# Our Thanks to Neutrogena

*We recognize with appreciation Neutrogena for pledging support to the Endowment Fund for* The Journal of Investigative Dermatology, *which will be used to support the growth and continued success of the Journal. This support will certainly strengthen and perpetuate the partnership between the pharmaceutical industry and basic and clinical investigators in cutaneous biology.*

*We salute Neutrogena for their contribution to the Endowment Fund and for their continued support of clinical and investigative dermatolgoy.*

*D.A.N., Denver, CO.*



# In This Issue . . .

Lela A. Lee

## The Pathogenesis of Non-Melanoma Skin Cancers

Although it has been known for decades that chronic exposure to the sun is correlated with the development of non-melanoma cancers of the skin, other factors are certainly also involved. The xeroderma pigmentosa syndromes illustrate the importance of genetically determined ability to repair DNA damage. The increased incidence of skin cancers in transplant patients implicates the immune system. The finding of papillomavirus in lesions of epidermodysplasia verruciformis provides evidence that viruses may be involved in certain cases. It seems reasonable to assume that genetic and environmental factors in addition to ultraviolet (UV) light might play a role in the development of skin cancer in general, not just in the isolated instances above.

In this issue, three articles address the possibility of factors in addition to UV dose that contribute to the development of skin cancer in the general population. The role of the immune response was examined by Yoshikawa, Streilein, and co-workers. Dr. Streilein had previously been involved in studies demonstrating that chronic, low-dose UVB radiation could impair the induction of contact hypersensitivity in certain mouse strains if the allergen was applied to the irradiated skin. His group is now demonstrating similar findings in humans. Localized, low-dose UVB impaired the induction of contact hypersensitivity to DNCB in a substantial percentage of normal individuals (40%) and in an extraordinarily high percentage of skin cancer patients (92%). Those individuals who had impaired contact hypersensitivity after UV were termed "UVB susceptible," and those who were unaffected were termed "UVB resistant." In addition, the skin cancer group contained individuals (45%) who developed an antigen-specific tolerance to DNCB, whereas the normal group did not.

Dr. Streilein has a fascinating continuation to this story. "We have shown that UVB susceptibility in mice maps to two genes, the TNF$\alpha$ (tumor necrosis factor-$\alpha$) gene and a gene that determines susceptibility to bacterial lipopolysaccharide." Both of these genes have two alleles. It appears that the alleles found in the UVB-susceptible mice both work to effect the release of a substantial amount of TNF$\alpha$ after UVB exposure. "The effects of UVB on contact hypersensitivity can be mimicked by injecting TNF$\alpha$, and can be prevented by giving anti-TNF$\alpha$ antibodies. However, the development of tolerance could not be linked to TNF$\alpha$ at all, and we suspect that another gene is invovled in tolerance." The genetic study of mice is being published in Immunogenetics by Drs. Yoshikawa and Streilein.

Although a genetic basis for UVB susceptibility has not been demonstrated in humans, it is plausible that there is a subset of individuals who have a genetically determined susceptibility to UVB-induced immunosuppression, perhaps mediated via TNF$\alpha$. In those individuals, chronic UVB exposure could conceivably result in a transient or permanent inability to respond to tumor antigens, thereby permitting the proliferation of abnormal cells in the skin.

Kawashima, Orth, and co-workers have examined the possibility that papillomaviruses are related to the development of skin cancer. They examined large numbers of premalignant and malignant lesions of sun-exposed skin, genital skin, and lip for the presence of human papillomavirus (HPV) DNA. Papillomaviruses have been implicated in a substantial portion of anogenital cancers, and the frequent finding of HPV in genital Bowen's disease and Bowen's carcinoma in this study confirms findings of previous studies. Despite comprehensive testing, including amplification of DNA using the polymerase chain reaction, very few lesions outside the genital area contained HPV DNA. Given the known oncogenic potential of at least some HPV, this study was important to perform and has resulted in valuable information about the genesis of skin cancers.

There are several factors that may account for these results, which imply that HPV have a minor role, if any, in the induction of ordinary skin cancers. First, clinically evident HPV infections are not particularly common on the face, the area that has the strongest predilection for the development of skin cancer. Second, skin is being examined after cancerous or precancerous lesions have already developed. It is possible that HPV infection played a role early in cancer induction but is no longer detectable. Third, although this study was quite comprehensive, it has not absolutely ruled out the possibility of HPV being present in the skin lesions. For example, as Dr. Orth states, "It is still possible that other types of HPV, not yet known, play a role in cancer development." Last, the types of HPV affecting those areas that ordinarily develop skin cancers may not be optimal for cancer induction. Recent studies have demonstrated that genital HPV with a high risk for malignant transformation produce proteins that bind the tumor-suppressor proteins, p53 and pRB, with more affinity than do genital HPV with low risk for

0022-202X/90/$03.50 

malignant transformation. Binding of p53 and pRB could inactivate their tumor-suppressive function. As Dr. Orth indicates, HPV type is not the only potential factor affecting oncogenesis. In epidermodysplasia verruciformis, HPV 5 is linked to cancer induction, whereas in the general population HPV 5 infections occur but do not apparently result in cancers. This illustrates the importance of the host as well as the HPV.

Finally, Alcalay, Freeman, and co-workers have examined excision repair of pyrimidine dimers in a group of patients with basal cell carcinomas. Persistence of pyrimidine dimers after UV irradiation could lead to errors in DNA replication and thus contribute to cancer formation. Pyrimidine dimers are not the only photoproducts that could lead to cancer formation, so there may be other important aspects of DNA repair that are not evaluated by this study. Nevertheless, there is experimental evidence for a correlation between pyrimidine dimer formation and UV-induced carcinogenesis.

Alcalay and colleagues measured numbers of pyrimidine dimers by treating skin biopsies with a pyrimidine dimer-specific UV endonuclease. They found that patients who have had basal cell carcinomas have a similar number of pyrimidine dimers formed after UV irradiation as do a group of control subjects who have not had skin cancers. The basal cell cancer group, however, had a smaller percentage of dimers repaired at six hours after irradiation than had the control group (22% versus 33%). Although the difference in repair between the basal cell and the control group is relatively small, it may be an important difference, at least in some individuals. Whether this difference is a result of the genetic makeup of the basal cell group or a result of other factors is not as yet identified.

Previous studies examining DNA repair have focused on repair in cultured cells, such as fibroblasts or keratinocytes. "One of the important features of this study is that this is an assay for UV-induced DNA damage directly in human skin rather than in cultured cells," says Dr. Freeman.

The three studies above address possibilities that are not mutually exclusive and could in some cases be related. For example, persistence of pyrimidine dimers could lead to abnormal DNA replication and synthesis of abnormal proteins. These "neoantigens" may fail to evoke an immune response in those subjects who are susceptible to UVB-induced immunosuppression. Second, if HPV are involved in some cases of skin cancer, the combination of HPV and UVB irradiation could lead to tolerance of HPV proteins that may contribute to oncogenesis.

The story of the pathogenesis of non-melanoma skin cancers often seems simple when compared to many other cancers, because there is an overwhelmingly important factor, UV light, without which most cancers would not occur. The studies in this issue serve to point out that skin cancer induction is not without its interesting complexities.

## Effects of Topical Retinoids

Three articles in this issue provide further information about the effects of topical retinoids. The first, by Rosenthal and co-workers, describes changes in photoaged human skin after chronic application of all-trans retinoic acid. Changes examined were presence and distribution of epidermal transglutaminase and the following keratins: K14, normally found in basal cells; K1 and K10, normally found in suprabasal cells; and K6 and K13, not normally found in the epidermis. The authors found a marked increase in the number of cell layers expressing epidermal transglutaminase and found a focal expression of K6 and K13 in treated skin. There were no changes observed in K1, K10, and K14.

There are several important points to be made about this study. First, "there were drastic changes induced by retinoids," says Dr. Rosenthal. Second, although improvement in the appearance of the skin was noted in many subjects, the changes induced by retinoids were not correlated with an improvement in the appearance of the photoaged skin and thus were not necessarily beneficial. Third, some of the changes were different from those seen when the effects of vitamin A or retinoids were evaluated in cultured cells. This serves to point out the limitations of cell culture and the importance of in vivo studies. Finally, this study does not address the functional implications of the retinoid-induced changes. Dr. Rosenthal notes that it is possible that changes induced in keratin expression will affect the barrier function of the skin, but that has yet to be determined.

A second study from De Lacharriere and colleagues examined the effects of topical all-trans retinoic acid on the skin of patients receiving systemic steroids after renal transplantation. The skin changes induced by steroid therapy are similar to, but not the same as, those induced by chronic UV exposure. After six months of topical retinoid treatment, there was objective evidence of skin thickening and increased elasticity, although the improvement was minor enough that gross changes in skin thickness were not demonstrable. Dr. De Lacharriere states, "The clinical differences between treated and untreated skin may be more evident following longer periods of treatment." If so, this would be a welcome addition to the currently virtually empty armamentarium of treatments for steroid-induced skin changes.

Finally, Willhite and co-workers examined teratogenicity of topically applied retinoids using hamsters. "The pharmacokinetics of retinoid metabolism are similar in hamsters and humans, and the fetal malformations seen are quite comparable," says Dr. Willhite. According to Dr. Willhite, the dose of retinoids applied to the skin of pregnant hamsters was "orders of magnitude" greater than that ordinarily used in humans for treatment of photoaging. Even so, no fetal hamster malformations were evident as a result of all-trans retinoic acid application to the skin of pregnant hamsters. As with any study examining teratogenicity in animals, one must be cautious about extrapolating these results to humans. For example, the vehicle used in this study was different from vehicles used in topical retinoic acid preparations for humans, a large dose of medication was applied to a very limited surface area, and the numbers of animals used were not great enough to detect a small increase in teratogenicity by all-trans retinoic acid. One sobering aspect of their data is the profound teratogenic effect of topical application of Ro 13-6298 arotinoid ethyl ester. As Dr. Willhite points out, physicians must remember the potential for systemic effects from topically applied medications and must therefore be cautious in their use.