber of the eye—a structure that also lacks demonstrable lymphatic drainage [18].

**Capacity of UVL-Treated Hamster Skin to Promote Induction of Contact Hypersensitivity**

UVL-irradiation in modest doses has a profound effect on murine epidermal Langerhans cells [9]. After irradiation on 4 consecutive days, virtually all ATPase cell-surface activity disappears from the epidermis, and all residual cells appear distorted; these changes persist for more than 1 week. However, by grafting criteria, we know that some Langerhans cells must remain at the site following UVL exposure, even though the surface membrane of these cells is severely perturbed [14]. These perturbations are concordant with the inability of UVL-treated murine skin to promote the induction of contact hypersensitivity. We therefore decided to examine the same issue in hamsters. Preliminary histochemical studies indicated that hamster Langerhans cells are more resistant to UVL or that hamster stratum corneum offers a greater barrier to UVL penetration than that of mice. As the Table indicates, 4 times more UVL irradiation was required to achieve a depletion of ATPase positive cells in hamster skin comparable to that achieved in murine skin. Nonetheless, with a dose of UVL of 8 min duration for 4 consecutive days, hamster skin was depleted significantly of ATPase positive cells. Following UVL treatment, panels of treated hamsters received 2 daily cutaneous applications of DNBFB on UVL treated skin as described above. Four days later their ears were challenged. The results of the ear swelling response in a typical experiment are presented in Fig 5. UVL treated hamster skin is virtually devoid of the capacity to promote induction of DNBFB sensitization. In fact, the ear swelling of these animals was indistinguishable from negative controls. Moreover, when UVL-treated, DNBFB-painted animals were subjected later to the conventional immunizing protocol—DNFB on shaved dorsal body wall skin—they remained profoundly unresponsive (Fig 6). Thus, just as in the mouse, UVL irradiation, a procedure which transiently, but severely depletes the epidermis of ATPase positive Langerhans cells in hamster skin, robs that skin of its capacity to present DNBFB in an immunogenic form. Apparently a “tolerogenic” signal is given instead, and the animals are rendered unresponsive.

**Adoptive Transfer of Unresponsiveness with Lymphoid Cells**

It was previously shown that both contact hypersensitivity and unresponsiveness of DNBFB could be transferred adoptively to naive hamsters with suspensions of viable lymph node and spleen cells [10]. It seemed appropriate to determine whether unresponsiveness, induced by cheek pouch painting and by painting UVL-treated skin with DNBFB, could be similarly transferred. Panels of LSH hamsters received 2 applications of 0.5% DNBFB either on intact cheek pouches or on UVL-treated skin as described before. One week later these animals were sacrificed, their lymph node and spleen cells harvested and one donor equivalent inoculated intravenously into lightly irradiated (250 R), naive syngeneic recipients. Immediately after the transfer, recipients were subjected to the conventional DNBFB sensitization protocol through shaved, abdominal skin. An experimental control panel of animals received pooled lymph node and spleen cells from normal donors prior to DNBFB sensitization. The results are illustrated in Fig 7. Significant suppression of contact hypersensitivity was transferred with cells from both UVL-irradiated and cheek pouch painted donors. However, considering the profound unresponsiveness that characterized UVL-treated animals, the 33% reduction in the response of transfer recipients was unexpectedly modest. None-

---

**Fig 5. Sensitization to 2,4-dinitro-1-fluorobenzene (DNFB) through skin treated with ultraviolet light irradiation. Conventional sensitizing regimen of DNBFB was applied to shaved abdominal wall skin previously exposed to UVL for 8 min x 4 days as described in “Materials and Methods.” Ears were challenged and measured as described in Fig 1.**

**Fig 6. Unresponsiveness follows primary application of 2,4-dinitro-1-fluorobenzene (DNFB) to UVL treated hamster skin. Two weeks after initial painting of UVL treated skin with DNBFB, a second identical regimen of DNBFB was applied to shaved, dorsal body wall skin. Ears were challenged and measured as described in Fig 1.**

**Fig 7. Adoptive transfer of unresponsiveness. Lymph node and spleen cells harvested from hamsters rendered unresponsive by exposure to DNBFB through UVL treated skin and intact cheek pouch epithelium were transferred into lightly irradiated syngeneic recipients. Immediately thereafter, the conventional sensitizing regimen of DNBFB was applied to abdominal wall skin. Ears were challenged and measured as described in Fig 1. Normal Control differs from Positive Control in that the former animals were lightly irradiated and inoculated with normal, syngeneic lymphoid cells, while the latter received no cellular inocula and were unirradiated.**
theless, unresponsiveness achieved in hamsters by these 2 protocols appears to be due to an active process of suppression, as it can be transferred adoptively to naive recipients with living spleen and lymph node cells. Just as in mice, exposure to chemical contactants through cutaneous skin, deficient in Langerhans cells not only fails to induce contact hypersensitivity, but elicits an actively maintained state of specific unresponsiveness.

**DISCUSSION**

The results of the studies described in this report provide additional circumstantial evidence to link the distribution and function of cutaneous Langerhans cells to the induction of contact hypersensitivity to simple chemicals. In hamsters, as in mice, a strongly positive correlation exists between the local concentration of normal Langerhans cells in a cutaneous site and the capacity of that site to promote the induction of contact sensitivity. Whatever the nature of the association, it transcends species barriers.

The studies with the hamster cheek pouch grafted heterotopically to the thoracic wall were of particular interest. It was found that heterotopically grafted cheek pouch epithelium resembles intact cheek pouch epithelium by failing to support contact hypersensitivity induction. This finding rules out the possibility that some unsuspected quality of the anatomic site of the intact cheek pouch could be responsible for its failure to support sensitization. Instead, the responsibility for this failure lies directly with pouch tissue itself. Two possibilities suggest themselves: (a) the cheek pouch lacks a lymphatic drainage and therefore antigen never leaves this site to become immunogenic; (b) insufficient numbers of Langerhans cells are present in cheek pouch to promote the induction of contact hypersensitivity. Since hamsters painted with immunizing doses of DNFB on cheek pouch epithelium were rendered systemically unresponsive, and since their lymphoid cells were capable of transferring this unresponsiveness to naive recipients, we conclude that antigen must leak out of the cheek pouch site, presumably by a blood vascular route. Thus, we can not choose at this time between these alternative hypothesis. A similar study in which tail skin was grafted heterotopically to murine thoracic walls gave comparable results [19]. It is presumed, but certainly unproven, that a "threshold" concentration of normal Langerhans cells is required in order for sensitization to take place through hapten-painted epidermis. We have little idea of the magnitude of the threshold, or why it exists. The fact that murine tail skin and hamster cheek pouch possess small numbers of Langerhans cells in uneven patterns of distribution merely underscores the notion that a "threshold" phenomenon is at work, but does not suggest a mechanism.

ATPase, as a surface marker of Langerhans cells, gives at best only an approximation of their quantitative presence. Our data, and that of others, suggest that the functional state of a Langerhans cells may dictate its capacity to display cell surface ATPase. Certainly, exposure to ultraviolet light erases this surface property transiently, but does not interfere with expression of murine H-2 Ia alloantigens. It is possible, therefore, that our contention, based on ATPase activity, that hamster cheek pouch and murine tail skin epidermal sites are relatively poor in Langerhans cells may be inaccurate, and that ATPase-negative Langerhans cells are nonetheless present. We have preliminary evidence to the contrary, using a monoclonal antibody directed at Ia antigens under fluorescent microscopy (unpublished observations). These data, using an independent criterion, confirm that pouch and tail skin normally contain fewer Langerhans cells than conventional body wall skin.

The observation in 2 different species that skin sites depleted of normal Langerhans cells permits (or promotes) the induction of specific unresponsiveness to externally applied haptenes begs for an explanation. Our attempts to transfer the unresponsiveness adoptively with lymphoid cells met with a modest, but significant measure of success. The protocol employed in hamsters was fashioned after that used fruitfully by Claman et al to transfer unresponsiveness in mice inoculated with hapten-derivatized syngeneic lymphoreticular cells. Their studies permitted the conclusion that in mur unresponsiveness results at least in part from a state of active suppression mediated by T lymphocytes [15]. Although the hamster homologues of murine Thy 1 are only now being identified, it seems reasonable to assume that the unresponsive state in hamsters achieved by painting Langerhans cell-depleted skin with DNFB also results from an active state of specific suppression, presumably mediated by T lymphocytes. We have preliminary evidence in favor of this hypothesis (work in progress). This realization has 2 rather different implications. On the one hand, it suggests that the mechanism of unresponsiveness produced by painting DNFB on Langerhans cell-poor skin is akin to the process initiated by injecting mice with hapten-derivatized cells and with free hapten salts; consequently, the lessons learned from one treatment protocol may apply directly to others. On the other hand, successful adoptive transfer of tolerance in hamsters with living lymphoid cells suggests the presence of a functional subset of T lymphocytes herefore not described in this species. In fact, previous work from this laboratory using in vitro syngeneic skin experiments to find evidence of active suppression directed at hamster alloantigens [20]. In a species in which the maturational state of the thymic system has been brought into question [21], this result has significant ramifications.

Contact hypersensitivity to simple chemicals accounts for significant human morbidity—poison ivy dermatitis being but one example. Understanding the physiologic basis for contact hypersensitivity has implications of wider dimension than alleviation of benign human dermatitis. Many immunologists and dermatologists believe that contact hypersensitivity is an expression of a more fundamental immunologic capability that has evolved to combat as yet poorly identified or understood threats. Contact hypersensitivity may be a T cell-dependent faculty important in ridding infected tissues of viral pathogens. A more provocative notion holds that contact hypersensitivity expresses inadvertently the physiologic process of immune surveillance by which malignant degenerates of normal tissues are identified and destroyed by T lymphocytes before reaching clinical significance. The findings reported in hamsters and the antecedent results from experiments in mice provide strong circumstantial evidence to support the notion that a critical factor in the development of contact hypersensitivity (and its putative physiologic counterpart) is the presence, concentration, and histologic distribution of epidermal Langerhans cells. The consequences of antigen exposure on cutaneous surfaces deficient in these cells may have ramifications beyond simple, specific unresponsiveness and may include persistent, unresolved local virus infections and the emergence of clinically significant malignant neoplasms.

We gratefully acknowledge expert technical assistance of Mr. Kevin Stanney and Ms. Debbie Bate. Careful preparation of the manuscript by Ms. Sara Howard is appreciated.

**REFERENCES**