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Current Concepts in the Management of Actinic Keratosis

This supplement to the Journal of Drugs in Dermatology, sponsored by Dermik Laboratories, is adapted from a recent roundtable symposium held in New York City featuring six respected dermatologists, each an expert on treating skin disorders. Their combined expertise and experiences with treating actinic keratoses provided the backdrop for their enlightening discussion; we hope you will find this supplement both educational and useful.

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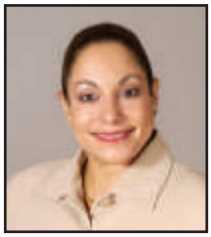

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Dr. Robins: I want to thank you all for coming. Our topic today is "Current Concepts in the Management of Actinic Keratosis," and we're going to discuss recognition, treatment, and prevention of actinic keratoses, or AKs. We'll start at the beginning: what are actinic keratoses and what do they look like?

Dr. Nehal: What we call an actinic keratosis actually has quite a range. It can be a lesion that simply has scaling with absolutely no erythema, or a scaling lesion with some erythema. AKs can also have some superimposed hyperkeratosis. There's quite a range in clinical appearance.

Dr. Robins: Where do you find most keratoses?

Dr. Hale: We find most on sun-exposed areas of the body. We find a lot on the face; on bald men, we find many on the scalp. The dorsum of the hands is a key place to look for them, as is almost any other exposed area of the body, including the chest, back, arms, shins, and dorsum of the feet. Essentially, any place that has had exposure to the sun should be checked.

Dr. Sarnoff: I would add that they are more common in middle-aged and elderly individuals and those with fair complexions, especially Fitzpatrick skin types I through III.

Dr. Perez: A few variants of actinic keratoses are more difficult to diagnose, for example, those that are segmented, darkening, or more expansive. You have to be careful in diagnosing those because they can be confused with other conditions such as melanoma and basal cell carcinoma, which are also usually located in sun-exposed areas.

Dr. Jorizzo: I'll chime in with the Southeastern, Celtic population perspective. We have a number of patients who defy the descriptions in the literature of a specific size cut-off for AKs. When first year dermatology residents examine a patient during their first few months, they tend to focus on hypertrophic actinic keratoses. Then one of our attending physicians examines the patient, and where the residents might have found four AKs, the attending finds 50. My pathology professor in medical school, Stanley Robins MD, used to talk about a "restless" epithelium. I think actinic keratosis illustrates this because the whole skin surface may contain damaged keratinocytes, and one sometimes finds so many lesions so close together that they almost seem to make a large map. As a result, simple size cut-off is not always useful.

Dr. Hale: I would add that the lesions are often subclinical. And sometimes it's difficult to count them because they occur in the setting of sun damage; it's a very subtle change from chronically sun-damaged skin to an actinic keratosis. It can help to make the diagnosis via a tactile approach, because sometimes you don't actually see the AK. But if you take your glove off and touch the area, you can feel a rough patch of skin that may indicate a lesion.

Dr. Robins: That brings up a very interesting point. Companies may report that they have a "98% cure rate," or a "96% cure rate," but you can't just accept these figures. If you ask three residents to count how many actinic keratoses a patient has, they will come up with three totally different numbers. It is often very hard to say if AK involvement is extensive, very extensive, or very, very extensive. We treated a patient yesterday, and it would have been impossible to count definitively how many AKs she had.

Dr. Jorizzo: The FDA has changed its standard for assessing products that treat actinic keratosis. It is really a change in dermatologic disease assessment overall. I think they have gotten tired of us saying that a psoriasis patient was 25% better if the scale went from 3+ to 2+, so they now require 100% clearance in a given area. We have been used to seeing numbers in the 80-90% range, but that, of course, requires counting, and as Dr. Robins pointed out, you at first tend to count a little arbitrarily. Often after two to three weeks, you have a tremendous increase in AKs because of all those subclinical lesions becoming inflamed. Then hopefully you have a reduction. But now, with the new standards, we are seeing different, lower percentages in the 40's and 50's for patients in whom complete clearance in an area is achieved. So we have to make an adjustment. In light of the new standards, products still claiming 80% or 90% clearance would be far less effective if the complete clearance standard is used.

Dr. Robins: The next question involves actinic keratoses in different populations. Do we see AKs in people with dark complexions? Do we see them in Asians and people from the Middle East? I haven't seen any in African-Americans. Has anyone?

Dr. Hale: They are certainly far more common in Caucasians, and as Dr. Sarnoff pointed out, they are far more common in Fitzpatrick types I through III. Very often a patient with rhinophyma or rosacea will present with actinic keratosis. In general, our population is living so much longer today that when patients come in, often they are in their 70's, 80's, or 90's, and even though AK is not what brought them into the office, we see it as an incidental finding in many of them.

Dr. Robins: Patients not only live longer, but can get to the sun quicker and more often, which is all part of the equation. Here's another question. Some discussions that I have participated in involved the possible recurrence of AK versus new lesions on the same area. This persistence vs. recurrence issue is frequently debated regarding basal and squamous cell carcinoma. Does anybody want to approach that with respect to actinic keratosis?

Dr. Perez: If we look at it from the molecular point of view, and we find out that the same mutations in the P53 gene that are present in many squamous cell carcinomas are also present in actinic keratosis, we know that the SCCs are a kind of clone of the original cell. Your body may be able to get rid of those original cells, but they are replaced by cloned daughter cells, then

subsequent daughter cells come to replace those, and, eventually, if there is an accumulation of enough mutations in that gene, we move from precancerous actinic keratosis to squamous cell carcinoma.

Dr. Sarnoff: I've heard Dr. Robins make a great analogy about a dart board. If you visualize a dart board, and right in the center at the bull's-eye there is a skin cancer, who's to say that the cells in the area around that skin cancer haven't been radiated as well, producing that "restless epithelium" that Dr. Jorizzo spoke about? It may be just a matter of time before that restless epithelium converts to a frank squamous cell carcinoma.

Dr. Jorizzo: I am uncomfortable with the recurrence idea as well, and in a number of manuscripts I have suggested that it be changed. For example, there are some techniques such as cryosurgery. The "frostbite-like effect" locally should completely eliminate the original lesion. The patient then notices that within that same general area they develop other lesions. We must educate patients to keep them from becoming skeptical about whether the original lesion was really fully removed. Sometimes they wonder if we are treating the same lesions again, and I believe strongly that we are not.

Dr. Hale: That's why it's important when you first diagnose someone with actinic keratosis that you explain that this condition is a marker—that they could well have sustained significant actinic damage which will cause more of these lesions to develop in the future.

Dr. Robins: The natural next question is, do you need new exposures to UV light to activate new AKs, or not? What if a patient says, "Dr. Robins, I have not gone in the sun since I came here three years ago. How come I'm still getting more lesions?"

Dr. Nehal: First of all, patients typically have the perception that they're not going in the sun. But we know that they do not live in caves. They are exposed in the parking lot going from the car to the office or when they walk down the street everyday. They are not putting on sunscreen every morning, using it properly and reapplying it the way we would like them to, so we know they are continuing to get sun exposure. They just don't perceive this, perhaps because they are not specifically going to the beach and sunbathing.

Dr. Jorizzo: I used to give patients an out by telling them, "These lesions were probably caused by the sun exposure that you had as a child," but truthfully, a couple of things are changing my opinion about this. One is the high prevalence of actinic keratosis on bald scalps, many of which became bald relatively recently. The second is the data that if you use sunscreens aggressively, you reduce appearance of new AKs over the short-term as well as over the long-term. In the past, I would have predicted that regular sunscreen use would reduce the number of actinic keratoses arising 10 or 15 or 20 years later. However, we now know that there is a balance between cellular immunity and the evolution of actinic keratosis or pre-actinic keratosis. Data now shows that if a patient uses sunscreen, he or she will have fewer actinic keratoses that year. I now try to explain to patients that even the short daily trips to and from the car—even these subclinical sun exposures—can shift the balance towards having more AKs the next year. So I assign them more responsibility. I empower them more to change their future.

Dr. Robins: As you know, our profession has an ongoing crusade against tanning parlors. Has anyone attributed an exacerbation of actinic keratosis to tanning beds?

Dr. Hale: I'm not sure that would be true, because very often people use tanning beds completely naked, and I don't really see a predominance of actinic keratoses on normally covered areas of the body. I also think the population that frequents tanning salons is by and large teenagers and young adults, who haven't matured to where we might start to see actinic keratoses. It may be a little too early with them to link AKs with their sunbed exposure, but time may tell.

Dr. Perez: What I'm seeing in the younger adults and teenagers who regularly tan is that they are developing macular hyperpigmentation of the lip. That's scary because of what is going to happen 10 or 20 years down the road—the development of melanomas and other skin cancers in this population of patients. It's very important for us to follow these patients closely, because we may be seeing a higher incidence of skin cancer in them over the next few decades. In addition to macular hyperpigmentation of the lip, we're seeing melasma and sarcoid-like changes of the chest in younger and younger patients.

Dr. Jorizzo: You even see the PUVA-type lentigo on the backs of these patients sometimes, so that is an issue as well. It makes you wonder if there's a combination of causative factors due to genetic predisposition, because with PUVA-derived lentigos there is a fair amount of research discussing why some people get them and some do not: does it have anything to do with DNA repair; is there a connection to the risk of melanoma? Whatever the answers are, I worry about some of these younger people and the skin changes they are developing.

Dr. Robins: Is the use of tanning machines still as prevalent?

Dr. Hale: Yes, it's as prevalent. In fact, there's a salon next door to my building. We share a common wall. Every day, they put a sign outside that says "safe tan," and every morning when I arrive at my parking lot I take that sign and hide it. Then they put it back in the street within a half hour. There's an arrow to come in for a safe tan, and for free tanning on Sunday. They're doing a lot of business, despite our best efforts to educate patients about tanning's dangers.

Dr. Robins: Let's go on to the histopathology of actinic keratosis.

Dr. Hale: Much of what we find about the histopathology of actinic keratoses mirrors what we've just seen clinically. However, most examples of actinic keratosis display a spectrum of changes that manifest in epithelial dysplasia, correlating with the restless epithelium we've talked about. The spectrum ranges from mild changes to those displayed in squamous cell carcinoma in situ, and in between, there are a number of distinct histopathologic variants, including atrophic solar keratosis, hyperplastic solar keratosis, acantholytic keratosis, and lichenoid keratosis, a variant with a dense lichenoid infiltrate.

Basically, run-of-the-mill AKs are characterized by alternating bands of hyperkeratosis and parakeratosis, and generally the parakeratosis overlies areas of the dysplastic atypical epithelium, whereas the orthokeratosis or hyperkeratosis overlies the uninvolved epithelium of the follicular orifices and the sweat gland orifices. This is interesting with respect to the question of whether actinic keratoses are precancerous or actually squamous cell carcinoma in situ. In frank Bowen's disease, which is squamous cell carcinoma in situ, there is parakeratosis overlying the entire dysplastic epithelium. There is no sparing of the adnexal structures, whereas in actinic keratosis the adnexal structures are spared, and only orthokeratosis or hyperkeratosis overlies those orifices. (Figures 1a, 1b, 2 and 3.)

Figure 1 shows both a low-power and a high-power view of regular actinic keratosis. You can see that in both cases, the lesions occur in settings with extensive chronic sun damage and solar elastosis (evident as blue deposits of elastotic material). Note the presence of marked elastosis and a patchy chronic inflammatory infiltrate. You can also see, in the low-power as well as in the high-power image, some areas with atypical keratinocytes. These would not qualify as full-thickness lesions, but rather as just scattered atypical keratinocytes with overlying parakeratosis.

Figure 2 shows a variant of hyperplastic actinic keratosis, with its characteristic hyperkeratosis. Parakeratosis can be seen alternating with bands of otherokeratosis. The orthokeratosis is seen overlying the dilated infundibula and the sweat gland orifices, while the parakeratosis covers the dysplastic epithelium. This is the classic pink and blue alternating pattern that dermatopathologists describe.

Figure 3 shows frank Bowen's disease, or squamous cell carcinoma in situ. The leason clearly demonstrates full thickness keratinocytic atypia. More atypia cells is seen, even in this low-power image, than in the images of actinic keratoses. Large hyperplastic keratinocytes with hyperchromatic nuclei and mitotic figures are visible. Unlike the previous example of actinic keratosis, in Bowen's disease, the dysplastic epithelium also involves the appendageal structures.

These figures reflect our earlier discussion of the wide clinical spectrum that these lesions fit into.

Dr. Robins: Does anyone want to add anything about the pathology of these lesions?

Dr. Jorizzo: One comment: When I was trained in these specific areas, the point was always made about the "umbrella" sign associated with actinic keratosis. With AKs, one observes a refreshment of the epidermis, with an umbrella of nice non-dyskeratotic cells coming up from the follicle. However, once the lesion progresses the next step to Bowen's disease, as we have discussed, you lose that. This kind of clinical distinction reveals some of the differences between the ways in which dermatologists and non-dermatologists work. That is, I am generally proud of what dermatologists do, but when non-dermatologists are in doubt, they often choose a destructive treatment for lesions and sun-exposed skin.

Dr. Robins: Yes, they tend to believe in, "when in doubt, cut it out."

Dr. Jorizzo: Yes, cut it out, freeze it out, put a topical agent on it, whatever. But only a dermatologist has the clinical pathologic training and skill to make the right treatment choices here—

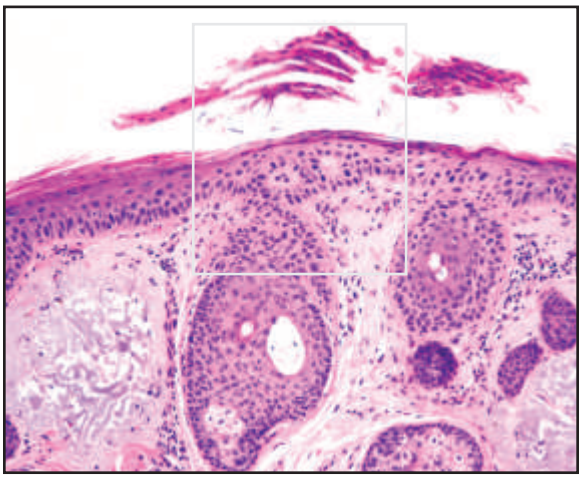

Figure 1a: Low power view of actinic keratosis.

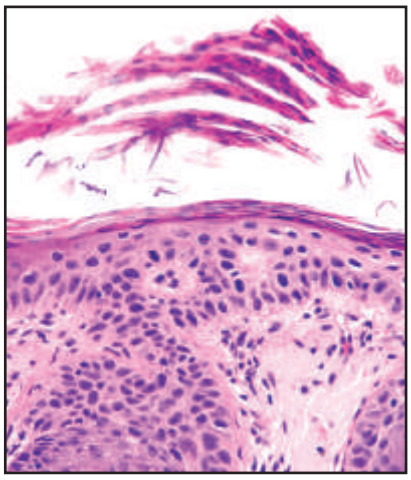

Figure 1b: High power view of actinic keratosis.

to appreciate fully the clinical correlates to these subtle changes and variations. We will excise the lesion, or at least examine a sample of it, whenever we suspect that there is an invasion or some progression along the actinic continuum, whereas the non-dermatologist all too frequently does not work in this way. When you have advanced lesions, the epidermal component is a lot easier to monitor through biopsy and surgical excision, whereas if it is eliminated via an inadequate technique such as cryosurgery or a chemical agent, you lose the ability to monitor the invasive part. So I think what Dr. Robins just pointed out is key to why the patient needs us.

Dr. Sarnoff: I agree completely. I would add that sometimes if you sample these lesions histologically, doing a shave excision or shave biopsy, if you don't go deep enough you could have a problem. Of course, we're all walking a tightrope, because you don't want to leave a divot if you don't have to. However, you could get back a report diagnosing actinic keratosis, but with the disclaimer that the atypical cells extend to the base of the specimen you've sampled; thus, if you haven't gotten down to the follicular structures or sweat gland structures and you have just a small piece, especially if it fragments in the bottle, you could have a dilemma. Because even if you're told that it's a simple AK, if it extends to the base, who's to say that had you gone a bit deeper, you wouldn't have found full-thickness atypia of the epidermis, meaning that you really may be sitting on a Bowen's disease lesion?

Dr. Jorizzo: One other key point: the dermatologist is really the only clinician who can have the confidence to say, "Even though I thought based on the clinical examination that this lesion was an actinic keratosis, and even though the biopsy report says that it is an AK, I am going to go back and look again." I think that because non-dermatologists lack the clinical training in dermatologic pathology, they may often look at a pathology report as if it's a biblical edict—as if it is a laboratory test that is simply positive or negative. In contrast, after reviewing the pathology report, dermatologists will often trust our clinical judgment about a lesion and go back and look at it again.

Dr. Robins: That brings us back to a point we started to touch on earlier: when is an actinic keratosis a superficial squamous cell carcinoma, when is it not, and is this a black and white issue or is there a big gray area?

Dr. Sarnoff: I still believe strongly that there is a spectrum of disease. We understand that an underlying defect in p53 occurs in both actinic keratoses and squamous cell carcinomas, but we need to treat the patient clinically and line the treatment up with the pathology report. If you have an isolated lesion that is fairly palpable and a histology of actinic keratosis, you need to remember that it's actinic keratosis, not an invasive disease. But in my mind, the key distinction is whether the disease is in the epidermis or the dermis. I treat the two very differently. I would treat disease of the endodermis as basic squamous cell carcinoma, taking it seriously. When the lesion is limited to the epidermis, I have many more options, such as cryotherapy. That's how I make my distinction, and I advise the patient accordingly.

Dr. Hale: Another thing that complicates matters histologically is Bowenoid actinic keratosis, one of the subtypes of AK. The question is, where do you draw the line between Bowenoid actinic keratosis and Bowen's disease? Again, histologically, is there parakeratosis overlying the dysplastic epithelium at the adnexa? Where is the dysplasia occurring, and what does it involve?

Dr. Sarnoff: Often it is important to correlate new findings with everything you already know about the patient. If you've sampled only a portion of the lesion and a broader plaque is found, even a subtle plaque, and more of the lesion remains, you're obliged to rebiopsy or do something more definitive if you have any uncertainty. But if there was a single tiny lesion that you've

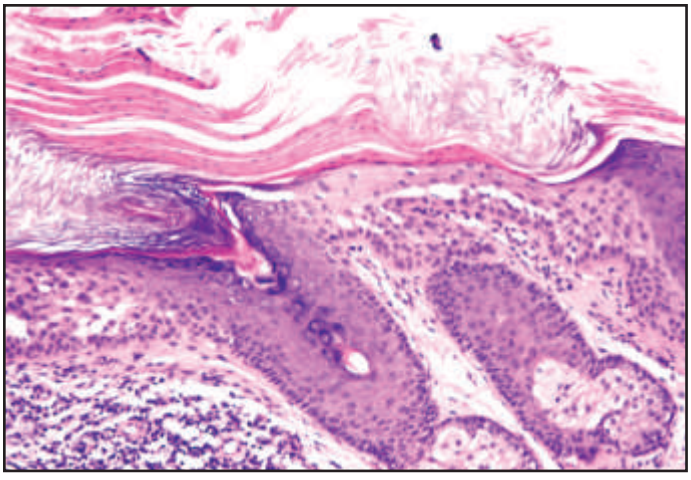

Figure 2: Hyperplastic actinic keratosis.

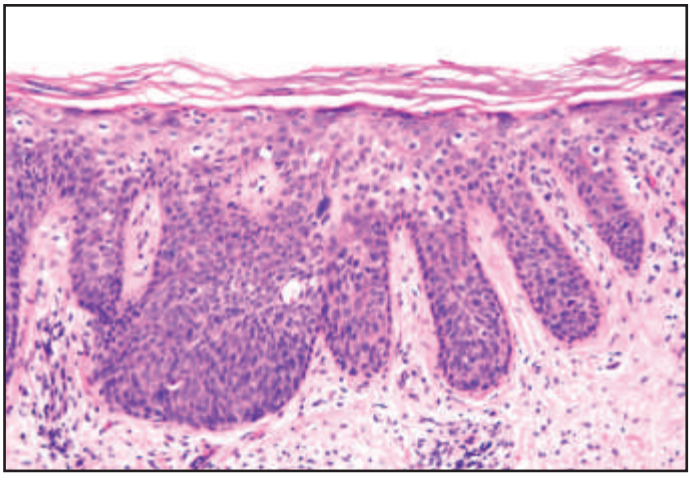

Figure 3: Bowen's disease (squamous cell carcinoma in situ).

already treated, and you get back a diagnosis of actinic keratosis, clinically there may be nothing you need to take issue with, and you can simply follow the patient clinically over time.

Dr. Perez: I tend to treat the patient and not the lab report. When you are treating patients with cancerous and precancerous lesions, it's very important to go back and look at the area where you performed the biopsy. For example, even if the pathology report says that the lesion is an actinic keratosis, if the remaining portion of the lesion is erythematous, scaly, and a bit black, to me that is the clinical diagnosis of Bowen's disease. Therefore, I will further biopsy or treat that that lesion, because if I don't, and the patient moves or otherwise loses contact, the real possibility exists that the lesion can ultimately morph into an invasive squamous cell carcinoma, with all its complications and implications for the future.

Dr. Jorizzo: Our residents do a roast of the faculty every year, and they once roasted me by showing me explaining to a male VA patient about how his actinic keratosis was really an abnormal Pap smear.

Dr. Sarnoff: I use that analogy all the time, because patients understand that. And I talk about how if you get back a report showing a little dysplasia, sometimes you need to do a conization. Women patients especially understand that, and the spouse of a male patient can understand that and relate to that. It's a very good analogy.

Dr. Robins: It's important to note that we're best equipped to recognize an actinic keratosis at its very earliest, using differential diagnosis. One reason we do biopsies expeditiously is to confirm our suspicion that a lesion is nothing more serious than what it seems to be clinically. Let's start with some differential diagnoses that one might consider.

Dr. Hale: Clinically, you have to differentiate among some of the conditions we've been talking about—AK vs. squamous cell carcinoma, verrucous carcinoma, Bowen's disease, or seborrheic keratosis. Those are some of the things I would consider.

Dr. Robins: Also melanoma—amelanotic melanoma.

Dr. Hale: And some of the pigmented keratoses that we see in sun-exposed areas on many of our male patients can mimic lentigo maligna melanoma.

Dr. Sarnoff: So can seborrheic keratosis.

Dr. Hale: Absolutely. That's one of the most common differential diagnoses. Sometimes you have just a small inflammation that isn't neoplastic at all—maybe a small guttate psoriasis lesion—and unless you consider it in context and look at the rest of the patient, you can begin to think it's an AK. If you specialize in skin cancer, you may start to believe you're seeing a lot of actinic keratoses, so it's important to put it all together.

Dr. Robins: You may be predisposed to believe the worst if you've been in practice as long as I've been. I've heard so many times that a plastic surgeon or general surgeon took a patient to the operating room and excised an actinic keratosis and said, "I've got great news for you, the operation was a success, and it wasn't malignant!" I used to hear this about once a year, and though it's not that frequent anymore, it's mind-boggling. I even know of a Mohs surgeon who put zinc chloride paste on an actinic keratosis because he was sure it was a squamous cell carcinoma—without doing a biopsy. Certainly, the two conditions can look alike, but you have to do a biopsy. Today, dermatologists are more and more equipped to recognize the differences, but we're also equipped—and compelled—to do a biopsy. Other surgical specialties are disinclined to do biopsies in these instances.

Dr. Jorizzo: There is another side to that coin—cost-effectiveness. Steve Feldman and Allen Fleischer in our department did a nice study in which they compared excision margins in surgeries performed by non-dermatology surgeons (plastic surgeons) and dermatologic surgeons (not including Mohs procedures). These were just simple excisions, with pathology specimens submitted by both types of surgeons, from lesions of the same basic size found in the same basic locations. The dermatologic surgeons' positive margin rates were found to be in the 3-4% range and the plastic surgeons' in the 30% range. I think that shows a pattern of inexact and non-cost-effective treatment by non-dermatologic surgeons similar to what you described.

Dr. Robins: Can you explain what those numbers mean?

Dr. Jorizzo: The numbers indicate the percentage of pathology specimens that had a positive margin (i.e., margins that still contained cancerous cells) after excision of the tumors. The non-dermatologic surgeons had a much higher rate of positive margins. To me, this is the other side of the coin, still reflecting badly on non-dermatologic surgeons, in this case removing too little tissue rather than unnecessarily removing a benign lesion. This data tells me that dermatologists know what they are removing and why they are removing it, and they plan an appropriate procedure based on their clinical diagnosis. If they think a lesion is a cancer, they cut out sufficient tissue to get a clear margin, whereas the non-dermatologist may randomly use the same margins in all instances. If the lesion proves benign or even precancerous, they then tell the patient the "good" news, but on the darker side, when the lesion proves malignant, they often have to go back and excise more tissue after initially cutting out a tiny, almost diagnostic, sample. We have actually heard non-dermatologic surgeons say, "That's our practice; we excise rather than biopsy." They simply do not do shave biopsies or small sample biopsies.

Dr. Sarnoff: The problem can also be traced to our medical/legal system. I recently was called to testify as an expert to help defend a dermatologist who had given absolute-

ly appropriate care. The issue was why he had shave-biopsied rather than punch-biopsied an actinic keratosis. In shaving it, he perhaps hadn't gone deep enough to learn that the lesion had actually been a Bowen's squamous cell carcinoma. So lawsuits are now focusing on these kinds of things. I think it's our obligation to get the word out that, unfortunate result notwithstanding, the kind of care provided by that dermatologist is the proper way to proceed.

Dr. Robins: Right. The shave biopsy remains the diagnostic method of choice for actinic keratosis, since the number of incidents where neoplastic cells reside deeper than the scope of the biopsy is so infinitesimally small. The destruction of more tissue and making larger holes or defects generally isn't warranted.

Dr. Sarnoff: That's what experience teaches dermatologists. We are the most qualified to handle these patients because of our histologic training as well as our clinical background.

Dr. Robins: I appeared once on "Nightline," and Ted Koppel asked me, "If I suspect that I have a skin lesion, should I go to my family practitioner?" I answered yes, that's a good idea, but if there's a dermatologist close by, it would behoove you to go to the dermatologist instead, because he or she is best equipped to identify and diagnose the problem at the very earliest.

Dr. Jorizzo: And the best equipped to perform the right procedure the first time. Health economists who do cost analyses like I described earlier have found that performing an operation in a surgical center is several times more expensive than doing so in an office space. So, if a non-dermatologic surgeon has to go back to a surgical center 30% of the time to repeat procedures because of positive margins, what does that do to cost? In contrast, dermatologists in an office setting can reach a clinically sound clinicopathologic diagnosis and plan appropriate treatment, with a high chance of resolving the problem and a very low chance of having to repeat the surgery. That is the argument being made today to insurers by dermatologists.

Dr. Hale: Isn't the American Academy of Dermatology very involved in this?

Dr. Jorizzo: Yes, the AAD is involved. It sponsors a forum for managed care managers, and Steve Feldman has presented them with this kind of data, which is helpful. All the data has then been provided to the AAD, to use at the state level.

Dr. Sarnoff: Before we leave the subject of differential diagnosis for good, I want to mention that a colleague has found pigmented actinic keratoses a couple of times. These can be very difficult to diagnose either clinically or histologically. And I've been seeing a patient who has a pigmented macula on her nose. We've biopsied it twice now, and both times the lab report has shown pigmented solar keratosis with scattered lentigo maligna melanocytes. So we may not have enough histologically to diagnose lentigo maligna, and clinically we're not certain. It's a difficult situation. Pigmented actinic keratosis vs. lentigo maligna is an important differential.

I'd like to make one last point on this subject. Self-tanning lotions with dihydroxyacetone have become very popular in the last few years, and I see a large number of female patients with actinic keratosis that they did not become aware of until they started using self-tanners. And as the self-tanner wears off, they harbor extra pigment both in their early solar lentigines and sometimes in their actinic keratoses. The keratoses start to appear brown and look like pigmented actinic keratoses. They're interesting to look for because they seem to come out more in summer after people have been using a self-tanner.

Dr. Robins: That's a very important point that I haven't heard mentioned before.

Now, I'd like us to touch on the recent increased awareness and incidence of actinic keratosis.

Dr. Nehal: I'd say that now more than ever before, people are concerned about their skin, thanks to the efforts of groups such as The Skin Cancer Foundation that make people aware of sun damage and skin cancer. Today, when people have a skin lesion that doesn't heal or go away, or increases in size, or perhaps even bleeds, they are more likely to report it to their physician or to a dermatologist. This is increasingly true for both males and females.

Dr. Robins: This general awareness of the skin is the greatest I've seen in the many years I've been in practice. It's really refreshing because it often leads you to detect not only AK, but also other malignancies, sometimes even melanomas. In addition, today we do regular total-body examinations, which wasn't the case in the past. In our practice, we do more body checks than ever before; if we don't do 10 body exams in a day, it's a bad day. Corporations are also promoting body examinations, often sending their employees for complimentary exams. So there's definitely a new awareness in the public, a willingness to come in sooner than before. But this awareness is still greatest among women. Men come in with large keratoses or other lesions and say, "Oh, I never noticed it before, I don't think it was there last week," and women come in with little lesions and say, "Oh, I'm afraid it's been there for months, years."

Dr. Sarnoff: The Internet also gives people access to information they never used to have. They read about health and medicine. In general, the consumer or patient is just more savvy and aware than ever before. Very often, because they have done their reading or looked online, patients will come in and say, "Do I have sun damage?" "Do I have actinic keratosis?" "Do I need this cream or this treatment?" So I think that this availability and exchange of information has made people more aware. Plus, people are simply living longer, which in itself allows them and their peer group to be better educated. One patient will be diagnosed with actinic keratosis or skin cancer,

and a friend will say, "Oh, I'd better go get checked as well." There's just more awareness overall.

Dr. Perez: It's not only the information on the Web, or from The Skin Cancer Foundation, or the American Academy of Dermatology, but also all the journals and magazines and television that are bombarding every single one of us with the idea that sun exposure is associated with skin lesions and skin cancer. It's also that we are in the generation of "the beauty." Let's be realistic; skin lesions look ugly. An actinic keratosis that is pigmented or a verrucous keratosis that is hyperplastic looks very prominent, and that's what often brings the patient to us. Fortunately, because of that ugly lesion, we might be able to diagnose other important lesions in that patient. So, it's not only the awareness of skin cancer in all the media, but also that we are in the generation of extended life and beauty.

Dr. Jorizzo: The fact is, with all the reading that they do in the popular media, patients who have a cosmetic concern may feel that they can choose from a number of different specialists for that problem. Often, when there is a bit of a battle among specialists over an issue like cosmetic care for sun-damaged skin, it is nice to be able to go to the high ground and say that the reason patients do best with dermatologists is our superior management of all aspects of sun-damaged skin. I view this management as a five-step process, and dermatologists are not just the only specialists who do all five of these steps—we are the only specialists who regularly do more than one. The first step is prevention. We talk a lot about sunscreens and sun avoidance, and I'm convinced that we are the only physicians who know how to teach patients effectively about prevention. Second, we examine all of the sun-damaged skin, and we know how to find actinic keratoses and skin cancers and melanomas. Third, we're able to do lesion-destructive techniques at the time of the visit. Fourth, we can use field AK techniques between visits. And finally, when these problems are under control, we can go on to cosmetic procedures. So, patients often go to a physician with a cosmetic concern, and if it is a dermatologist they are very likely to get comprehensive care for the whole problem. If it is not a dermatologist, they might very well get stretched skin with a sandpapery feel, which is not the best approach.

Dr. Sarnoff: I always tease my husband, who is a plastic surgeon, that I care about skin quality, while he cares about skin quantity. We always have to address quality as well as quantity.

Dr. Robins: I know of a clinic that for years did routine free examinations on all the executives, complete screening from A to Z. But they found out that all these preventive screenings did not cause people to live longer. The percentage of serious problems that they discovered was no different from the percentage normally discovered when people with problems went to a dermatologist. Now, the one country that does not allow these screenings is Holland. I've asked dermatologists from Holland why they don't do this screening, and they give very similar reasons—it's because the screenings weren't proven to detect any more lesions than would have been detected when people with problems simply went to a dermatologist. They also found out that most of the people who went to the free screenings didn't have anything seriously wrong with them. The people who really had something wrong with them tended to go to a dermatologist instead, where the treatment was covered by their free health insurance anyway. Since the free screenings weren't any cheaper than the coverage with their free health insurance, they felt they might as well go to the doctor they wanted. A couple of papers from Holland have been written on this.

Dr. Perez: But they have free medical services that we don't have in the United States. I feel that quite a number of the melanomas we diagnose in this country were first detected at our annual free skin screenings around the country in May. Many of these people don't have medical coverage and have never gone to a dermatologist, so they take advantage of the free screenings, and it allows us to diagnose problems we might otherwise never have seen.

Dr. Jorizzo: In any event, the marketing of the screenings may be more important than what is actually accomplished at the screenings, because all the publicity involved tremendously increases awareness about skin cancer and dermatology.

Dr. Sarnoff: With respect to heightened awareness, I think the idea that actinic keratoses are precancerous really makes a mark with patients. They remember that they actually have had a precancerous lesion. That's why, if you clinically diagnose AK at the first visit, it's important to confirm the diagnosis with a biopsy so that you can tell them it's definitively actinic keratosis. Often, when new patients come into the office and you ask them about their skin history, they say that they've had precancers before; it's what tells them that they've had significant skin damage and need to protect themselves.

The wonderful materials from The Skin Cancer Foundation and the American Academy of Dermatology also have been vital in increasing awareness. Like a patient reminded me just yesterday, one picture is truly worth a thousand words. He had simply looked at a brochure in the office, saw a photo of an AK, and asked me to check a spot on his skin that he had not really come in for. And it did turn out to be an AK. So I think that it's a very visual thing for patients. Often, laypersons don't have to know all that much if they see a photograph. That alone may enable them to realize that they have something on their skin worth looking into. And that's very valuable.

Dr. Jorizzo: I have started to modify what I tell patients a bit. I have always called AKs precancers, and I still tell patients that is what most people consider them to be, but I add that the newer studies suggest that they have cells with all the markers of cancer.

Dr. Hale: One thing that's important to explore is the whole reason why we treat actinic keratoses. Is it cosmetic; is it because of their appearance? Or are we treating them because

we're concerned about progression to squamous cell carcinoma? It troubles me that there are no reports on what percentage of AKs go on to become squamous cell carcinoma. Because it's my feeling that if you have a 50-year-old patient with an extensive history of actinic keratoses, they are going to live long enough so that a number of those lesions will progress to SCC. So, that's what I tell patients when I explain why we are treating the lesions. We treat them because we can't predict which ones are going to change, and inevitably a number of them will change over the patient's lifetime.

Dr. Robins: To be on the safe side legally, I often add the word "invasive" before SCC; I say, "progress to invasive squamous cell carcinoma."

Dr. Perez: Especially in the medical/legal environment today, we need to protect both our patients and ourselves. We know that the molecular damage in actinic keratosis is the same as the damage in squamous cell carcinoma, although it has different behavior. We know that any one of those lesions has the potential to change into invasive SCC. So in my opinion we should all be treating those lesions, not for cosmetic reasons but for medical reasons.

Dr. Nehal: Often a patient may have so many lesions of actinic keratoses that an overall treatment is necessary to clear the background skin with liquid nitrogen, curettage, other destructive methods, or topical therapy. But the caveat is that when the patient comes back, and any of those lesions persist, or if the areas itch or bleed, it might indicate that you need to biopsy that particular site.

Dr. Robins: Basically, you can classify AK treatments as either surgical or medical. Let's discuss surgical treatments first. In a nutshell, you can excise, desiccate, or curette, or some combination of the three; except if you excise first, you obviously can't use the other methods. In my opinion, there isn't a place today for excision with actinic keratosis. We have other methods that are less disfiguring and require less down time for healing. Certainly, some surgeons might decide to excise a lesion and send it to the laboratory for diagnosis, but I don't believe it is the treatment of choice. Curettage is probably the most commonly used method among dermatologists. I think the curette is the best instrument we have in dermatology, and Mohs surgeons are especially convinced of that. We couldn't perform surgery without it. However, the curette is used most often for isolated, single lesions rather than for large, extensive areas of lesions found on multiple sites on the body and face. For a small, isolated lesion, curettage is fast, easy, and usually successful.

Once curettage has been used, it's rare to use electrodesiccation, except when there's some bleeding. Some patients are on aspirin or blood thinners, so if you curette something, there might be some heme, and it can be difficult to control the heme with aluminum chloride or Monsel solution. In those instances, a light desiccation will accomplish hemostasis.

Are there any other surgical methods we should discuss?

Dr. Jorizzo: I would like to speak about cryosurgery. Some patients have so many AKs—frequently 50 or 75—that even an experienced dermatologist can mistake them for some sort of photoeczematous eruption. Cryosurgery allows one to treat a lot of lesions quickly, with relatively little down time for the patient. It has several advantages as part of a comprehensive management program for AKs: it is easy to perform; it has a high success rate; scarring is not an issue unless secondary infection occurs; and it can treat hypertrophic lesions. I think that the 10 - 15 percent of actinic keratoses that do not go away in trials with effective topically applied treatments would not go away after three months or three years of treatment, because there is a barrier issue. Those AKs are probably the more hypertrophic lesions, and while curettage is an acceptable way to address them, so is cryosurgery.

Dr. Hale: However, there can be hypopigmentation secondary to cryosurgery.

Dr. Jorizzo: Yes, potentially. I would look at it as a complication of cryosurgery. But it probably relates less to the degree of cryosurgery than to the care after cryosurgery. I explain that to the patient. Because even though I do not advocate it, you can do cryosurgery with a thermocouple for basal cell carcinoma and not have any dyspigmentation afterwards. But secondary infection is a big problem with cryosurgery. In my practice, we treat patients of all races, creeds, and colors, and the typical patient has a dermatosis plus actinic keratosis. In a half-day clinic, I will end up freezing 5-10 actinic keratoses on a good two-thirds of my patients. In that environment, it would be difficult for me to practice without cryosurgery.

Dr. Sarnoff: My experience with cryosurgery is similar. But sometimes, on a background of photodamage and bronzy discoloration or actinic bronze-like changes, perhaps what we're seeing is just relative hypopigmentation; there's a disparity between the area that was treated and the surrounding sun damage. However, that translates clinically into macular hypopigmented areas, which sometimes are not cosmetically acceptable, particularly on the face. That especially can be true with the ethnically diverse patients that I see in New York City.

I received my training from Dr. Robins, who greatly believes in the curette, and I came to embrace the curette in my own practice. Twenty years later, I use a procedure in my office that my patients and staff refer to as the "steel peel." Basically, I prepare the face with EMLA or some other kind of topical anesthetic an hour prior to treatment, then simply take the curette and map the entire face, showing the patients that the curette really can't do much to the integrity of normal skin. There is some bleeding, and we have to be careful about problems such as hepatitis related to the bleeding; we can control it with aluminum chloride. Very often, immediately following the procedure, I will employ a beam of light—perhaps intense

pulsed light or a 532 nm pulse wavelength—to diminish the erythema and to treat a large area en masse at the same time. I find that the steel peel keeps people from becoming hypopigmented and allows them to heal rapidly, usually within a week to 10 days. In that time, I often can bring them to a point that would have taken a few weeks with topical 5-FU, and bring them there quickly. There is definitely some down time, but we get no hypopigmentation, and we're often successful at treating multiple lesions relatively quickly.

Dr. Hale: One important point you made is that there is a little more pain associated with curettage. You need to give time and attention to using a topical or injected anesthetic. One of the advantages of cryosurgery is its rapidity, partly because you don't necessarily have to use anesthesia.

Dr. Jorizzo: It is very important to educate patients about all this. We have cryosurgery sheets that we give to each patient, emphasizing their responsibility in preventing secondary infection, because there are only so many things that we can do. Why is it, for example, that a herpes simplex lesion does not generally scar? I think it is because they often occur on the lips, whereas if the patient has a zoster lesion, they do tend to scar. Under the microscope, in both cases, it is a granular layer pathology, but patients pick at the zoster lesions, which gets them infected. I think this can also happen with a cryosurgery wound. The lesion itself should not produce a scar, but infection of the site will do it, and if we freeze aggressively, they can get bullae, and the bullae can become infected. The patient picks, the split gets pushed below the lamina densa, and hence you have scarring or just dyspigmentation because the melanocytes are sensitive to the inflammation.

Dr. Robins: For the single isolated lesion, all the methods we've discussed work. I am not a big enthusiast of the laser for AKs, however, because it's almost overkill, but you do what works best in your office. As Dr. Sarnoff said, just curetting these isolated AKs is effective. As for cryotherapy and hypopigmentation, it depends on how heavy your hand is with the liquid nitrogen, with the spray gun. How many times do you freeze the lesion? Do you freeze it once, thaw, then freeze again and thaw again? Another problem is that many elderly patients who have a lot of actinic keratoses also have solar lentigos, so you can't tell what the color of the skin is and what the hyperpigmentation is. With so much actinic damage, I don't think that hypopigmentation or hyperpigmentation matter that much. But if you have a small, isolated lesion, either curette it or very lightly use liquid nitrogen. We talked earlier about how to treat a biopsy that comes back showing actinic keratosis. I think that, whether prophylactically or just subliminally for the patient, it's important to give the site at least a squirt of liquid nitrogen, so that you've done something. In the past 20 years, I've found that none of these lesions developed into squamous cell carcinomas, but at least this way we have demonstrated a treatment for the patient.

Dr. Nehal: Some people apply the liquid nitrogen with a cotton-tipped applicator, and some apply it with a CRY-AC device. There's a learning curve in figuring out just the right amount of nitrogen to use and duration of the freeze/thaw time.

Dr. Robins: Is anyone still using the dipstick applicator method?

Dr. Sarnoff: Yes, that's my custom and practice. I'll try to make the cotton a little fluffier, but I find that it gives me better control.

Dr. Jorizzo: It is not as deep a freeze.

Dr. Robins: Well, I just give the gun one quick squirt.

Dr. Jorizzo: Unfortunately, there is a proliferation of cryosurgical devices in non-dermatology offices. It is important to know what is being frozen, and dermatologists really know what they are freezing. They have experience with the techniques they choose to use that non-dermatologists can not match. So they run into fewer problems.

Dr. Robins: Do you explain to the patient all the options in treating their lesions, or do you just tell them, "This is my recommendation; this is what you need." Do you have to go through the whole list of possible methods?

Dr. Sarnoff: Proper informed consent as we know it today means always discussing alternative treatments.

Dr. Robins: Now, what about medical treatments? There are a number of topical products on the market today: 5-fluorouracil (5-FU), Solaraze, etc. When and how should we use these different topical preparations?

Dr. Perez: As we've discussed, today there are very effective surgical procedures, such as cryotherapy and curettage, that can be used to treat most AKs. But we all still see some patients who have widespread actinic bronzing, who are covered with solar lentigos full of actinic keratosis. We can't just submerge them in a tank of liquid nitrogen. Therefore, we instead select a topical application. We'll lighten those lentigos. And we'll separate the actinic keratosis medically from that background of photodamage, using either immunomodulators or substances that get incorporated into the DNA of the keratosis, destroying the precancerous lesions so that they can be replaced with normal cells. Among the immunomodulators we use are those such as imiquimod, which stimulates production of gamma interferon and induces the lymphocytes to attack the actinic keratosis. And 5-fluorouracil is one of the key substances we use, particles of which become incorporated into the DNA of AKs to kill the precancerous cells.

Dr. Jorizzo: In my 18 years at Wake Forest, I have treated a number of patients who require the same surgical destructive treatments every six months or every year. In my office, they

are typically getting cryosurgery again and again, and they can become somewhat discouraged. Also, their skin is left with a sandpapery feel from untreated lesions, which does not please them at all cosmetically. So, the concept of an interval therapy that can reduce the amount of freezing they might need on a subsequent visit is very appealing. Carac is my preferred form of 5-fluorouracil for interval therapy.

Immunomodulators are another story. It is important to remember that along with the impact of genetics—including light skin type and genetic damage from sun exposure—the other key predisposing factor associated with actinic keratosis is reduced cellular immunity. As people age and their immune surveillance becomes less effective, a higher percentage of their actinic keratoses appear to progress to invasive squamous cell carcinoma. However, young people with a lot of actinic keratosis can also suddenly have their cellular immunity paralyzed, say by a renal transplant with immunosuppressive therapy, and they start developing invasive squamous cell carcinomas about every two months. So, there is a question of immune balance, and you may need to shift this balance to the patient's benefit. That is why the theoretical concept of an immune modulator is so appealing. Imiquimod, or Aldara, is the only topical immune enhancer that is available. On the plus side, it does not produce any phototoxicity, so you can use it year-round. Also, if you use it long-term, even if you have underestimated the lesion and it turns out to be invasive, the patient may not be the worse for it; since imiquimod is theorized to penetrate through the lesion and to stimulate the immune system to reject it from below, the treatment may eliminate the lesion in any event. The negative is that the treatment produces a lot of inflammation, which you cannot suppress, since that is how the therapy works. You cannot suppress the inflammation and still have the chemotherapeutic effect.

Dr. Sarnoff: Another down side is the expense. Many of our patients have Medicare, but no drug plan associated with Medicare, and those 12 little packets are quite costly for the patient.

Dr. Jorizzo: Unfortunately, the treatment is still off-label for actinic keratosis.

Dr. Robins: And it's a long treatment. The interval therapy for imiquimod is not as clearly established as for Carac. There are impressive data for Carac showing that you can get rid of almost 75% of actinic keratoses in one week. That's what swayed me to use it for interval therapy. With Aldara, when I have used it as interval therapy, I have empirically chosen to use it five days a week for two consecutive weeks, but I need to have more concrete data as to what kind of responses it produces.

Dr. Sarnoff: I would add that there has been a resurgence of interest in the retinoids as preventive therapy. As Dr. Jorizzo mentioned, some patients have to have cryotherapy many, many times, and we want to do something to prevent this. When I'm seeing a patient like that, I think of retinoids as maintenance therapy, along with 5-FU.

Dr. Robins: It's worth focusing on 5-FU in some detail. There are two companies that manufacture it—Dermik and Valeant Pharmaceuticals, which make Carac and Efudex, respectively. It's not a new treatment, but has been on the market for about 30 years. It was the first topical medicine we had for AK. However, Dermik's product is a new formulation contained in a molecule that allows us to apply it once a day for four weeks, achieving good results and greater compliance than the other 5-fluorouracils, which require twice-a-day treatments for three to four weeks to get comparable results. It also comes in a strength that is just 1/10th the strength of its competitor's.

Dr. Nehal: If I'm going to choose topical therapy, I typically choose Carac, partly because of the once-a-day regimen. It improves compliance. I'll generally tell the patient to apply it once a day, but I warn them that they're not going to see much of a response until day 7 to 10, and that the response will continue to increase in terms of redness and crusting. I typically recommend a three to four- week course of therapy. I see them the day I give them the prescription, and I see them again at three to four weeks to observe the extent of the effect. At that point, I typically give them a prescription for hydrocortisone 2.5% cream to reduce inflammation. I feel that the degree of irritation with Carac isn't as minimal as we might expect. It may be 50% less severe compared to other topical products but there still is a significant degree of inflammation with a full course of treatment.

Dr. Hale: Very often I give my patients in New York a choice; I tell them what inflammation to expect, and if they don't want to do the full course of treatment covering the entire area of actinic damage, we can select specific, circumscribed areas to treat. Perhaps they just want to focus on the forehead area, or perhaps the dorsum of the hands, one hand at a time to leave them one uninvolved hand to do their everyday duties with. They sometimes like that much better than treating everything at once, and they can accept the erythema and down time because it's a partial, segmental area.

I find that in the pretreatment counseling, it's very important to show these patients pictures of what they could well experience during and after treatment. Often, the inflammatory response doesn't peak until after the first or second week, and even after they've stopped the therapy, inflammation will persist, and they need to know this beforehand.

Dr. Sarnoff: Good point. If you don't do this, you can count on a phone call from them. They'll worry that they're allergic to the medication. And usually the phone call is at 2:00 in the morning.

Dr. Robins: Once in a while you have a patient with such extensive actinic keratosis that you are a little reluctant to subject them to daily treatment—even if you're treating small areas one cosmetic unit at a time. So we try a different approach. We say, "Let's use pulse therapy—treating every other day, or two days

in a row followed by two days off, or one week followed by one week off." We've used all three approaches, and all three have worked. I can't say necessarily that we had 80% or 90% improvement, because we didn't count the number of lesions we started with, but we had decisive improvement. After using any one of those regimens, you wait a month or two and then repeat it. In this fashion, we've removed a substantial amount of actinic keratosis without seeing the extensive inflammatory reaction you would see with everyday treatment. It's slower, but it works.

Dr. Jorizzo: Based on my personal experience as well as data I've seen, I'd say that most dermatologists do not use chemical treatments. Only a well-defined, finite percentage of dermatologists use them. It's a fairly small market. The reason, I believe, is that physicians have always been confused about what is required to gain FDA approval for a treatment. In the past, to obtain FDA approval for an actinic keratosis treatment, you had to show that some 80%+ of lesions would be cleared, and it generally took 8 to 12 weeks to secure the approval. Today, you only have to show that 40% or 50% of the patients' lesions clear in a given area. But in dermatology, we seldom practice monotherapy, and seldom use the exact treatment regimen that was used to get FDA approval.

Dr. Robins: In other words, we use "off-label" regimens.

Dr. Jorizzo: Yes, off-label treatments. I always remember that in my first week at the University of North Carolina, I put 5-FU on a couple of patients who had a lot of actinic keratoses. The patients then called to complain in the middle of the night, and came back to see me. If I had been setting up practice in Chapel Hill, I would have had to leave town, because in the Southeast, in the Bible Belt area, if your patient can not go to church for two months, his or her reputation is ruined. There are many patients to whom I cannot suggest 5-FU without them putting their hands up and saying, "There's no way." So, yes, you have to come up with a regimen that works for the individual patient. If you have patients who work with the public, you have to schedule their visit for a time when they know they will have three to four days or a week to heal from cryosurgery or the like.

Ideally, I want a treatment that will significantly reduce the amount of freezing I have to do every 6-12 months. Patients with sun damage and actinic keratoses are usually our patients for a long period, and over time, the interval between their visits may taper from every three months to every six months to every year or two. However, they seldom are dismissed totally from our practice, because they are at ongoing risk. As long as you are seeing the patient back periodically, a treatment that reduces AKs by 50-75% is a huge success. So, that's why interval treatments serve a purpose. My interval regimen, using Carac, involves one week of treatment, and the data suggest that you can reduce the number of keratoses by as much as 50-75% with that approach.

Dr. Robins: We've found out that this is very effective for the people who have anxiety about using 5-fluorouracil. It's not a true pulse technique, but I call it that; you use a staggered schedule and get less response, but you still clear up a good portion of the AK. We recently did a study comparing Solaraze vs. Carac, using Carac on one side of the face and Solaraze on the other. This study is only in a preliminary phase, but we found that the Solaraze itched more than the Carac. And yet, Solaraze appeared to take longer to show results. Granted, it was only one week, but we saw no response from Solaraze.

Dr. Hale: It was very interesting, because the side that was treated with Carac definitely seemed to have more inflammation of these lesions, more erythema, and more scaling, but the patients complained about pruritis on the contralateral side, which was treated with Solaraze. So it was surprising.

Dr. Robins: Solaraze takes about 3-4 months to produce real results.

Dr. Nehal: What is the longest period of time that you treated these patients with, say, the once-a-week Carac interval therapy?

Dr. Robins: Two months.

Another point recommending Carac and 5-FU in general is that you can suppress the inflammation, yet still have a chemotherapeutic effect. There was a study at Dartmouth back when I was a resident, some 27 years ago. They treated the whole face with 5-FU, then treated half the face with Lidex and half with placebo, and there was no difference in the clinical response. In contrast, with Solaraze you cannot suppress the inflammation, because then you will not have a clinical effect.

Dr. Perez: To summarize the advantages of Carac, it offers a once-a-day treatment that can eliminate the phototoxic effects you once might have experienced with 5-FU, since you can apply it after the sun is down. The patient has no risk of phototoxicity whatsoever. Thus, with patients who have extensive actinic damage, you can decrease the amount of new sun damage and new actinic keratosis that might develop in between visits to your office. Plus, you can suppress the inflammatory reaction without compromising the treatment response. So, Carac has really expanded our armamentarium for the treatment of patients with extensive actinic damage.

Actually, there's yet another beneficial effect of Carac. I do not exactly promote it to patients, but I tell them, "Don't be surprised if after the bout of inflammation, your skin takes on a more supple appearance and has a better texture." That's because the inflammatory reaction gets rid of a lot of the damage in the skin and in some way induces new collagen formation. Even though it's not really an indication of the treatment's success, it makes you look better.

Dr. Robins: After you've gone through a full course of 5-FU, how do you treat the patient? And what long-term protection do you advise for the patient?

Dr. Jorizzo: Over a 23- or 24-year period, I really never used a full course of 5-FU. Then after Carac debuted, I began to use interval therapy. Now, I will prescribe treatment of a one-week interval—one week of treatment between every visit. If I see the patient every two months, say, because he or she is a transplant recipient, the patient will receive treatment for a week between the two months. If patients are getting treatment only every six months because they have fewer actinic keratoses and less risk of invasive cancer, the interval will be one week every six months. And if the patient comes only once a year, I will do the treatment for one week every year. That's my approach—some sort of interval therapy between every visit.

Dr. Robins: I meant, what kind of treatment should be used after the patient starts to have a clinical response to the 5-FU?

Dr. Hale: I've always used an anti-inflammatory type of medicine; usually my custom on the face would be a mild steroid.

Dr. Robins: Mid-strength or low strength?

Dr. Hale: Probably low on the face. Mid-strength would be OK on the body. But I find that if you can get rid of the erythema faster, the patient is happiest.

Dr. Jorizzo: With just one week of therapy, they get less inflammation, but they get some. If so, I can provide topical corticosteroids. I usually do not have to use something as strong as the Lidex level used in the Dartmouth study. 2.5% hydrocortisone cream or ointment is often adequate.

Dr. Perez: Since the regimen for my patients is a one-day application, I use 5-FU at night and the topical mild steroid in the morning. They'll apply one at night, and the other in the morning for three weeks, then while that area is recuperating, we move to another anatomical location. We just go area by area—arms, chest, back, etc., and then in six months the patient will have a complete skin exam and we will start all over again. When the patient is not seeing me, we just keep up a kind of maintenance course.

Dr. Hale: Yes, it's important to inform the patient that this is ongoing treatment. As was said earlier, it's rare that a patient who has had sun damage or skin cancer is completely discharged from your practice. So the treatment is really ongoing—we'll use such and such a modality to take care of the problem, and practice daily sun exposure, but even if they just have incidental sun exposure, new lesions are going to develop. So it's important for someone who has been heavily sun-damaged to understand that even after doing a full course of Carac or 5-fluorouracil all over, they're first of all going to need some interval therapy, and a few years later, even if they have done a lot of interval therapy, they'll need to reinitiate full topical therapy.

Dr. Nehal: I explain to them that it's like going to the periodontist. You can have all this work done in restoring your gums in all four quadrants, but you're still going to have to go for cleanings every three months or your predisposition to gum disease will continue. It's very important to maintain the skin in the same way.

Dr. Hale: Also, they need to understand that their inflammatory reaction to treatment is proportional to the amount of damaged cells. The first time they use the treatment they may experience significant erythema and burning irritation, but if you've explained this to them, they'll be very pleased with the results, and they'll be more apt to use it the next time as maintenance therapy. And if they've really done their job with the topical applications and practiced sun protection, they can probably expect less erythema and slightly less irritation the next time.

Dr. Robins: That's true, and it's been documented. Do you recommend seeing the patient in 3-month, 6-month, or yearly intervals?

Dr. Perez: It depends on their background of sun damage and prior medical history.

Dr. Robins: But a minimum of once a year.

Dr. Hale: Yes, at least once a year.

Dr. Perez: Also, let's not forget to emphasize to all of our patients the appropriate use of sun protection, with a six-inch-brim hat, proper application of the right sunblock creams at least every two hours whenever you're outdoors, and avoidance of the sun in the middle of the day. That goes hand-in-hand with the treatment, if you want to have safer, healthier patients.

Dr. Robins: What SPF do you use for sunscreen?

Dr. Sarnoff: SPF 60. Patients in New York think bigger is better, the higher the number the better.

Dr. Robins: What do you use in North Carolina?

Dr. Jorizzo: As long as it is 15 or above, you should be able to block about 94% of UVB. But there is a difference with the higher numbers. If you properly use sunscreen with a high enough SPF, there is probably about a 97% UVB block potential with a true SPF 50 sunscreen. I have a lot of lupus and dermatomyositis patients in my practice, and I insist that all use the highest SPFs. As for my sun-damaged patients, I encourage them to experiment with sunscreens and to find one that they can use every day, as long as it is above 15. If they find that the one I recommend to my lupus patients is not cosmetically acceptable, I will accept their using a little lower number, as long as it's above 15.

Dr. Nehal: As we've discussed, an SPF of 15 blocks 94-95% of UVB and an SPF of 30 blocks 97%. We believe that the added protection of SPFs beyond that is probably insignificant.

Dr. Robins: The FDA has been talking about changing the numbers for several years now, but the new rules haven't come into effect yet. They've talked about limiting the maximum SPF on labels to 30. And there's been a lot of static about that, both from the sunscreen industry and from dermatologists, who believe that higher SPFs are helpful for certain patients, such as those with photosensitivity disorders or a history of skin cancer.

Dr. Perez: The manuscript was submitted to the FDA, but there has been confusion about how to test for ultraviolet A protection. It's very difficult to run a test that documents UVA protection. So the jury is still out. According to the proposed new rules, labels for SPFs above 30 are just supposed to read 30+, but the rules haven't gone through.

For my patient population, in any event, the most important thing is ingredients. I tell patients that physical blocks and chemical blocks have a different mechanism of action, and that they need a combination of both. I treat my patients with actinic damage the same way I treat patients with lupus. A patient with lupus will have special photosensitivity, but a patient with a lot of actinic keratoses and skin cancer has surpassed the tolerance for any more mutations to be induced into their skin, so they need frequent applications of 30+ sunscreens with the right ingredients, just like patients with lupus. I also take care of a lot of patients with pigmentary disorders like melasma, and I follow the same sunscreen rules for them because I know that one exposure to the sun will send them back to square one. So I tell them that SPF 15 or above is OK for patients who do not have significant actinic damage or sun-induced problems. However, patients with significant actinic damage, pigmentary problems, or a systemic disease requiring greater photoprotection all need SPFs of 30 or higher.

In my opinion, not only the photoprotective ingredients in sunscreen are important, but also the background vehicle. It's a very individual thing. I try to explain to patients that you might have one favorite product and your child might like a different one, and your spouse might like yet another one. You need to experiment, because what feels aesthetic and comfortable on your skin and what pleases you and is truly noncomedogenic to you varies from patient to patient.

Dr. Jorizzo: I also think that patients believe they need to put on sunscreen only when they "go in the sun," meaning only when they are going to be outdoors for long periods, but I tell them that they need to use it the way a man uses aftershave or a woman uses moisturizer—putting it on every single morning.

Many moisturizers now, in fact, do have SPF 15 sunscreen in them. I do not know exactly what active compounds they contain or whether they are the way to go. Probably, when patients have pigment disorders or severe actinic damage, they need real, dedicated sunscreens.

Dr. Robins: I would like each of us to make any concluding statements that we might have about actinic keratosis.

Dr. Hale: I would just say that the treatment of actinic keratosis is incredibly important. We treat these lesions not only to make the patient look better and feel better, but also to destroy premalignant potential. With respect to topical 5-FU, yes, it does cause inflammation, which can be disconcerting to patients, but those who bear with the course of treatment end up being more than pleased with the results. Their skin feels better and fresher, and they often feel rejuvenated. And as a physician, you feel satisfied because you have really made a positive change in patients, improving them cosmetically and decreasing their chances of developing invasive squamous cell carcinoma.

Dr. Sarnoff: I want to mention a study from Baylor University a while back showing that a low-fat diet helps prevent actinic keratosis. I just want to say that it's worthwhile to discuss nutrition with your patients along with all the medical regimens we've considered here. I've mentioned this study to many of my patients, and they've been thanking me because it's also making them fitter and helping them to lose weight.

Dr. Perez: What we have demonstrated here is that dermatologists have a complete armamentarium of treatments for actinic keratosis and sun-damaged skin, not only for clinical intervention, but also for the subsequent management of all complications. We are well equipped for the treatment of these patients.

Dr. Jorizzo: This is an exciting time in the management of patients with actinic keratosis. Important changes are taking place in the field. I have become especially convinced of the importance of interval therapy combining surgical and medical treatment. In my practice, this consists of lesion-specific cryosurgery combined with chemical "field" treatment.

Dr. Nehal: As we've heard today, there are many therapeutic options for actinic keratoses, and it is important to try to individualize the treatment for each patient, tailoring it based on the patient's age, history, and needs; we can use a combination of treatments to accomplish this.

once-a-day Carac® fluorouracil cream 0.5%

Rx Only
Brief summary.
Please see full prescribing information for complete product information.

Carac Cream 0.5%
(fluorouracil cream)

FOR TOPICAL DERMATOLOGICAL USE ONLY (NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE)

INDICATIONS AND USAGE
Carac is indicated for the topical treatment of multiple actinic or solar keratoses of the face and anterior scalp.

CONTRAINDICATIONS
Fluorouracil may cause fetal harm when administered to a pregnant woman. Fluorouracil is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

No adequate and well-controlled studies have been conducted in pregnant women with either topical or parenteral forms of fluorouracil. One birth defect (ventricular septal defect) and cases of miscarriage have been reported when fluorouracil was applied to mucous membrane areas. Multiple birth defects have been reported in the fetus of a patient treated with intravenous fluorouracil.

Animal reproduction studies have not been conducted with Carac. Fluorouracil, the active ingredient, has been shown to be teratogenic in mice, rats, and hamsters when administered parenterally at doses greater than or equal to 10, 15, and 33 mg/kg/day, respectively, [4X, 11X, and 20X, respectively, the Maximum Recommended Human Dose (MRHD) based on body surface area (BSA)]. Fluorouracil was administered during the period of organogenesis for each species. Embryolethal effects occurred in monkeys at parenteral doses greater than 40 mg/kg/day (65X the MRHD based on BSA) administered during the period of organogenesis.

Carac should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of fluorouracil is catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD). DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytotoxic activity and potential toxicities.

Carac is contraindicated in patients with known hypersensitivity to any of its components.

WARNINGS
The potential for a delayed hypersensitivity reaction to fluorouracil exists. Patch testing to prove hypersensitivity may be inconclusive.

Patients should discontinue therapy with Carac if symptoms of DPD enzyme deficiency develop.

Rarely, unexpected, systemic toxicity (e.g. stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with parenteral administration of fluorouracil has been attributed to deficiency of dihydropyrimidine dehydrogenase "DPD" activity. One case of life threatening systemic toxicity has been reported with the topical use of 5% fluorouracil in a patient with a complete absence of DPD enzyme activity. Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever, and chills. Physical examination revealed stomatitis, erythematous skin rash, neutropenia, thrombocytopenia, inflammation of the esophagus, stomach, and small bowel. Although this case was observed with 5% fluorouracil cream, it is unknown whether patients with profound DPD enzyme deficiency would develop systemic toxicity with lower concentrations of topically applied fluorouracil.

Applications to mucous membranes should be avoided due to the possibility of local inflammation and ulceration.

PRECAUTIONS
General: There is a possibility of increased absorption through ulcerated or inflamed skin.

Information for the Patient: Patients using Carac should receive the following information and instructions:

1. This medication is to be used as directed.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. It is for external use only.
4. Avoid contact with the eyes, eyelids, nostrils, and mouth.
5. Cleanse affected area and wait 10 minutes before applying Carac.
6. Wash hands immediately after applying Carac.
7. Avoid prolonged exposure to sunlight or other forms of ultraviolet irradiation during treatment, as the intensity of the reaction may be increased.
8. Most patients using Carac get skin reactions where the medicine is used. These reactions include redness, dryness, burning, pain, erosion (loss of the upper layer of skin), and swelling. Irritation at the application site may persist for two or more weeks after therapy is discontinued. Treated areas may be unsightly during and after therapy.
9. If you develop abdominal pain, bloody diarrhea, vomiting, fever, or chills while on Carac therapy, stop the medication and contact your physician and/or pharmacist.
10. Report any side effects to the physician and/or pharmacist.

Laboratory Tests: To rule out the presence of a frank neoplasm, a biopsy may be considered for those areas failing to respond to treatment or recurring after treatment.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Adequate long-term studies in animals to evaluate carcinogenic potential have not been conducted with fluorouracil. Studies with the active ingredient of Carac, fluorouracil, have shown positive effects in *in vitro* and *in vivo* tests for mutagenicity and on impairment of fertility in *in vivo* animal studies.

Fluorouracil produced morphological transformation of cells in *in vitro* cell transformation assays. Morphological transformation was also produced in an *in vitro* assay by a metabolite of fluorouracil, and the transformed cells produced malignant tumors when injected into immunosuppressed syngeneic mice. Fluorouracil has been shown to exert mutagenic activity in yeast cells, *Bacillus subtilis,* and *Drosophila* assays. In addition, fluorouracil has produced chromosome damage at concentrations of 1.0 and 2.0 mcg/mL in an *in vitro* hamster fibroblast assay, was positive in a microwell mouse lymphoma assay, and was positive in *in vivo* micronucleus assays in rats and mice following intraperitoneal administration. Some patients receiving cumulative doses of 0.24 to 1.0 g of fluorouracil parenterally have shown an increase in numerical and structural chromosome aberrations in peripheral blood lymphocytes.

Fluorouracil has been shown to impair fertility after parenteral administration in rats. Fluorouracil administered at intraperitoneal doses of 125 and 250 mg/kg has been shown to induce chromosomal aberrations and changes in chromosome organization of spermatogonia in rats. In mice, single-dose intravenous and intraperitoneal injections of fluorouracil have been reported to kill differentiated spermatogonia and spermatocytes at a dose of 500 mg/kg and produce abnormalities in spermatids at 50 mg/kg.

Pediatric Use: Actinic keratosis is not a condition seen within the pediatric population, except in association with rare genetic diseases. Carac should not be used in children. The safety and effectiveness of Carac have not been established in patients less than 18 years old.

Geriatric Use: No significant differences in safety and efficacy measures were demonstrated in patients age 65 and older compared to all other patients.

Pregnancy: Teratogenic Effects: Pregnancy Category X: See **CONTRAINDICATIONS.**

Nursing Women: It is not known whether fluorouracil is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fluorouracil, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS
The following were adverse events considered to be drug-related and occurring with a frequency of ≥1% with Carac: application site reaction (94.6%) and eye irritation (5.4%). The signs and symptoms of facial irritation (application site reaction) are presented below.

Summary of Facial Irritation Signs and Symptoms - Pooled Phase 3 Studies

Clinical Sign or Symptom	Active One Week N=85	Active Two Week N=87	Active Four Week N=85	ALL Active Treatments N=257	Vehicle Treatments N=127
	n (%)	n (%)	n (%)	n (%)	n (%)
Erythema	76 (89.4)	82 (94.3)	82 (96.5)	240 (93.4)	76 (59.8)
Dryness	59 (69.4)	76 (87.4)	79 (92.9)	214 (83.3)	60 (47.2)
Burning	51 (60.0)	70 (80.5)	71 (83.5)	192 (74.7)	28 (22.0)
Erosion	21 (24.7)	38 (43.7)	54 (63.5)	113 (44.0)	17 (13.4)
Pain	26 (30.6)	34 (39.1)	52 (61.2)	112 (43.6)	7 (5.5)
Edema	12 (14.1)	28 (32.2)	51 (60.0)	91 (35.4)	6 (4.7)

During clinical trials, irritation generally began on day 4 and persisted for the remainder of treatment. Severity of facial irritation at the last treatment visit was slightly below baseline for the vehicle group, mild to moderate for the 1 week active treatment group, and moderate for the 2 and 4 week active treatment groups. Mean severity declined rapidly for each active group after completion of treatment and was below baseline for each group at the week 2 post-treatment follow-up visit.

Thirty-one patients (12% of those treated with Carac in the Phase 3 clinical studies) discontinued study treatment early due to facial irritation. Except for three patients, discontinuation of treatment occurred on or after day 11 of treatment.

Eye irritation adverse events, described as mild to moderate in intensity, were characterized as burning, watering, sensitivity, stinging, and itching. These adverse events occurred across all treatment arms in one of the two Phase 3 studies.

Summary of All Adverse Events Reported in ≥ 1% of Patients in the Combined Active Treatment and Vehicle Groups – Pooled Phase 3 Studies

9721 and 9722 Combined

Adverse Event	Active One Week N=85	Active Two Week N=87	Active Four Week N=85	ALL Active Treatments N=257	Vehicle Treatments N=127
	n (%)	n (%)	n (%)	n (%)	n (%)
Body as a whole	7 (8.2)	6 (6.9)	12 (14.1)	25 (9.7)	15 (11.8)
Headache	3 (3.5)	2 (2.3)	3 (3.5)	8 (3.1)	3 (2.4)
Common Cold	4 (4.7)	0	2 (2.4)	6 (2.3)	3 (2.4)
Allergy	0	2 (2.3)	1 (1.2)	3 (1.2)	2 (1.6)
Infection Upper Respiratory	0	0	0	0	2 (1.6)
Musculo-skeletal	1 (1.2)	1 (1.1)	1 (1.2)	3 (1.2)	5 (3.9)
Muscle Soreness	0	0	0	0	2 (1.6)
Respiratory	5 (5.9)	0	1(1.2)	6 (2.3)	6 (4.7)
Sinusitis	4 (4.7)	0	0	4 (1.6)	2 (1.6)
Skin & Appendages	78 (91.8)	83 (95.4)	82 (96.5)	243 (94.6)	85 (66.9)
Application Site Reaction	78 (91.8)	83 (95.4)	82 (96.5)	243 (94.6)	83 (65.4)
Irritation Skin	1 (1.2)	0	2 (2.4)	3 (1.2)	0
Special Senses	6 (7.1)	4 (4.6)	6 (7.1)	16 (6.2)	6 (4.7)
Eye Irritation	5 (5.9)	3 (3.4)	6 (7.1)	14 (5.4)	3 (2.4)

Adverse Experiences Reported by Body System:
In the Phase 3 studies, no serious adverse event was considered related to study drug. A total of five patients, three in the active treatment groups and two in the vehicle group, experienced at least one serious adverse event. Three patients died as a result of adverse event(s) considered unrelated to study drug (stomach cancer, myocardial infarction, and cardiac failure).

Post-treatment clinical laboratory tests other than pregnancy tests were not performed during the Phase 3 clinical studies. Clinical laboratory tests were performed during conduct of a Phase 2 study of 104 patients and 21 patients in a Phase 1 study. No abnormal serum chemistry, hematology, or urinalysis results in these studies were considered clinically significant.

DOSAGE AND ADMINISTRATION
Carac cream should be applied once a day to the skin where actinic keratosis lesions appear, using enough to cover the entire area with a thin film. Carac cream should not be applied near the eyes, nostrils, or mouth. Carac cream should be applied ten minutes after thoroughly washing, rinsing, and drying the entire area. Carac cream may be applied using the fingertips. Immediately after application, the hands should be thoroughly washed. Carac should be applied up to 4 weeks as tolerated. Continued treatment up to 4 weeks results in greater lesion reduction. Local irritation is not markedly increased by extending treatment from 2 to 4 weeks, and is generally resolved within 2 weeks of cessation of treatment.

OVERDOSE
Ordinarily, topical overdosage will not cause acute problems. If Carac is accidentally ingested, induce emesis and gastric lavage. Administer symptomatic and supportive care as needed. If contact is made with the eye, flush with copious amounts of water.

HOW SUPPLIED
Cream - 30 gram tube NDC 0066-7150-30

Store at Controlled Room Temperature 20 to 25°C
(68 to 77°F) [see USP].

Prescribing Information as of December 2003(a).

Keep out of the reach of children.

Rx Only

Manufactured for:

Dermik Laboratories
Berwyn, PA 19312 USA
Manufactured by:
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DERMIK®

Knock out AKs with Carac®.

- Carac® delivers >90% AK lesion reduction after 4 weeks of treatment[1,2*]
- Complete AK lesion clearance demonstrated in up to 4 weeks of treatment as tolerated[1,2†]
- Carac® is the only topical 5-FU with the added value of once-a-day dosing[3]

*Percent reduction based on least squares means of integrated results from 2 vehicle-controlled, randomized, double-blind, multicenter studies consisting of 384 adult male and female patients with actinic keratoses.[1,2]
†Patients in clinical studies (n=384) using Carac® for 1, 2, or 4 weeks achieved significantly higher rates of total AK lesion clearance than those using vehicle cream.[1,2]

A powerful combination of proven efficacy and once-a-day convenience.

In clinical trials, the most common drug-related adverse event was application site reaction (94.6%), which included: erythema, dryness, burning, erosion, pain, and edema. Some patients also experienced eye irritation (5.4%), including stinging and burning.[3] Carac® is contraindicated in women who are or may become pregnant, in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency, and in patients with known hypersensitivity to any of its components.[3]

Please see brief summary of full prescribing information on back.

References: 1. Weiss J, Menter A, Hevia O, et al. Effective treatment of actinic keratosis with 0.5% fluorouracil cream for 1, 2, or 4 weeks. *Cutis*. 2002;70(2S):22–29. **2.** Jorizzo J, Stewart D, Bucko A, et al. Randomized trial evaluating a new 0.5% fluorouracil formulation demonstrates efficacy after 1-, 2-, or 4-week treatment in patients with actinic keratosis. *Cutis*. 2002;70:335–339. **3.** Prescribing Information, Dermik Laboratories, 2001.

Carac® contains 0.5% fluorouracil, with 0.35% incorporated into a patented porous microsphere (Microsponge®).[3]