

## UNDER MY SKIN

## Terminal Crankiness

It has been a tough week. If my staff ever decides to change careers, they should be well trained for work in a complaints department.

First there was Doris, a 50-something-year-old woman who's been my patient

for years. Her rosacea flared up, so I wrote a prescription for doxycycline to help treat her face for her daughter's upcoming wedding. The next day I got a request that I fax another prescription to a mail-order pharmacy somewhere in Outer Darkness where rent and wages are low. Two days later the mail-order droid requested a clarification: hyclate or monohydrate? (Why does no other pharmacy ever ask me this?) I faxed back my answer.

Now here was Doris berating my secretary loudly and at length because the mail-order droid was still preparing her order. She demanded that we pay for overnight shipping to compensate for our sloppy incompetence. For good measure, she canceled her next appointment.

Asking us to pay for shipping was a new one. (A patient once did demand that I pay for dry-cleaning a dress when bacitracin from a dressing got on it.) I called Doris back, and left a polite voice

mail message suggesting that she direct complaints of this nature to the mail-order pharmacy whose procedures were perhaps more pertinent than ours to her dilemma.

Later the same day Alfred came in, a slovenly and truculent man in his early 70s. His real concern was that we take off his facial keratoses. (You really can't tell a cosmetic patient by appearance.)



BY ALAN ROCKOFF, M.D.

Alfred had a slightly raised patch on his right cheek that seemed at an earlier visit to be a vascular macule but had now developed a bit of texture. I explained that laser surgery would not work and suggested light curettage

both to remove the spot and test it to rule out skin cancer.

Alfred would agree to this only if I guaranteed—in writing—that there would be no mark left afterward. I explained that I couldn't offer such a guarantee and why I felt it would be best to test the lesion (adding that leaving it there would guarantee that he would still have a spot). "Oh, so now we're just speculating," he growled and walked out.

And you have a nice day too, sir.

The next day was even better. My PA, Megan, who has a soft manner and infi-

nite patience, told me she had just endured a telephone tirade from a woman whose 21-year-old daughter had tinea of her toenails. We had actually diagnosed this 7 years earlier, offered the patient treatment with oral terbinafine, and asked her mother to arrange for liver function testing as a possible prelude to treatment.

They never got the testing done, and the patient had been back several times

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over the years for other issues without ever raising the fungal concern. Megan heard our mother patiently, spoke soothingly, and talked about treating with terbinafine when her daughter returned from school in May.

"In my family we don't use generics," came her frosty reply.

I called Mom back. (At the time she was in Florida with her daughter, on spring break.) I explained that generic drugs can indeed be okay. ("I had a bad

experience with one," she reported.)

I told her that we could certainly start antifungal treatment after this semester, if her daughter wanted us to. And so on. She sounded mollified.

The question of course is: Why now? After having fungal toenails for 7 years, why did her daughter suddenly find it urgent to treat them? What about all those visits in between, spanning most of her adolescence?

People just get cranky, I suppose, and it was our misfortune to encounter three in a row. I guess I ought to make allowances for matrons aflutter in the run up to their daughter's wedding, or for gents who care deeply about their appearance, or for parents of excitable young ladies with acutely intolerable toenails, all of whom have decided to relieve their inner tension by beating up on me or my staff in full-throated arias of crankiness.

Only I'm feeling cranky myself just now, so I'm not in the mood for making allowances. You'll understand, won't you?

You won't? Too bad. ■

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## COMMENTARY

## Tracking Melanoma's Genetic Tentacles

The American Cancer Society and the National Cancer Institute estimate that 62,480 people in the United States will be diagnosed with melanoma this year, and that 8,420 people will die from it.

Although melanoma rates have risen steadily in recent decades, data from the Centers for Disease Control show that those rates are particularly high among young women, probably because of the increase in tanning and use of tanning booths in that population.

Many public health campaigns have focused on exposure to ultraviolet light as a risk factor for melanoma. However, many melanomas occur in areas of the skin that are not exposed to high levels of sun, and many arise outside of previously existing nevi.

In general, the risk factors for melanoma include a history of severe sunburn, numbers of nevi, pale skin, red or blonde hair, light-colored eyes, freckles, history of dysplastic nevi or melanoma, exposure to sunny climates, age, gender, and of course, genetics.

For example, if you are a fair-skinned male living in Australia, your lifetime risk for developing melanoma may be as high as 4%. In the United States, one's lifetime risk of melanoma is about 1%, and this risk almost doubles with a family history of the disorder. If one has a family history of melanoma and a personal history of dysplastic nevi, one's risk for melanoma soars, so that someone with two relatives with melanoma and who has dysplastic nevi has an estimated 500-fold risk of developing a melanoma.

Dysplastic nevus syndrome is a distinct disorder that is inherited in an autosomal dominant manner. Dysplastic nevi are a precursor to malignant melanoma, though only about 5% of all melanomas arise from such high-risk settings.

Genetic testing in these high-risk cases is available but is not routinely recommended. Four loci—CDKN2A, CDK, ARF, and chromosome 1p22—have been associated with dysplastic nevus syndrome. The risk incurred by mutations in CDKN2A, which accounts for about 10%-40% of the families with dysplastic nevus syndrome, confers a roughly 76% lifetime risk of developing melanoma.



BY GREG FEERO, M.D., PH.D.

Findings from a recent study suggested some value in conducting genetic testing in these families by showing that individuals with a positive test result increased their self-screening beyond recommended levels. Of course, this could lead to more false-positive biopsies, but that may be a reasonable trade-off in this population. There is no indication to use this type of genetic testing in a screening setting, but taking a family history in routine care might identify those needing specialized—and potentially lifesaving—surveillance.

Over the last year or so, genome-wide association studies have begun to shed some light on the underpinnings of sporadic cases of melanoma. Some of the

associations are not that surprising because genes that seem to be related to traits such as fair skin or eye color (ASIP, TYR, and TYRP1) turn up as melanoma risk factors.

More recently, an area on chromosome 20q11.22 that contains a number of potentially important genes has been identified.

As with most results from genome-wide association studies, the effect sizes are very small (odds ratio less than 2) but are highly significant. In addition, we are finding that seemingly unrelated disorders can share common genetic defects. A most striking example of this is the shared association found for melanoma, diabetes, and heart disease with the CDKN2A/2B genes.

What mechanistic relationship do these disorders share? Could it be a link through immune function?

It is increasingly likely that in a few years we will have more answers and perhaps be able to develop more effective treatments. In the meantime, advise your patients to cover up—especially when visiting Australia—and watch out for those who have a family history of this serious disorder. ■

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**Seemingly unrelated disorders can share genetic defects. One striking example is the association between CDKN2A/2B and melanoma, diabetes, and heart disease.**