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OPINION ARTICLE

# Dermatological Uncertainties

## Las incertidumbres dermatológicas

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Is dermatology an inward- or outward-looking specialty? I think the evidence points toward the second attribute. As our knowledge increases we assume wider responsibilities, becoming aware that the functions of the skin extend beyond its role as an organ for external protection—as we understand the skin's involvement in essential body processes that were previously unknown, we perceive its primordial role in general homeostasis.

Over only a few decades, traditional skin diseases have been fundamentally transformed by the effects of external factors on a long-lived population. Individuals are exposed to environmental elements from infancy and there is an increasing rate of cutaneous neoplasia at ever earlier ages, especially in that section of the population with therapeutic immunodepression due to transplant or disease. At the same time, there are increasing options for improving personal appearance and physical attractiveness; the impact of photoaging is therefore attenuated even as the average age of the population advances.

Dermatology is moving outward from its traditional territory of treating skin diseases and now faces greater demands for cosmetic skin treatments, with related financial incentives and pressure to cross what might be termed the medical boundaries of the discipline. Many other factors affecting the specialty include emigration toward other medical areas of venereology and, to a lesser extent, toward sharing the treatment of skin conditions with the specialty of internal medicine.

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An example of the intimate relationship between the skin and the rest of the body can be seen in the functional relationship of skin exposure to sunlight and vitamin D formation—a process that places the dermatologist firmly at the crux of the matter. What do we know about this process?

Skin exposed to UV rays supplies the body with 25-hydroxyvitamin D (25[OH]D). The maximum endogenous 25(OH)D production with whole-body irradiation is some 250 ng/d in order to maintain levels superior to 50 ng/mL, although measurement of 25(OH)D levels was notoriously difficult before July 2009. The application of sun screens proportionally reduces the ability of irradiated skin to synthesize the vitamin. The ingestion of 400 IU/d of vitamin D used to be a routine medical recommendation. Was this enough? Possibly not. But, why do our bodies have the ability to synthesize such large amounts of vitamin D?

In an attempt to understand the role of vitamin D, the University of Stanford Medical Center studied 1081 men with osteoporosis-related fractures, finding that 178 of them had cutaneous carcinoma and that those with levels of vitamin D superior to 30 ng/mL had 45% fewer basal cell carcinomas. Half of all elderly people with fractured hips have vitamin D levels lower than 12 ng/mL. Around 70% of young people under 21 years old do not have a sufficient intake of vitamin D *(USA Today)*.

The list of benefits grows as we come to know this vitamin better.

Levels of vitamin D are related to improved learning capacity; reduced fractures of the vertebrae and neck of the femur; the prevention of diabetes, cardiovascular disease, pancreatic and breast cancers; increased fertility;

better weight control; and improved memory. In adults more than 50 years old, those with very low levels of vitamin D (*Intimes,* November 16) had twice the rate of cerebral infarction, more heart disease and double the rate of heart failure. The study included data from 27 686 individuals.

Researchers at the University of Michigan (*Health Day,* December 3) established that a variant in the *CYP27B1* gene (*Pharmacogenomics*) reduces vitamin D activation in patients with hypertension, exposing them to double the level of congestive heart failure of normal subjects.

Earlier it had been observed that mutations that inactivated the gene also reduced conversion of vitamin D to its active hormone form.

Researchers at the Mayo Clinic (*Am Soc Hemat*) who studied a group of 374 patients with large B cell lymphoma reported that mortality was twice as high in patients with low levels of vitamin D as it was in patients with normal levels.

The role of vitamin D raises a tough problem for the dermatologist who is effectively facing the dilemma of asking the patient to choose between cutaneous carcinoma and a hip fracture.

Vitamin D plays a fundamental role in innate immunity, which does not rely on immunological memory, is less complex, and comes into play before adaptive immunity does. The innate immune process is mediated by neutrophils, eosinophils, natural killer cells, mast cells, cytokines, complement proteins, and the antimicrobial peptides human β defensin, cathelicidin (LL-37), dermcidin, and RNAse 7. Innate immunity is more important than the adaptive immune system for antibacterial defense.

UV rays induce the innate immune response and suppress the adaptive response. Both effects are beneficial as they protect against bacterial infections and reduce autoimmune and allergic reactions—although excessive exposure to UV is a health threat. Vitamin D is a direct regulator of several innate immune responses. LL-37 production is positively correlated with vitamin D receptor expression, suggesting that the process of vitamin D synthesis induces the LL-37 that eliminates *Mycobacterium tuberculosis*. This mechanism is also related to the relatively higher susceptibility of black people than white people to tuberculosis.

A better understanding of the complexity and extent of skin functions imply that dermatologists must broaden their knowledge beyond the traditional areas of pathology or immunology, expanding their horizons into biology and molecular biology.

Fortunately, these new frontiers do not present insuperable barriers for those equipped with curiosity and the desire for self-improvement.

We dermatologists have always had both those qualities.