Questions Raised About Anti-Wrinkle Cream

Retin-A does seem to smooth wrinkles, but how much, and what exactly is happening to the skin, is not yet clear

LIKE most things that sound too good to be true, the widely heralded anti-aging effects of Retin-A have probably been overbilled, say a number of dermatologists around the country. This is not to say that the drug, a vitamin A derivative, is not promising, they add, but its benefits appear to be fairly modest, and its possible long-term effects are not yet known.

Retin-A, a cream containing retinoic acid, has been used since the 1960s to treat acne. Almost immediately, Albert Kligman of the University of Pennsylvania noted its anti-aging benefits on the skin of his older acne patients. But this new study, conducted by John Voorhees and his colleagues at the University of Michigan Medical Center and published in the 22 January issue of the *Journal of the American Medical Association*, provides the first evidence of an anti-aging effect from a double-blind trial (*Science*, 29 January, p. 457).

In the small, 4-month trial, all 30 subjects showed a slight to marked improvement—fewer fine wrinkles and a "pink rosy glow," the investigators report. In some, coarse wrinkles were reduced, skin became smoother, and sun spots faded. The subjects, ages 35 to 70, applied Retin-A to one forearm and a control cream to the other, and half of them also applied Retin-A to their faces. Effects were far more pronounced on the forearm, where 40% of the subjects showed "major improvement." By contrast, only 1 of the 15 subjects who applied Retin-A to their faces was considered much improved. Biopsies taken from the forearm revealed histological improvements as well.

What accounts for these changes, and how dramatic they really are, is the subject of some debate. Voorhees calls the effects "striking." At the end of 4 months, when the controlled trial ended, improvement was "mild to moderate," he says, but the effects increase the longer the drug is used. Since the trial was completed, Voorhees has continued administering the drug to the same 30 subjects, and to 200 others as well.

"When you get to 9 to 12 months, the results get better and better," he says. "Some look spectacular, some look very good, some good. Fair is as bad as you get at 9 months." These observations, however, have not been confirmed in a clinical trial.

Others working with the drug consider its effects to be far more modest. "The cosmetic effects do exist, but they are modest and they take a long time to become apparent," says Arthur Balin of the center for investigative dermatology at Rockefeller University, who is conducting a 15-month trial to assess Retin-A's possible role in treating premalignant skin lesions.

Balin and other investigators agree that topical Retin-A appears to be safe, given its long track record in acne treatment. Retinoic acid can be highly toxic systemically, but in topical use its only adverse effects appear to be dermatitis (redness and inflammation) and increased photosensitivity.

What Retin-A is actually doing in the skin to produce the cosmetic changes is largely unknown. Many suspect that at least some improvement is related to the irritation the drug causes. "How much of the improvement is secondary to Retin-A chapping, and how much is a specific biochemical reaction to Retin-A is not clear," says Gary Peck of the National Cancer Institute.

Voorhees is convinced that the improvements stem from a biochemical effect. Retinoic acid is known to boost the turnover rate of epidermal cells, spurring new cell growth in the basal layers and speeding the shedding of dead cells. Those changes were evident in the histological analysis, Voorhees says. Treated areas showed increased cell proliferation and a thickening of the epidermis, which thins with sun and age, and a smoother, more compact texture in the stratum corneum, the outer dead layer of the skin. Both of those changes would reduce fine, surface wrinkles, Voorhees says. In addition, the melanocytes, which produce pigment, diminished in number and size, thus accounting for lighter sun spots. The pink glow apparently comes from a dilation of the blood vessels in the dermis.

The effect on coarse wrinkles, which start in the dermis, is trickier to explain. Mouse studies suggest that Retin-A causes increased production of collagen, the structural protein of the dermis, which might work to fill in creases, but so far, human evidence is lacking.

At NCI, Stuart Yuspa has been studying how retinoic acid affects cellular differentiation of the epidermis as part of research into the potential anti-cancer effects of retinoic acid. His finding may partially explain the softer, smoother skin apparent in Voorhees's study, he says.

According to Yuspa, retinoic acid shuts off synthesis of two proteins, keratin 1 and keratin 10, that are normally expressed as basal cells migrate up toward the skin surface. These two large, rigid proteins are normally abundant in epidermis and may be important in forming the skin's outer barrier. Retinoic acid also appears to reduce the activity of membrane-bound transglutaminase, the enzyme that cross-links proteins to create the dense barrier layer of the epidermis. It also seems to turn on the expression of another enzyme that is normally expressed only in internal tissues. The expected result, says Yuspa, would be fewer dense keratins and a less cornified envelope. "The skin has been reprogrammed completely."

Whether completely reprogramming the skin is beneficial "is a very good question," Yuspa says. "The barrier function of the skin is critical, and we don't know what the consequences of changing it would be. From the standpoint of carcinogenesis, one might worry about thin skin. One needs to be cautious about long-term effects. This is going to be widely used." ■

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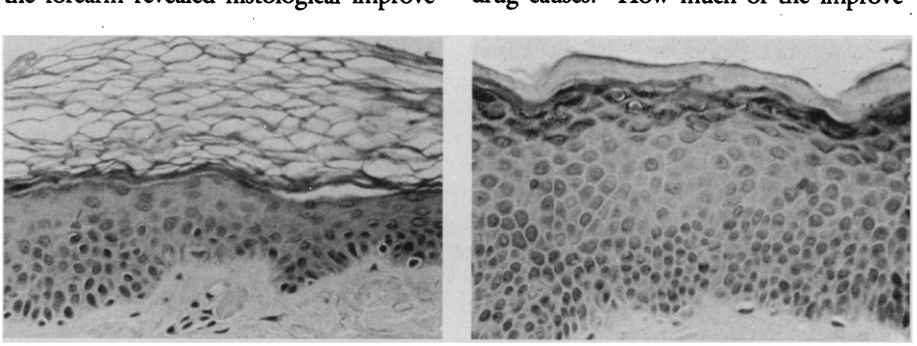

Before and after: *Forearm skin before (left) and (right) after 16 weeks of Retin-A therapy. The outer horny layer is compacted and smoother, and the underlying epidermis is thicker.*