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Photoimmunology

—Past, Present and Future—

Raymond A. Daynes, Hun-Taeg Chung* and Lee K. Roberts

Departments of Pathology and Medicine, University of Utah Medical Center
Salt Lake City, Utah 84132, USA

ABSTRACT

The experimental exposure of animals to sources of ultraviolet radiation (UVR) which emit their energy primarily in the UVB region (280-320 nm) is known to result in a number of well-described changes in the recipient's immune competence. Two such changes include a depressed capacity to effectively respond immunologically to transplants of syngeneic UVR tumors and a markedly reduced responsiveness to known inducers of delayed-type (DTH) and contact hypersensitivity (CH) reactions. The results of experiments that were designed to elucidate the mechanisms responsible for UVR-induced immunomodulation have implicated: 1) an altered pattern of lymphocyte recirculation, 2) suppressor T cells(Ts), 3) deviations in systemic antigen presenting cell (APC) potential, 4) changes in the production of interleukin-1-like molecules, and 5) the functional inactivation of epidermal Langerhans cells in this process. The exposure of skin to UVR, therefore, causes a number of both local and systemic alterations to the normal host immune system. In spite of this seeming complexity and diversity of responses, our recent studies have established that each of the UVR-mediated changes is probably of equal importance to creating the UVR-induced immunocompromised state.

Normal animals were exposed to low dose UVR radiation on their dorsal surfaces under conditions where a 3.0 cm^2 area of skin was physically protected from the light energy. Contact sensitization of these animals with DNFB, to either the irradiated or protected back skin, resulted in markedly reduced CH responses. This was observed in spite of a normal responsiveness following the skin sensitization to ventral surfaces of the UVR-exposed animals. Systemic treatment of the low dose UVR recipients with the drug indomethacin (1-3 micrograms/day) during the UVR exposures resulted in a complete reversal of the depressions observed following DNFB sensitization to "protected" dorsal skin while the altered responsiveness found in the group exposed to the skin reactive chemical through directly UVR-exposed sites was maintained. These studies implicate the importance of EC as effective APC in the skin and also suggest that some of the systemic influences caused by UVR exposure involve the production of prostaglandins. This concept was further supported by finding that indomethacin treatment was also capable of totally reversing the systemic depressions in CH responsiveness caused by high dose UVR exposure (30 K joules/m^2) of mice. Attempts to analyze the cellular mechanisms responsible established that the spleens of all animals which demonstrated altered CH responses, regardless of whether se-

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*Dr. Chung is currently a visiting Professor from the Department of Microbiology and Immunology, Won Kwang University Medical School, Iri, Korea

nsitization was through a normal or an irradiated skin site, contained suppressor cells. Interestingly, we also found normal levels of T effector cells in the peripheral lymph nodes of the UVR-exposed mice that were contact sensitized through normal skin. No effector cells were found when skin sensitizetion took place through irradiated skin sites.

In spite of such an apparent paradox, insight into the probable mechanisms responsible for these observations was provided by establishing that UVR exposure of skin results in a striking and dose-dependent blockade of the efferent lymphatic vessels in all peripheral lymph nodes. Therefore, the afferent phases of immune responses can apparently take place normally in UVR exposed animals when antigen is applied to normal skin. The final effector responses, however, appear to be inhibited in the UVR-exposed animals by an apparent block of effector cell mobility. This contrasts with findings in the normal animals. Following contact sensitization, normal animals were also found to simultaneously contain both antigen specific suppr essor T cells and lymph node effector cells. However, these normal animals were fully capable of mobilizing their effector cells into the systemic circulation, thereby allowing a localization of these cells to peripheral sites of antigen challenge.

Our results suggest that UVR is probably not a significant inducer of suppressor T-cell activity to topically applied antigens. Rather, UVR exposure appears to modify the normal relationship which exists between effector and regulatory immune responses *in vivo*. It does so by either causing a direct reduction in the skin's APC function, a situation which results in an absence of effector cell generation to antigens applied to UVR-exposed skin sites, inhibiting the capacity of effector cells to gain access to skin sites of antigen challenge or by sequestering the lymphocytes with effector cell potential into the draining peripheral lymph nodes. Each of these situations result in a similar effect on the UVR-exposed host, that being a reduced capacity to elicit a CH response. We hypothesize that altered DTH responses, altered alloresponses, and altered graft-versus-host responses, all of which have been observed in UVR exposed animals, may result from similar mechanisms.

INTRODUCTION

There is an extensive literature which describes the biologic changes that result from the exposure of experimental animals and man to the effects of ultraviolet radiation (UVR). Many of the reported studies have focused on UVR-induced alterations of an exposed host's immune system, definable changes which have led to the genesis of the term "photoimmunology" to describe this area of investigation. The field of photoimmunology is proving to represent a correlative scientific discipline that interrelates many areas of investigation including dermatology, immunology, photobiology and physiology. The goals of investigators in the field of photoimmunology are to gain an appreciation of the biologic consequences of UVR exposure on the host's immune system in hopes of providing a clinically valid prediction of the potential benefits and/or detrimental effects that are associated with the continued exposure of skin to solar or artificially derived sources of UVR. Such information is important for a variety of reasons. These include both the probability that many biologic life forms on our planet may eventually be faced with increasing doses of UVR due to a reduction in the fidelity of the protective ozone layer, and the recent interest by many individuals to maintain a year-round tan through the use of artificial sources of UVR.

The major objectives of this review will be to consolidate many of the observations that have been reported in the field of photoimmunology during the past few years. Many of the local and systemic changes that take place following the UVR-exposure of skin will be described as they relate to changes in immunologic, histologic, pathologic and physiolo-

gic processes. Our goal is to develop the hypothesis that many of the immunologic consequences which follow acute or chronic UVR-exposure actually reflect the body's mobilization of a number of normal host defense mechanisms in response to the inflammatory effects of this physical agent. A large body of recently acquired expecimental evidence will be presented to support this general hypothesis. While our results do not support the concept that UVR-mediated effects on immune function are unique, they do demonstrate the fact that the biologic changes which manifest following skin exposure to this physical agent are quite diverse. The immunomodulatory influences of UVR, therefore, appear to result from its capacity to affect a large number of interrelated biologic systems.

Immunobiology of Experimental UVR Carcinogenesis

UVR is a known carcinogen for the induction of skin tumors in both experimental animals and in man (Blum 1959; Fears, Scotto, and Schneiderman 1977 ; Tanenbaum et al. 1976). In addition to its carcinogenic properties, UVR can also function as a co-carcinogenic promoting agent and an immunologic modulator (Epstein and Epstein 1967; Elmets and Bergstresser 1982). It must be appreciated that associated with the transformation event are the immunomodulatory effects of UVR that have a direct influence on the emergence and progression of skin neoplasia (Eisher and Kripke 1982; Roberts and Daynes 1980). Historically, it was the discovery that subcarcinogenic doses of UVR induce an immunologic state of UVR tumor susceptibility in syngeneic mice, which in fact suggested that UVR was an immunomodulatory agent (Daynes et al. 1977 ; Kripke and Fisher 1976). It is the tumor-permitting immunomodulatory potential of UVR that distinguishes it from other carcinogenic agents.

UVR-induced tumors, like most experimetally ihduced tumors (e. g., chemically and virally induced), express tumor-associated antigens (TAA) that can elicit specific immune responses in their syngeneic host (Roberts, Lynch, and Dayne 1982; Pellis and Kahan 1976; Leffell and Coggin 1777; Rogers and Galetto 1985). For example, a state of tumor-specific immunity is induced in mice that are immunized with syngeneic UVR-induced tumors (either fragments or cell lines maintained *in vitro*) (Daynes et al. 1977; Roberts, Lynch, and Daynes 1982; Kripke 1982; Spellman and Daynes 1978; Roberts, Spellman, and Daynes 1980). This implies that the major rejection response elicited in tumor-immunized hosts are directed toward unique tumor specific transplantation antigens (TSTA). In addition, experiments employing hyperimmunized animals have established that common tumor-associated transplantation antigens(TATA) are also shared by different UVR tumors (Roberts, Lynch and Daynes 1982; Spellman and Daynes 1978; Roberts, Spellman, and Daynes 1980). Thus, it would appear that any given UVR tumor expresses both unique and common TAA that are capable of becoming involved in the host immune response to varying degrees. The immune response elicited by these TAA dictates whether the tumor is rejected or allowed to grow.

Aside from a few reports, very little is known about the biochemical nature of the TAA expressed by UVR tumors. Employing tumor-reactive monoclonal antibodies, DeWitt has identified a membrane-bound TAA that appears to have a molecular weight of 200-300 KD (Daynes et al. 1985). Although the exact biochemical nature of these antigens is not understood, preliminary data suggests that one of these monoclonal antibodies recognizes a glycolipid moiety (DeWitt, personal communication). Fortner, et al. (1982), have reported that UVR tumors express a virally encoded gp 70 antigen on their cell surface. Similarly, DeLuca, et al., have reported that cross-reactive antibodies in the serum of UVR tumor-immune mice have specificity for murine leukemia viral products (DeLuca, Kripke, and Ma-

rchalonis 1979). Beeson, et al., have demonstrated the presence of oncofetal antigens on UVR and chemically induced tumors that are also expressed on placental and fetal tissues (Beeson, Scott, and Daynes 1983). These particular viral-associated or oncofetal antigens could very easily function as cross-reactive TAA. Finally, Ristau, et al. (1980), have reported that UVR tumors express a cross-reactive TAA that appears to be a 200KD glycoprotein. Although these studies have begun to identify some of the common TAA that are expressed by UVR tumors, the exact biochemical nature and immunogenic properties of individual TAA are currently unknown.

Unlike the tumors that are experimantally induced by chemical carcinogens, a majority of the UVR-induced tumors are rejected when transplanted into normal syngeneic hosts (Daynes et al. 1977; Kripke 1974; Roberts, Bernhard, and Daynes 1984). These UVR-induced regressor-type tumors will grow, howver, when implanted into immunologically compromised hosts or syngeneic animals that have been exposed to subcarcinogenic doses of UVR (Daynes et al. 1977; Kripke and Fisher 1976; Kripke 1974). Thus, it would appear that the predominant immune response elicited by UVR tumors, when implanted into normal syngeneic animals, leads to their rejection. A number of mechanisms have been investigated to determine how UVR tumors are able to escape the immune surveillance capability of their host.

Tumor rejection or progression is a dynamic process involving complex interactions between the tumor and its host. Conditions that allow for tumor progression are related to the inabillty of the host to mount an effective immune response, as well as the capacity of the tumor to modulate its tumorigenic potential in response to immunologic pressures. A number of studies have been designed to investigate the ability of UVR tumors to modulate their tumorigenic potential. Schreiber and coworkers have analyzed immune responses elicited by the TSTA expressed on a UVR regressor tumor and a number of epitope loss variants derived from that tumor (Wortzel et al. 1983 ; Wortzel, Urban, and Schreiber 1984). Through the use of cloned tumor-specific cytotoxic T-cell (Tc-cell) lines, these investigators have provided compelling evidence that a number of TSTA epitopes are expressed by a single UVR tumor. Fqrthermore, the loss of specific TSTA epitopes by various tumor variants derived from the original tumor was found to be associated with the acquisition of a progressor phenotype, i.e., the capacity to grow when implanted into normal syngeneic recipients. Thus, the loss of an immunodominant epitope(s) on a UVR-induced regressor tumor may represent a possible mechanism that allows for its progression. In this regard, tumorigenic heterogeneity of UVR tumors was observed by Schmitt, et al., who isolated clones from a UVR regressor tumor that was capable of progressive growth when transplanted into normal regressor clone could be converted from a regressor-type tumor to one capable of progressive growth in normal recipients subsequent to culture with normal lymphoid cells *in vitro*, or following passage through immunologically compromised hosts (Schmitt et al. 1983). These investigators also provided suggestive evidence that the regressor to progressor conversion process correlated with a somatic cell hybridization between cells of the tumor and those of host origin. This is not a unique concept, since in other tumor systems it has been shown that somatic cell hybridization correlates with incressed metastatic potental of the tumor (Kerbel et al. 1983; Larizza, Schmirrmacher, and Pfluger 1984). Although these studies would suggest a UVR tumor is capable of modulating its tumorigenic potential in response to the host immunologic pressures, it was necessary to confirm that UVR tumors were clonal in nature and not derived from the progressive growth of both progressor and regressor clones arising from multiple transformants with the tumor mass. To investigate this possibility, Burnham, et al., employed the tool of x-chromosome inactivetion mosaicism

with the x-linked enzyme phosphoglycerate kinase 1 (PGK-1) to evaluate the clonality of UVR-induced tumors. Out of 13 primary UVR tumors that were induced in (C3H×C3H. PGK-1^a) F_1 heterozygote female mice which phenotype as PGK-$1^{a/b}$, all were found to express only a single PGK-1 enzyme form(Burnham, Gahring, and Daynes 1986). Based on this finding, it was concluded that the majority of UVR-induced tumors are monoclonal in origin and result from the progression of a single transformed cell. These experiments also suggest that the heterogeneity observed within a single tumor with regard to its tumorigenic potential must arise from events taking place subsequent to the original transformation process.

Although the ability to modulate TSTA epitopes and a certain level of tumorigenic heterogeneity within UVR regressor tumors indicates that these tumors may escape immunol logic rejection through their ability to modulate their growth characteristics in an immunologically comperent host, the exact mechanism of how these tumors are capable of emerging are progressing within their autochthonous host is unclear. It is intriguing that UVR regressor tumors are rejected when transplanted into normal syngeneic recipients, but are capable of progressive growth in the antochthonous host as well as syngeneic animals that have been exposed to subcarcinogenic doses of UVR, especially since UVR-exposed animals appear to possess virtually normal immunologic competency (Spellman, Woodward, and Daynes 1977; Norbury, Kripke, and Budmen 1977; Kripke et al. 1977). This sugests that UVR regressor tumors employ an escape mechanism (s) to evade the immunologic rejection response of their host. Transplantation studies have shown that the progressive growth of UVR regressor tumors is, in certain ceses, dependent on a population of UVR- induced suppressor T-cells (Ts-cells) (Spellman and Daynes 1978).

In contrast to the Ts-cells that arise in response to the TSTA expressed by progressor-type tumors (both UVR and chemically induced), the UVR-induced Ts-cell population possesses functional antigenic specificity for a common TAA that appears to be expressed by virtually all UVR tumors and some chemically induced tumors (Roberts, Lynch, and Daynes 1982; Spellman and Daynes 1978; Roberts and Daynes 1986). Because this population of Ts-cells arises prior to the appearance of overt tumors, it would appear that these Ts-cells dictate the emergence and progression of these neoplasia. The functional characteristics of this Ts-cell population, as well as the process for their induction, have been the subject of recenet investigations.

It has been shown that the regulation of immune responses to a number of complex multideterminant antigens is mediated through the recognition of distinct immunoregulatory epitopes (Yowell et al. 1979; Hashim et al. 1976). We have hypothesizd that the immune response to UVR tumors may be viewed in a similar context, since epitopes associated with the various types of tumor antigens could function as either strong tumor rejection epitopes or weak immunoregulatory determinants (Roberts and Daynes 1980; Roberts, Lynch and Daynes 1982; Roberts, Spellman, and Daynes 1980). Thus, the UVR-induced Ts-cell population would function through an associative recognition mechanism. Through its ability to recognize common TAA expressed by virtually all UVR tumors, it would inhibit the development of immune rejection responses elicited by the stronger TSTA and other comon TA TA. This hypothesis implies that the UVR-induced Ts-cell population is homogeneous, i. e., consists of a single clone or limited number of clones of Ts-cells that are restriced in their ability to recognize a common TAA epitope. This has been confirmed by recent studies employing a number of interleukin-2 dependent Ts-cell lines derived from animals that have been exposed to subcarcinogenic doses of UVR (Roberts, Spellman, and Warner 1983; Roberts 1986). In these studies, it was shown that both the parental and cloned Ts-cell lines were capable of rendering normal

syngeneic hosts susceptible to the growth of a battery of UVR regresor tumors. *In vitro*, these cloned Ts-cell lines appear to mediate their effect by inhibiting the differentiation of Tc-cells from the draining lymph node (DLN) cell populations obtained from tumor-immune mice. Thus, this Ts-cell population, through its ability to recognize these common TAA, would provide an immunologic environment which would allow for the emergence and progression of virtually any neoplastic cell which expresses these antigenic determinants, regardless of their expression of other stronger tumor rejection antigens.

Although the exact mechanism for the induction of the UVR-induced Ts-cell population is unknown, previous studjes suggested that neoantigens, which are cross-reactive with TAA, are expressed in the skin of UVR-exposed mice (Palaszynski and Kripke 1983; Spellman and Daynes 1984; Sielstad et al. 1985). Palaszynski and Kripke demonstrated that normal syngeneic mice were rendered susceptible to the growth of UVR regressor tumors when grafted with large pieces (5×2.5 cm) of skin from UVR-treated donors (Palaszynski and Kripke 1983). In contrast, Spellman and Daynes (1984) found that animals grafted with smaller pieces (1 cm diameter) of UVR-exposed skin were effectively immunized against a transplantable UVR tumor. In both studies, normal skin grafts failed to produce any detectable immunologic alterations. We have recently detected TAA cross-recative antigens in cellular extracts from UVR-exposed epidermal cells employing TAA-specific monoclonal antibodies in an enzyme-linked immunosorbent assay (Sielsted et al. 1985). Collectively, these studies strongly support the contention that UVR induces TAA cross-reactive antigens in the skin before the recognized emergence of neoplasia. It is conceivable that these skin-associated TAA are responsible for eliciting the Ts-cell response that is observed in animals that are exposed to subcarcinogenic doses of UVR.

We have recently conducted a series of experiments to further define the immunogenicity of the cross-reactive TAA that are expressed in the skin of UVR-exposed mice (Hong and Roberts 1986). A combined protocol of *in vivo* immunization and *in vitro* culture of DLN cells was employed for the analysis of TAA-specific Tc-cells. For these studies, mice were first immunized by injecting their footpads with viable tumor cells or skin cells. After 8-10 days, the DLN were removed from these animals, and the cells were suspended in tissue culture. After 4 days of tissue culture, the DLN cells were harvested and the Tc-cell activity was analyzed in a cell-mediated cytotoxicity assay. The results of these studies are summarized as follows. First, it was determined that Tc-cells capable of lysing cross-reactive tumors differentiate from the DLN of UVR tumor and UVR skin-immune, but not normal skin-immune mice. Second, these Tc-cells are capable of lysing a range of tumor targets, including syngeneic and allogeneic UVR tumors and syngeneic methylcholanthrene-induced tumors. However, these cells did not lyse Con A activated syngeneic lymphoblasts, thioglycolate-induced peritoneal exudate cells, or YAC 1 lymphoma cells, which are sensitive targets for the lysis by natural killer cells. Third, cold cell inhibition experiments demonstrated that these Tc-cells recognize common cross-reactive TAA. Finally, the expression of these cross-reactive TAA in the skin of UVR-exposed mice appears to be the direct effect of UVR exposure, since the only cells that were effective in immunizing syngeneic mice against TAA were those that were obtained from skin that was directly exposed to the effects of UVR. These studies were further expanded to characterize the immunogenic potential of the cross-reactive UVR tumor and UVR skin-expressed TAA. In these experiments, cellular extracts (obtained by CHAPS detergent) from UVR tumors and epidermal cells of either UVR-exposed or normal mice were incorporated into liposomes for the immunization of normal syngeneic animals. The lytic activity of 4 day cultured DLN cells from these immunized animals was compared

with the DLN cells derived from mice immunized with either whole cells or nonincorporated soluble cell extracts. The results of these experiments indicated that the cross-reactive TAA expressed by UVR epidermal or UVR tumor cells can elicit a Tc-cell response when incorporated into liposomes and used to immunize normal syngeneic animals. Although the levels of lytic activity were different, similar results were obtained when whole cells were used for immunizatipn. In this study, normal epidermal cells did not display any appreciable level of TAA expression. Interestingly, soluble cell extracts alone were incapable of eliciting a Tc-cell response in the DLN of immunized mice. Therefore, *in vivo* experiments were conducted to identify the difference in the immunogenic potential of whole cells, liposome-inocrporated TAA, and soluble cell extracts for the ihduction of TAA-specific Tc -cells. The results of these experiments suggested that presentation of the antigens on a membrane surface is required to elicit an effective immune response, while presentation of soluble antigen alone may induce tolerance. In the first part of this study, groups of mice were immunized repeatedly with viable epidermal cells obtained from UVR-exposed or normal syngeneic donors. These immunized animals were then challenged with a UVR progressor tumor that was capable of progressive growth in untreated normal hosts, as well as those animals that were immunized with normal epidermal cells. However, mice immunized with UVR skin cells rejected the UVR tumor implants. In a second series of experiments, groups of mice received intravenous injection of soluble epidermal cell extract obtained from UVR-exposed or normal syngeneic donors. These animals ware then challenged with a UVR regressor tumor. This tumor grew progressively in UVR-treated hosts and was retained for an extended period of time in recipients of soluble UVR skin cell extract. The tumor was rejected at a similar rate by normal mice and recipients of soluble normal skin cell extracts. From these studies, we have concluded that, similar to what was observed *in vitro*, cross-reactive UVR skin expressed TAA that was capable of eliciting an *in vivo* immune response. When presented to their host in a soluble form, these antigens elicit a UVR tumor rejection response. When presented to their host in a soluble from, these antigens elicit a UVR tumor tolerance reaction. This supports the possibility that by shedding a soluble cross-reactive TAA, UVR-exposed skin cells may elicit the TAA-specific Tc-cells that arise in UVR-treated mice before the appearance of any overt neoplasia.

In conclusion, the UVR-induced Ts-cell population appears to arise in response to neoantigens in the skin of UVR exposed animals. These Ts-cells, by an unknown mechanism suppress the ability of their host to mount an effective immune rejection response to emerging neoplasia. As a result, highly immunogenic tumors can emerge and progress to the death of the host that would have otherwise been eliminated had the individual possessed its normal immunologic potential. We have hypothesized that this particular immunoregulatory network may have arisen as a mechanism to protect the host during repair of UVR-damaged skin, i. e., through an immunosuppressive mechanism, mediated by antigen-specific Ts-cells, damaged skin can undergo repair processes without the elicitation of an autoimmune type response. Through the ability of emerging neoplasia to express a common TAA that is also expressed by UVR-damaged skin cells, they are able to use this particular Ts-cell population as an immune surveillance escape mechanism. Although not necessarily the sole mechanism for providing the growth of UVR-induced tumors, this particular Ts-cell population does appear to be responsible for the progression of a majority of UVR-induced neoplasia.

The Effects of UVR Exposure on the Skin and its Associated Lymphoid Tissue

It is now appreciated that many types of specialized immune responses are initiated

whose effector responses are primarily restricted to specific anatomic compartments within the body. For example, those immune responses which are associated with the gut-associated lymphoid tissue (GALT) and the bronchial-associated lymphoid tissue (BALT) represent two well-described examples of immunologic responses whose effector arms are anatomically compartmentalized. This anatomic restriction to both the afferent and efferent mechanisms in GALT- and BALT-associated immune responses provides for a means to achieve a marked enhancement to the protective capabilities of these systems (Guy-Grand, Griscelli,and Vassalli 1974; Bienenstoco, Johnson and Perey 1979).

It has been proposed that an immunologic circuit exists which is dedicated exclusively to the immune surveillance and protection of the skin (Streilein 1978). This specialized circuit has been given the acronym SALT for Skin-Associated Lymphoid Tissue. The evidence to support the existence of such a specialized system is somewhat indirect, and includes the observed epidermotropism for some subsets of normal and rtansformed lymphocytes, a demonstration of the antigen presentation capabilities of certain epidermal cell subsets, and a demonstration that antigen recognition and responsiveness of lymphocytes can occur exclusively in the skin. In addition, this concept is supported by the knowledge that the integrating and regulatory elements capable of controlling certain types of immune responses can be found, both in the skin itself, as well as in the draining peripheral lymph nodes (Streilein 1985). It is quite probable that UVR-induced skin damage can mediate a pronounced alteration to the fidelity of the SALT system.

The elegant experiments performed by Macher and Chase (1969) established that cells and/or soluble factors derived from hapten sensitized skin were required in the development of a contact hypersensitivity (CH) response. This work was followed by the finding, greater than 10 years later, that the majority of antigen presenting cell (APC) capacity of normal skin resides with the epidermal Langerhans cell (LC) (Stingl et al. 1978). Furthermore, the exposure of experimental animals (Toews, Bergstresser, and Streilein 1980) or man (Cooper et al. 1985) to low doses of UVR in the UVB range (280-320 nm) was found to markedly reduce the number and functional properties of LC in the exposed skin, with a parallel depression in the capacity of these individuals to elicit a CH response to skin rective chemicals applied directly to the UVR-exposed skin sites (Toews, Bergstresser,and Streilein 1980). Interestingly, the exposure of animals to high doses of UVR (>10 KJ/m^2) causes a systemic depression in their ability to elicit a CH response, a condition which dose not correlate with a reduction in LC presence or function at the non-UVR-exposed sites of hapten application (Noonan, DeFabo, and Kripke 1981; Lynch, Gurish, and Daynes 1983). These two phenomena, local and systemic suppression of CH responses, have been the object of intense investigative effort over the past few years. In a later section of this review we will describe the results of recent experiments which implicate the formation of arachidonic acid metabolites in the mechanism (s) responsible for these changes in immune function.

Greene, et al. (1979), demonstrated that the UVR exposure of animals results in a decrease in their splenic APC potential. They concluded that this UVR-induced APC reduction was ultimately responsible for many of the immunomodulatory influences of UVR, including the acquisition of tumor susceptibility, the observed depressions in humoral and cellular immune responses, and the reduced capacity of UVR-exposed animals to elicit CH responses. Subsequent investigations by Gurish, Lynch, and Daynes (1982), established that the UVR-induced reduction in splenic APC function was paralleled by a marked increase in the APC activity within peripheral lymph nodes which drain the skin sites of UVR exposure. The results of these experiments sugge-

sted that the reported changes in APC function following UVR exposure actually reflect a redistribution of APC from central to peripheral lymphoid compartments. This was further supported by the finding that splenectomized UVR-exposed animals did not demonstrate an incerease in their peripheral lymph node APC activity. Investigations by Lynch, Gurish and Daynes (1983), in mice and Cooper, et al. (1985), in humans established that Ia-positive cells with APC activity regain access to the epidermis by 3 days following an acute UVR exposure. These cells may not be LC since the results with humans indicate that the epidermis infiltrating cells are DR-positive and T6 negative. Collectively, the results of these experiments indicate that Ia-positive cells with APC function are highly mobile *in vivo*. Under normal conditions, the cell types having this functional and surface phenotype are distributed among a number of distinct anatomic compartments. These include the peripheral blood, spleen, lymph nodes, skin, as well as other tissue sites. Exogenous stimulation of an animal with an inflammatory agent (i. e., UVR) results in: a) a functional inhibition of any directly UVR-exposed immunocompetent cells, and b) a marked anatomic redistribution of the cells with APC potential, with enhanced numbers going to the tissue sites of inflammatory insult. This is manifest by increased numbers of APC entering the skin, and eventually localizing to draining peripheral lymph nodes following their entrance via the afferent lymphatic vessels. This hypothesis is fully consistent with the recent findings of Hendricks and Eestermans(1983) who have analyzed the recirculation patterns of rat macrophages *in vivo* and conclued that their entry into peripheral lymph nodes is predominantly through afferent lymphatic drainage.

Studies performed by Spangrude, et al.(1983), have established that the exposure of normal mice to UVR results in a marked change the lymphoid tissue localization properties of recirculatinglymphocytes. This is reflected experimentally by a significant increase in the percentage of intravenously injected radiolabeled lymphocytes recovered from the draining peripheral lymph nodes of UVR-exposed animals. This UVR-induced alteration in lymphocyte localization patterns is quite protracted and persists for greater than 6 weeks following the cessation of UVR exposure. Recent experimental evidence has now provided us with an appreciation of the mechanisms that are responsible for this effect. Immunohistologic staining of peripheral lymph node sections with the monoclonal antibody MECA-325, which is specific for high endothelial venules(HEV), revealed that the HEV content of lymph nodes from UVR-exposed donors is far greater than the HEV content of a similar lymph node from a normal animal(Samlowski and Daynes, unpublished). Since the quantity of HEV in a lymph node dictates the rate of lymphocyte entry into the tissue, an enhancement of HEV expression would result in an increase in lymphocyte localization potential. This is due to the fact that HEV contain the lymphocyte recognition structures which are essential for the entrance of lymphocytes into various types of lymphoid and nonlymphoid tissues(Gallatin, Weissman, and Butcher 1983). Specific lymphocyte-HEV interactions have also been proposed to control the distribution of lymphocytes between peripheral, mucosal, and central lymphoid organs(Butcher 1983).

It is now appreciated that the integrity of peripheral lymph node HEV(both the presence and the magnitude) is controlled by humoral or cellular factors which drain into the nodes via the afferent lymphatics. This conclusion was based on the results of studies which established that severing of the afferent lymphatic vessels resulted in a disappearance of HEV structures in the draining lymph nodes(Hendriks and Eestermans 1983). This reduction in HEV expression was followed by a markedly decreased rate of lymphocyte entry into these manipulated nodes from the blood. Such experiments suggest that the skin actually functions as a transducer, in someway

converting exogenous inflammatory stimuli into humoral and/or cellular signals which have an influence on the presence and extent of vascular endothelium which can function as lymphocyte receptive HEV.

There are a couple of obvious candidates which can be considered important in the transmission of HEV regulating signals from the skin to the lymph nodes. These include the highly mobile macrophages and APC or their products, as well as soluble mediators produced directly by cells within the skin in response to an exogenous stimulation. Recent evidence from our laboratory emphasizes each of these factors in the regulation of the lymphocyte content of a preipheral lymph node. We now appreciate that subsequent to the treatment of animals with agents capable of interfering with macrophage function (silica or carrageenan), or following surgical splenectomy, that exogenous stimulation with UVR does not result in an enhanced HEV expression. Such an activity can be returned to a splenectomized animal by the adoptive transfer of adherent splenocytes prior to stimulation with UVR-exposure(Chung and Daynes, unpublished). Therefore, the extent to which peripheral lymph node HEV can be stimulated via an exogenous inflammatory insult appears to be dependent upon the integrity of the animals macrophage/APC function.

The lymphocyte content of a given lymphoid organ is a reflection of not only the rate at which bolod-borne cells are capable of entering the tissue, but is also dependent opon the length of time that the lymphocytes are sequestered within the lymphoid organ prior to gaining recirculation potential. We have recently determined that thc exposure of animals to UVR causes blockade in the efferent lymphatic vessels, a situation which results in the sequestration of lymphocytes within the lymph nodes draining the site of UVR exposure (Chung, et al., submitted). A similar condition can be induced by the intravenous injection of murine α and β mterferon into normal mice. Of interest was the parallel finding that treatment of mice with indomethacin ($1 \sim 3 \mu g$/day) totally abrogated the development of the efferent blockage by UVR and α/β interferon. The efferent blockade caused by the direct injection of prostaglandin E_2 was not influenced by indomethacin injection, suggesting that prostaglandins were involved in the responsible mechanism.

In summary, the exposure of animals to UVR is capable of modifying many components of the SALT system. Both macrophage/APC and the recirculation and tissue localization properties of lymphocytes are equally affected. The role played by such changes in the modulation of immune responses by this physical agent are currently unresolved although the parallelism which exists certainly suggests a cause-effect relationship to some of the observed changes.

Proinflammatory Properties of Ultraviolet Radiation

It is well recognized that animals exposed to UVR(especially UVB) undergo a pronounced and dosage dependent inflammatory response. While the cellular and molecular alterations in the skin that ultimately result in a sunburn reaction are both numerous and complex it is now appreciated that the generation of biological mediators, and the elaboration of cytokines by epidermal cells or infiltrating cell types may play an important role in the immunomodulatory changes that are observed following UVR exposure.

Keratinocytes of the skin are capable of producing protein mediators termed epidermal-derived thymocyte activating factor(ETAF), a group of multifunctional homones that are functionally, physiochemically, and structurally identical to macrophage-derived interleukin-1 (IL-1)(Luger et al. 1983). ETAF/IL-1 is now appreciated to function as a major mediator in both immune and inflammatory responses(Luger and Oppenheim 1983). Based upon the knowledge that number of inflammatory processes are initiated by UVR and that the epidermal cells of the skin are a major target of

this physical agent, we have analyzed whether modifications in the levels of ETAF production, plus a number of known host responses to this mediator, were affected by UVR-exposure. Our results established that UVR exposure dose not adversely affect ETAF production at subcytotoxic doses(Gahring et al. 1984).

There are many biologic effects that have been ascribed to the stimulation and release of ETAF/IL-1 *in vivo*. ETAF and IL-1 can stimulate numerous target organs throughout the body including the brain, bone marrow, liver, and lymphoid organs. Target cell interactions with ETAF/1L-1 result in elevations in core body temperature, the number of circulating neutrophils, the enhanced production of acute phase proteins by the liver, as well as lymphocyte activation and chemotaxis(Powanda and Beisel 1982; Moissec, Chai-Li, and Ziff 1984). Exposing mice to UVR results in an elevation in the number of peripheral blood neutrophils as well as an increase in plasma concentrations of several of acute phase proteins(Gahring et al. 1984; Dinarello 1984). Further, ETAF/IL-1 can be detected in the serum of these animals 24 hours after exposure to UVR. Since UVR exposure is inflammatory, and mononuclear cells have been known to migrate into irradiated skin sites, we cannot discriminate whether the observed elevation in acute phase proteins *in vivo* is due to an increase in the production of ETAF by keratinocytes or is due, in part, to IL-1 produced by macrophages which have infiltrated the sites of inflammation.

A recent observation in our laboratory has provided insight into another possible source of ETAF/IL-1. Normal murine and human stratum corneum contains a substantial amount of ETAF/IL-1(Gahring, Buckley, and Daynes 1985). The physiologic role of this stratum corneum-associated ETAF/IL-1 remains to be determined, however, one could speculate that it provides a preformed pool of the mediator which is capable of initiating inflammatory responses following wounding or subsequent to protocols which increase the rate of percutaneous absorption. UVR is known to be capable of increasing the percutaneous absorption of small molecular weight substances through the skin. Therefore, keratinocyte production of ETAF, percutaneous absorption of preformed mediator, and/or mononuclear cell production of IL-1 may all influence the generation of a UVR-induced systemic inflammatory response.

We have demonstrated that daily exposure of mice to UVR results in an increase in the production of acute phase proteins and have speculated that this is due to elevations in ETAF/IL-1. It is interestjng to note that this heightened response is followed by an eventual return to normal plasma levels of these acute phase proteins despite a continued UVR exposure of the animal. The cause of this 'desensitization' to the effects mediated by UVR exposure is currently unknown. We have, however, established that keratinocytes obtained from a skin site exposed to daily UVR are still fully capable of producing ETAF *in vitro*. While some control of ETAF/IL-1 effects *in vivo* may reside at the level of the keratinocyte, the possibility that regulation takes place at the site of action(e. g., liver, brain, etc.) or in the delivery system(plasma) of this important mediator also needs to be considered.

Relationship Between UVR Exposure-Inflammation and Modifications to Normal Immunologic Potential

In the preceding sections of this review article a number of known immunologic, physiologic and pharmacologic changes were described which take place following the exposure of experimental animals to UVR. These alterations include the acquisition of tumor susceptibility, a condition which parallels overt tumor induction, suppressor T-cell induction, alterations in macrophage and lymphocyte components of the SALT system, puls the stimulation of both prostaglandin and ETAF/IL-1 mediated effects. When experimentally analyzed individually, each of these known chan-

ges which take place could individually be hypothesized to have a modifying influence on the immunologic potential of the immunologic potential of an UVR-exposed host.

If should be appreciated that UVR exposure of skin is capable of initiating all of the reported changes simultaneously in the exposed host, making it highly probable that significant overlaps, cause-effect relationships, and a number of biologic generalizations can be formulated. Furthermore, many of the changes inducible by UVR are not unique to this physical agent as evidenced by the knowledge that a large number of distinct inflammatory stimuli are capable of initiating a similar cascade of immunologic and physiologic changes. In an attempt to support the concept that many of the apparently distinct immunomodulatory effects of UVR-exposure significantly overlap with one another mechanistically, we will focus this section on two immunologic changes which take place subsequent to UVR exposure.

The experimental exposure of mice to UVR results in a marked reduction in their capacity to elicit contact hypersensiti vity (CH) responses to epicutaneously applied skin reactive chemicals. Mice exposed to low doses of UVR(4×400 J/m²/day) demonstrate a reduced capacity to elicit CH responses which is site specific (localized to the skin area of direct UVR exposure), whereas high-dose exposure of mice to UVR(15~30 KJ/m²) causes systemic alterations which leave the animals hyporesponsive to CH induction regardless of the skin site of hapten application(Toews, Bergstresser, and Streilein 1980; Noonan, Defabo, and Kripke 1981). Both of these types of UVR-mediated alterations have been previously reported to be associated with suppressor T-cell induction(Toews, Bergstresser, and Streilein 1980; Noonan, Defabo, and Kripke 1981). The capacity of low-dose UVR to depress the capacity of animals to respond to skin reactive chemicals has been concluded to be due to a dfrectfunctional inactivation of LC by this physical agent (Toews, Bergstesser, and Streilein 1980). The state of systemic suppression requires high doses of UVR for induction, and while it too is associated with the generation of hapten specific suppressor T-lymphocytes, it is not dependent upon a functional or phenotypic modification of the resident LC at the site of hapten application(Lynch, Gurish, and Daynes 1983; Morison, Bucana, and Kripke 1984). Due primarily to their ease of manipulation, these phenomena now sevrve as prototypes to thlp establish the mechanisms responsible for the immunologic changes which follow UVR exposure.

It was originally concluded that a cause effect relationship existed between the functional inactivation of epidermal LC and the depression in CH responsiveness that is observed following the exposure of animals to low doses of UVR. While attractive, the validity of this hypothesis was dependent upon the generalized capacity of low-dose UVR-exposed animals to respond normally to skin sensitization at non-UVR exposed sites. We therefore undertook an experiment to test this prediction formally. Groups of normal mice were exposed on their dorsal surfaces to UVR in low doses(400 J/m²/day). Each of the animals had a small 3.0cm² patch of UVR-opaque tape applied to a specified dorsal skin sites just prior to the irradiation treatment. A phenotypic analysis of epidermal LC in the exposed, protected, and unexposed skin sites confirmed that tape treatment had protected the covered area from UVR exposure. Subsequent to the UVR exposures, the treated animals were divided into 3 groups and contact sensitized with DNFB. The first group was sensitized through an unirradiated skin site on the abdomen. The second group of animals was contact sensitized through an irradiated dorsal skin site and the third group had hapten applied to the tape-protected dorsal skin site. An additional group of normal animals were contact sensitized through a normal dorsal skin site to serve as a positive control. All animals were challenged with DNFB five days later.

Table 1. The Effect of Low-Dose UVR-Exposure on Contact Hypersensitivity Responses Elicited to DNFB

Group	Sensitization Site[a]	Treatment[c]	Percent Depression of CH Responses[d]
1	Abdomen	None	0
2	Back	None	0
3	Abdomen	UVR	7.1
4	Back	UVR	64.1
5	UVR-Shielded Back[b]	UVR	61.5
6	None	None	–

a. Normal C3H mice were contact sensitized with a solution of DNFB on day 0 and day 1 by topical application to their shaved ventral or dorsal skin surfaces.
b. The UVR-shielded site was created by applying UVR-opaque tape to a specified area on the dorsal skin of normal C3H mice.
c. Animals were exposed to UVR by irradiating them with a bank of 6 FS-40 bulbs which emit approximately 2.5 J/m²/sec of UVB energy. All experimental animals received 400 J/m² of total energy per day for 4 consecutive days.
d. % depression was calculated as a relationship to the positive normal control.

Table 2. Indomethacin Treatment Abrogates the Immunodepression Observed Following Contact Sensitization of Low-Dose mVR-Exposed Animals Through Protected Skin Sites

Group	Sensitization Site[a]	Treatment[c]	Indomethacin[d]	Percent Depression of CH Responses[e]
1	Back	None	–	0
2	Back	UVR	–	61.8
3	Back	UVR	+	62.3
4	UVR-Shielded Back[b]	UVR	–	60.5
5	UVR-Shielded Back[b]	UVR	+	3.6
6		None	–	–

a. Normal C3H mice were contact sensitized wiht a solution of DNFB on day 0 and day 1 by topical application to their shaved ventral or dorsal skin surfaces.
b. The UVR-shielded site was created by applying UVR-opaque tape to a specified area on the dorsal skin of normal C3H mice.
c. Animals were exposed to UVR by irradiating them with a bank of 6 FS-40 bulbs which emit approximately 2.5 J/m²/sec of UVB energy. All experimental animals received 400 J/m² of total energy per day for 4 consecutive days.
d. Indomethacin treatment was accomplished via the subcutaneous implantation of a pellet designed to release the drug at a constant rate of 1.25 μg/day for 20 days.
e. % depression was calculated as a relationship to the positive normal control.

The results of this experiment (Table 1) established that UVR-exposed animals that had been sensitized through their abdominal wall skin responded normally, a finding which is fully consistent with the original observation (Toews, Bergstresser, and Streilein 1980). Likewise, the animals that were contact sensitized through the irradiated dorsal skin(LC deficient) exhibited a marked reduction in their capacity to elicit a CH response. Interestingly, the animals that were contact sensitized through the UVR-protected dorsal skin site were also found to be hyporesponsive, in spite of the fact that LC density in this area of the skin was totally normal. This finding suggested that LC inactivation by UVR is not sole responsible for the reductions in CH responses elicited by these animals.

We next questioned whether the known capacity of UVR to stimulate prostaglandin synthesis was involved in immunologic the changes that were taking place in low-dose UVR-exposed animals. This was based on the known capacity of UVR to stimulate an in-

Table 3. Indomethacin Treatment Prevents the Development of Systemic Suppression of Contact Hypersensitivity Responses by High-Dose UVR Exposure

Group	Sensitization Site[a]	Back Skin Treatment[b]	Indomethacin[c]	Percent Depression of CH Responses[d]
1	Abdomen	None	−	0
2	Abdomen	High-Dose UVR	−	56.6
3	Abdomen	High-Dose UVR	+	6.4
4	None	None	−	−

a. Normal C3H mice weve contact sensitized witht a solution of DNFB on day 0 and day 1 by topical application to their shaved ventral or dorsal skin surfaces.
b. Animals were exposed to UVR by irradiating them with a 100 watt mercury arc lamp which emits approximately 500 J/m² of UVB energy. All experimental animals received 15,000 J/m² of UVB energy.
c. The indomethacin pellets used in this study delivered 2.5μg of drug per day.
e. % depression was calculated as a relationship to the positve normal control.

crease in the systemic release of IL-1-like molecules and to also cause both inflammation and pain(Gahring, et al. 1984; Eagl stein, Sakai, and Mizuno 1979). Two large groups of skin patch protected mice were prepared and exposed to low doses of UVR. One group of animals to be UVR-exposed received a subcutaneously implanted pellet of indomethacin, designed to deliver a daily dosage of 1.25μg over a 20 day period. After subjecting all experimental animals to the 4 daily UVR exposures they were segregated into 4 separate groups. One group of indomethacin-treated and one group of untreated UVR-exposed mice were contact sensitized with DNFB through irradiated dorsal skin sites. Likewise, a second group of indomethacin-treated and a parallel group of untreated UVR-exposed animals were contact sensitized through the protected area on their dorsal skin surface. To establish the effect of the indomethacin treatment, all experimental and control groups were challenged with hapten five days later. The results of this experiment (Table 2) clearly demontrate that the *in vivo* inhibition of prostaglandin synthesis had no effect on the reduced capacity of animals which were hapten sensitized direrctly through an irradiated skin site to elicit a CH response. In contrast, the redced capacity of UVR-exposed animals to elicit a CH response following sensitization through a patch-protected dorsal skin site was not observed in the indomethacin treated group. These animals responded normally to the DNFB sensitization suggesting that the diminished CH responses to haptens applied to normal(UVR-protected) skin sites is dependent upon the mobilization of arachedonic acid and the biosynthesis of its metabolites. Further studies confirmed that the plasma of UVR-exposed animals contained elevated levels of PGE_2 and that the indomethacin treatment of such animals inhibited this elevation in PGE_2 production.

We next turned our attention to the phenomenon of systemic suppression of contact hypersensitivity, and hypothesized that the induction of this condition might also require the *in vivo* stimulation of prostaglandins. Two group of animals were exposed to high-dose UVR (30 KJ/m²). Each individual from one of these groups was given an indomethacin pellet to inhibit their capacity to synthesize prostaglandins. After a 3 day rest following the UVR exposure, all experimental animals plus a group of normal controls were contact sensitized with DNFB on their unirradiated ventral skin surfaces. Five days later all animals were challenged and the extent of ear swelling evaluated after 24 hours. The results of this representative experiment (Table 3) clearly demonstrate that the ability of high-dose UV R exposure to cause a systemic depression in CH responsiveness is inhibited by the treat-

Table 4. Contact Sensitization of High-Dose UVR-Exposed Animals Results in the Simultaneous Induction of Both Suppressor and Effector Cells for CH Responses

A. Group	Donor Treatment[a]	Recipient Treatment[b]	Percent Suppression[c]
1	−	Challenge	−
2	−	Sensitization Plus Challenge	0
3	None	Sensitization Plus Challenge	54.6
4	High-Dose UVR	Sensitization Plus Challenge	64.0
5	High-Dose UVR Plus Indomethacin	Sensitization Plus Challenge	62.1

B. Group	Donor Sensitization[d]	Donor Treatment[e]	Percent Normal Response[f]
1	−	−	0
2	+	−	100
3	+	High-Dose UVR	93.1

a. Donor animals were untreated or exposed to high dose UVR (30 KJ/m²) in the presence or absence of indomethacin.
b. Recipient animals received 10^8 splenocytes from DNFB sensitized donors. The recipient animals were subsequently skin sensitized with DNFB.
c. Percent suppression was calculated as a relationship to normal mice or mice which received an adoptive transfer of normal cells.
d. Donor animals were footpad and belly sensitized with DNFB. Peripheral lymph node lymphocytes (30×10^6) were adoptively transferred to naive recipients which were immediately challenged with DNFB.
e. Certain donors were exposed to high-dose UVR (30 KJ/m²) 3 days previously.
f. The capacity to elicit a CH response was calculated as a percentage of the positive (normal) control.

ment of the test animals with indomethacin. These results strongly suggest that the mechanisms responsible for UVR-induced systemic suppression of CH responses involves the stimulation of prostaglandin synthesis.

Previous investigations have implicated hapten sepcific T-suppressor (Ts) cells in the mechanisms pesponsible for high-dose UVR-induced suppression of CH responses (Noonan, Defabo, and Kripke 1981). These conclusions were drawn from the finding that the spleens of hapten sensitized UVR-exposed animals contained hapten-specific Ts which, upon adoptive transfer to naive recipients, were capable of causing a depression in the recipients capacity to elicit a CH response to the immunizing hapten (Noonan, Defabo, and Kripke 1981). We therefore questioned whether suppressor cell activity could be demonstrated in indomethacin-treated UVR-exposed animals subsequent to skin sensitization. The results of our study determined (Table 4A) that the induction of splenic suppressor cells represented a normal consequence of skin sensitization with the hapten DNFB. Not only was suppressor cell activity present in the spleens of high-dose UVR -exposed donors, regaradless of indomethacin treatment, but suppressor cell activity could also be found in the spleens of the DNFB-sensitized normal animals as well. Normal splenocytes adoptively transferred into naive recipients were without inhibitory effect. In parallel to an analysis of suppressor cell activity, the draining lymph nodes were removed from both normal DNFB-sensitized donors and high -dose UVR-exposed DNFB-sensitized donors for adoptive transfer to naive recipients. This protocol tests for the development of effector cell potential. Recipient animals were immeditely challenged with hapten. The results (Table 4B) demonstrate that DNFB-sesnitized high-dose UVR-exposed animals and DNFB-sensitized normal animals generate an equivalent effector cell activity in their peripheral lymph nodes. Our results, therefore, suggested that the depressed capacity of high-dose UVR

Table 5. UVR Inhibits the Capacity of Animals to Execute a Contact Hypersensitivity Response in the Presence of Normal Immunolpgic Potential

Experiment Number	Group	Treatment of Recipients[a]	Adoptive transfer of DNFB-Primed Lymphocytes[b]	Ear Swelling[c]	Percent Depression of CH Response
I	1	None	−	4±.1	0
	2	None	+	29±.5	0
	3	Indomethacin	+	27±.5	8
	4	15 KJ/m² UVR	+	8±.2	84
	5	15 KJ/m² UVR+Indomethacin	+	25±.5	16
II	1	None	−	3±.1	0
	2	None	+	28±.2	0
	3	Indomethacin	+	43±.4	0
	4	15 KJ/m² UVR	+	9±.1	76
	5	15 KJ/m² UVR+Indomethacin	+	22±.1	24

a. UVR was administered 3 days prior to the adoptive transfer of DNFB-primed lymph node cells. Indomethacin pellets were employed which release 2.5μg of drug/day.
b. Normal animals were sensitized with DNFB on their ventral surface, ears and footpads. Lymph nodes were excised after 4 days and 30×10^6 cells adoptively transferred to the normal and treated recipients.
c. Ear swelling was measured 24 hours subsequent to DNFB challenge. % depression of the CHresponse was calculated by comparing it to the positive control.

-exposed animals to elicit a CH response was not due to: a) apparent modifications in suppressor cell generation, b) a depression in the capacity of these animals to generate effector cells in response to hapten application. Subsequent experiments, where UVR-exposed animals were contact sensitized through irradiated or UVR-protected skin sites, determined that splenic suppressor cell activity was induced under all conditions employed, while adoptively transferrable effector cell activity was only found when skin sensitization took place through a skin site having normal LC function (data not shown).

Insight into the mechanisms responsible for the depressed capacity of UVR-exposed animals to elicit CH responses was derived from experiments where normal, UVR-exposed, and indomethacin-treated UVR-exposed animals served as recipients of CH-effector cells obtained from normal hapten primed donors. Both normal animals and the indomethacin-treated UVR-exposed groups were capable of eliciting a demonstrable CH response. However, the UVR-exposed recipients of normal CH-effector cells exhibited a tremendous reduction in their capacity to manifest a CH response (Table 5). Therefore the capacity of UVR to inhibit the elicitation of a CH response to agents initially applied to normal skin sites dose not appear to represent the result of a diminished capacity of the animal to generate an immune response to the inducing hapten. Rather, the depressions in the intensity of CH responses observed in UVR-exposed animals appears to reflect some prostaglandin-induced alteration in the capacity of the effector arm of the CH response to function, possibly through a modification in lymphocyte receptiveness of the microvascular endothelium associated with the blood vessels at the specific site of a given immunologic or inflammatory response.

General Conclusions and Future Directions

The major objective of this review was to present the interrelationships which exist between the seemingly diverse effects that UVR has on normal immunological and physiological processes. Each of these inducible changes may be similar mechanistically to those elicited by other types of inflammatory stimuli.

Ultimately, the changes caused by UVR-exposure produce a condition in which immunologic responsiveness of animals is dampened, either through the dominance of specific suppression following antigenic stimulation, or due to intrinsic mechanisms which exist to functionally inhibit certain types of effector cell responses. We have hypothesized that these immunoregulatory responses are reflections of normal host defense mechanisms. Such mechanisms may exist to protect the individual against the possible development of autoimmune conditions during the essential repair processes taking place subsequent to the UVR-mediated damage to skin. While seving to protect a host from possible autoimmune manifestations represents a beneficial aspect to such processes, the creation of a condition where the development of immune responses are continually being suppressed would clearly be detrimental. This represents the condition which would take place under situations of chronic UVR exposure. These could come about from either changing mores, where individuals increase their daily exposure to solar or artificial UVR for personal or cosmetic reasons, or from a reduction in the function of the ozone layer which currently provides a degree of protection from UVR to the eacth's surface.

Photoimmunology is providing the basic and clinical scientists with fresh insight into the types of mechanisms which can operate *in vivo* to control immunologic responses. It has long been appreciated that the molecular characteristics and the mode of presentation of a given antigen to an immunocompetent host can play a significant role in the immunologic outcome of such an interaction. Likewise, it is known that an immune response can take many froms, with both humoral and cell-mediated components functioning simultaneously to either effectuate or regulate the type or intensity of a given adaptive immunologic response.

Photoimmunology, the effect of light energy on immunologic responsiveness, has served to expand our understanding of immunologic control mechanisms. The importance of anatomic compartmentalization, the relationship between inflammation and adaptive immunity, and the means by which suppressor cell dominated responses can be preferentilly stimulated are all apparent from the immunobiologic analysis of the UVR-exposed host. Further, the use of UVR to altes a host's immunologic potential, is now uncovering the role played by interleukin-1, prostaglandins, steroids, and other hormones in many forms of immunologic control processes. Such information should prove useful, both in the elucidation of the diverse range of processes with interact to ultimately control the immune response, as well as in the clinical manipulation of given immunologic situations.

While it is impossible to accurately predict the futute of this interesting field of study, the tremendous advancements made during the past decade might be used as an indication of the future. Based upon the number of diverse areas of investigation that are involved in the field of photoimmunology, one might hypothesize that the future will bring significant advances from both the basic and clinical scientists. These advances should provide valuable information concerning the means by which environmental influences can modulate the immunologic potential of a normal host, as well as important insight into mechanisms that can be used to manipulate certain types of immunologic responses for clinical benefit.

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