COMMENTS AND OPINIONS

Is Pityriasis Rosea Skin Healthier Than Healthy Skin?

In the September issue of the Archives, Kempf et al. published an article in which our hypothesis about the human herpesvirus 7 (HHV-7) etiology of pityriasis rosea (PR) is brutally denied. We would like to analyze the "evidence" their conclusion is based on.

By nested polymerase chain reaction (PCR), Kempf et al. detected HHV-7 DNA sequences in 8% of the PR skin biopsy specimens and in 14% of normal skin. By immunohistochemical analysis, they also detected HHV-7-specific antigen only in those PR skin specimens that PCR had proven to contain DNA sequences. Human herpesvirus 7 viral antigen was found in perivascular cells that were reported, on the basis of morphological studies, to represent monocytes and/or macrophages or dendritic mononuclear inflammatory cells of the lineage. In conclusion, the authors suggest that our finding HHV-7 in PR lesional skin may have resulted from contamination.

The first point that should concern the reader is the origin of the authors’ skin samples. The fact that this point has not been elucidated in their “Materials and Methods” section, and that plasma and peripheral blood mononuclear cell (PBMC) specimens were not available (and they do not explain why), may suggest that their study was in fact a retrospective analysis performed with stored skin specimens. The reader does not need to be a virologist to understand that the conservation of the specimens is crucial for PCR results to be credible. In the words of Kempf and an earlier team of coworkers, “partial DNA degradation, inevitably present in paraffin-embedded archival samples, might . . . result in a negative HHV-7 reaction, even if some viral sequences were indeed present.”

That the more recent study by Kempf et al. was in fact a retrospective one is also suggested by previous articles of which Kempf was the first author. In one of them, HHV-7 infection was detected in more than 63% of normal skin in which the cells infected by HHV-7 seemed to the authors to be stromal connective tissue and not, as in the PR study we are commenting on, monocytes and/or macrophages. Of course one wonders why the previous figure in normal skin is now reduced sharply to 14%? Were the samples in fact stored skin specimens?

Another wonder is why HHV-7 should be present in 8% of PR skin specimens and in more than 63% of normal skin? Is PR skin healthier than healthy skin, or is it a virus scavenger?

As virologists, Kempf et al. should know very well that the failure to detect a virus in a tissue does not mean that the disease is not associated with that virus. In many exanthems (measles, for instance) with a well-known viral etiology, the causative virus is not detected in the tissues. Exanthema pathogenesis is far from being fully understood, and may be the result of virus-host interactions, as in the case of hypersensitivity reactions or of virus-virus interactions. On the other hand, we are fully aware that finding a virus in the tissues does not always mean that it plays a causative role. For herpesviruses especially, such a role should be suggested by a series of studies, including those on cultures, plasma, and PBMCs, and not only by PCR.

Lacking any evidence from their plasma and PBMCs, Kempf et al. consider our finding of the virus free in plasma or in PBMCs just the consequence of a transient immunodepressive state, as in herpes labialis and varicella-zoster. It is a pity that in the states of reactivation of herpes labialis and varicella-zoster infections, no one has ever found the causative viruses circulating free in the patients’ plasma. On the contrary, HHV-6 has been found in plasma during exanthema subitum, and this finding has been considered a marker of active replication and primary infection.

In fact, we concluded that a herpesvirus is involved in PR etiopathogenesis by studying the problem at different levels, including cultures and electronmicroscopy on different tissues. The cytopathic effect we observed in PR cell cultures is of great importance as a parameter of active viral replication that is confirmed by the presence of cell-free viral DNA in plasma. Recently, we added a further piece of evidence by finding, in both epidermis and dermis of PR skin, herpesvirus-like particles that are very similar to those we previously detected in the supernatant of cultured PR cells (unpublished data, 1999). Nonetheless, we did not reject the idea that other viruses may cause the disease, alone or interacting with HHV-7.

In any case, no investigator can be so sure of his own results, especially in the case of PCR amplification products, as to come out with such a dogmatic title. Our title was more prudent, even though we respected all precautions to exclude cross-contamination and product carryover during specimen extraction and PCR amplification. In particular, we controlled by PCR amplification every routine component for PCR except template DNA. With such precautions, we were able to
find a relationship between Epstein-Barr virus and primary cutaneous amyloidosis,\textsuperscript{11} a finding that has been authoritatively confirmed.\textsuperscript{12}

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In reply

Pityriasis rosea is an inflammatory skin disease of unknown origin. Several laboratories, including ours, were unable to confirm or extend the findings of Drago et al\textsuperscript{1,2} on an association between PR and HHV-7.\textsuperscript{3,4}

Drago et al\textsuperscript{1,2} investigated the presence of HHV-7 sequences in skin, plasma, and PBMCs of patients with PR, and reported all (1) PR specimens to be HHV-7 positive by PCR. The cocultures of PBMCs and SupT1 cells showed cytopathic effects. Herpesvirus-like particles were detected in the supernatant of the cultures. The authors concluded that “the finding of HHV-7 DNA in plasma which reflects viral replication and virulence strongly supports its causative role in pityriasis rosea.”\textsuperscript{1,2} Below we comment on (1) the methodologies and significance of the reports by Drago et al\textsuperscript{1,2} (2) their criticisms of our study, and (3) evaluation of their findings in the context of other studies.

(1) The presence of HHV-7 sequences in PBMCs is of low significance for the purpose of establishing a correlation between PR and HHV-7 because 80% of healthy individuals harbor the virus in a latent form in their PBMCs.\textsuperscript{5,6} Moreover, it is well established that HHV-7 can be reactivated on culture of PBMCs. This is indeed the procedure by which Frenkel et al\textsuperscript{7} first isolated and discovered HHV-7.

(2) The appearance of a cytopathic effect, or the presence of herpesvirus-like particles in cocultures of PBMCs and SupT1 cells, is also of little significance, for the same reasons. Furthermore, in their studies, Drago et al\textsuperscript{1,2} reported no effort to identify the virus or the cytopathic effect as induced by HHV-7 by immunocytochemical analysis or PCR techniques. The observed virus particles may well represent a herpesvirus other than HHV-7 (eg, HHV-6) reactivated concomitantly with the disease or on culture of the PBMCs.

(3) Positive findings of plasma and skin may be a key to establish an association, but the results of Drago et al\textsuperscript{1,2} rely exclusively on PCR. This is particularly crucial because the authors did not sequence the amplification products, despite the fact that primers display a high extent of identity (75%-80%) with human DNA in a BLAST search. In addition, neither uninvolved skin from individuals with PR nor skin from healthy individuals was investigated. In conclusion, one does not know what the incidence of HHV-7 DNA or HHV-7 DNAemia would be in normal specimens and in those with other pathological conditions, respectively, under the analytical conditions used (see Table 1 in reference 1). Additionally, the sensitivity of their PCR protocol was not reported.

In our study, (1) the novel aspect was a coupled immunohistochemical-PCR investigation (ie, it included an assay independent of PCR). The monoclonal antibody to HHV-7 used has been extensively characterized. Parenthetically, we make this antibody available to any person. The antibody recognizes an HHV-7–specific linear epitope a few amino acids long,\textsuperscript{10} and shows reactivity in all the assays tested, including immunohistochemical and immunocytochemical analyses, enzyme-linked immunosorbent assay, Western blots, immunoprecipitations, and immunofluorescence studies. Therefore, reactivity is maintained under various conditions of antigen conservation or extraction. By means of it, we readily detected the HHV-7 antigen in archival specimens with a sensitivity even higher than that of PCR.\textsuperscript{11,12}

(2) The nature of our study and the origin of the specimens are clearly stated under the heading “Design: A Retrospective Cross-sectional Survey,” and in the Section “Participants and Methods,” which describes in detail the characteristics of the specimens and patients, eg, histological characteristics, clinical course of the disease, median age, etc.

(3) As stated in the text, the control specimens in our study consisted of samples from various body areas of healthy individuals, and matched the PR samples with respect to age and sex and also in terms of fixation and storage of the samples. This is a different group of samples than those analyzed previously,\textsuperscript{1,2} which consisted of a very specific set of skin specimens obtained from women undergoing breast reductive plastic surgery. The differences between the 2 groups are clearly stated and commented on in the first paragraph of the “Results” section. Notwithstanding that in the 2 groups the frequency of HHV-7 positivity varies, the frequency of HHV-7 DNA that we detected in PR samples was low (1 in 13).

(4) Our PCR conditions were those described and extensively used in the literature.\textsuperscript{13} The amplification product, when detected, was sequenced. The sensitivity of the PCR reaction was reported.

No laboratory has been able to reproduce the findings of Drago et al\textsuperscript{1,2} even when very similar analyses were performed. Specifically, (1) Watanabe et al\textsuperscript{7} searched for HHV-7

DNA in plasma samples by applying the same PCR protocol as Drago et al.,1,2 sequenced the amplification product, and could detect HHV-7 sequences in only about 50% of the samples, as opposed to 100% in the reports by Drago et al. The search for antibodies showed the absence of IgM antibodies, as well as no increase in IgG titer (except for 1 case), both of which are expected to increase in primary and/or reactivation infections.

(2) Yoshida et al. applied the same nested PCR protocol as Drago et al. to peripheral blood DNA of patients with PR and healthy individuals, and found a signal of equal intensity in all samples. This finding argues against an increase in viral load in the PBMCs of patients with PR and against the specific occurrence of the viral sequences in the PR samples. This finding argues against an increase in viral load in the PBMCs of patients with PR and against the specific occurrence of the viral sequences in the PR samples.

(3) Yasukawa et al.3 amplified HHV-7 DNA from PBMCs in only 1 of 14 patients, failed to isolate HHV-7 from cocultures of PBMCs and SupT1 cells, and failed also to detect any increase in anti–HHV-7 IgG relative to normal control subjects.

In their letter above, Drago et al raise the interesting issue of whether an infectious agent, or markers thereof, must, or must not, be constantly present in an acute lesion induced by a herpesvirus. Both our knowledge on the biology of herpesvirus infections and the investigative tools available today have changed so much that there is currently a need to establish clear-cut criteria for pathogenetic association and causality. To review these criteria is beyond the purpose of the present reply. At the risk of oversimplifying the problem, in general, during acute phases of infections with herpesviruses (primary and reactivation), either 1 or both of the following conditions seem to apply: (1) the virus is present in the lesion and/or (2) there is an increase in the antibody response. At the current state of the art, in our opinion, the key issue concerning PR is whether the available evidence does, or does not, support an association with HHV-7 infection or reactivation. Establishing a causative role should be a subsequent step. To establish an association, consistency of the association is a minimum requirement. Independent laboratories have failed to confirm the presence of HHV-7 in PR lesions, or to reveal serologic or immunologic markers of an active infection or reactivation in all patients with PR. At the current state of the art, even without taking into consideration our own study, it seems to us that the association between HHV-7 and PR is not yet firmly established.

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Tumor Screening and Biology in Malignant Melanomas

We read with interest the recent article and editorial that emphasize the increasing incidence of thin malignant melanomas (MMs).1,2 Similar results have been reported in different institutions,2 and that is certainly our experience as well. The analysis of those data highlights interrelated aspects of public health (screening) and tumor biology.

Although nondysplastic nevi have been reported to confer a small (2-fold) risk, clinically atypical (dysplastic) melanocytic nevi (AMN) confer substantial MM risk (2-fold for 1 AMN; 12-fold for ≥10 AMN).3 Based on this, clinicians can identify a population at high risk for MM for screening and intervention. Except for heritable MM,4 AMNs seem to represent a risk marker rather than a true precancerous lesion,3 especially for low-grade AMNs (unpublished data, 1999). The other risk factors for MM such as intermittent sun exposure are, on the one hand, less susceptible to intervention and, on the other hand, not significantly associated with an increased risk of mortality from MM.3 However, AMN diagnosis was controversial before the pathologist consensus convened by the World Health Organization Melanoma Programme5 explained the variable AMN incidence (Figure). The increased sensitivity for diagnosing early MM also determines the decreasing incidence of AMN with severe melanocytic dysplasia in the last few years (Figure), because many of those lesions are now classified as melanomas in situ. Therefore, the strong commitment of dermatologists and pathologists to the early diagnosis of MM to provide a better prognosis would partly explain this increase of MM incidence, as Berwick suggests.2
Regarding MM biology, tumor thickness, apart from determining prognosis, identifies 2 biologically different types of MM. This is not specific for MM, but applies generally to tumor pathobiology. Evidence from other organ systems including the uterine cervix (squamous cell carcinoma), endometrium or stomach (adenocarcinoma), and urinary bladder (transitional cell carcinoma) reveals the same 2 main types of malignancies. In general, most tumor risk factors and true precancerous lesions that are susceptible to screening programs are mainly associated with malignancies of protracted natural history, which explains the unchanged incidence of high-grade neoplasms in those organs. These high-grade tumors normally develop de novo and show no associated precancerous lesions, as expressed in thick MMs that are frequently nodular and mostly fast-growing tumors. This sort of tumor is not susceptible to any screening, which explains the failure of efficient early detection programs.1 This equally answers the open question that is the editorial’s title:2 no current screening program will effectively address the early diagnosis of thick nodular MM in a potentially curable stage. Unfortunately, our technology does not yet offer this possibility. Only the advent of new diagnostic techniques to detect subtle genetic or functional changes of early transformed melanocytes can offer a better prognosis for patients with nodular MM.

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An Alternate Explanation for the Increase in the Incidence of Melanoma Being Restricted to Patients With Thin Lesions

Drs Lipsker et al1 recently reported that in a carefully conducted population-based study there was a dichotomy between the rising incidence of thin melanomas and the stable incidence of thicker lesions. The authors point out that the excision of increasing numbers of thin melanomas has had no effect on the incidence of thick melanomas. They propose as an explanation that thin and thick melanomas have different epidemiological features, and that the increased incidence of this cancer is owing to the recognition of a thin form of melanoma that is innocuous and unlikely to cause death if not treated.

However, there is an alternate interpretation that leads to a different conclusion. It flows from a simple mathematical analysis of the differing impacts of (1) the increasing incidence of melanoma, and (2) early detection on the proportion of patients who will have thin as opposed to thick lesions at diagnosis. It is illustrated by the following example: Assume that at baseline there are 100 new melanomas per year in a given population, and that 50% of these are diagnosed while still thin; 50 thin melanomas will then be diagnosed per year. Suppose that at a later date the incidence of melanoma has doubled, but that as a result of earlier detection the proportion diagnosed while still thin improves by half to 75%. The incidence of melanoma will now be 200 new cases per year, 75% (150) of which will be thin, and the number of thick melanomas will remain at 50 per year. Thus, a doubling in the incidence of melanoma coupled with a 50% improvement in early diagnosis results in a tripling of cases diagnosed while still thin, with no changes in the number of thick lesions.

The data presented by Drs Lipsker et al1 is remarkably consistent with this interpretation. The number of new melanomas in Strasbourg, France, more than doubled between 1980 and 1997, from fewer than 40 per year to more than 90 per year (see their Figure 2). During the same time the number of melanomas diagnosed while still thin increased 4-fold from less than 15 per year to approximately 60 per year (see their Figures 6 and 7), while the number of thick melanomas increased only slightly.

Are these different interpretations of more than academic importance? Yes, because their implications are very different. That of Drs Lipsker and colleagues1 implies that the effort to reduce melanoma mortality by early detection and treatment is ineffective because the lesions being detected and removed would not have caused death in any event. By contrast, the interpretation pro-

References
We thank Dr Bystryn for his interest in our recently published work in this journal. Dr Bystryn proposes an alternate explanation for the increase in the incidence of thin melanomas. His explanation relies on a mathematical analysis of the differing impacts of increasing incidence and early detection. According to his model, the combined effect of an overall increase in melanomas and simultaneous improvement in early detection of thin lesions could lead to a stable number of thick melanomas (because their proportion decreases) and an increase in the number of thin melanomas (the proportion of which increases). We agree that the increase in incidence of thin melanomas is in part related to better and earlier detection of melanomas. We also agree that early detection is the best treatment of melanoma and remains essential.

However, we do not think that this mathematical analysis explains the difference we observed between incidence rates of thick and thin melanomas. Indeed, this model implies 3 postulates, which Dr Bystryn did not address. First, it supposes that every thick melanoma is the result of a thin melanoma. Second, it supposes that the time lapse during which a thin lesion becomes a thick lesion is long enough to allow efficient detection at the thin stage in all cases. That would mean that this time is compatible with detection and that people would consult with a physician during this period. Third, it supposes that the whole population would be screened. If any of these postulates would not hold true, improvement of detection alone could not explain the stability in incidence of thick melanomas while there is a steady increase in thin melanomas.

Our data support the notion that the lapse of time during which thin tumors become thick tumors is not always long enough to allow detection. Indeed, this time lapse can be very short and was less than 3 months in some patients with thick, fast-growing, nodular melanomas. Furthermore, our data showed a constant and regular increase in the incidence of thin melanomas over 18 years, while the incidence of thick melanomas remained stable during this period. According to Dr Bystryn’s model, this would mean that there was a proportional, year-by-year improvement in incidence of thick melanomas while there is a steady increase in the number of thin melanomas. His explanation relies on a mathematical analysis of the differing impacts of increasing incidence and early detection.

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VIGNETTES

Treatment of Labial Lentigos in Atopic Dermatitis With the Frequency-Doubled Q-Switched Nd:YAG Laser

Recently, atopic dermatitis has been increasing throughout the world, and there have been many labial lentigos caused by a postinflammation of atopic dermatitis. Laser therapy, such as the normal ruby laser and the Q-switched ruby laser, is one of the treatment methods. We make the first report of 4 cases of labial lentigos in atopic dermatitis treated with the frequency-doubled Q-switched Nd:YAG laser at a wavelength of 532 nm. We achieved rapid results and a dramatic clearing of the lesions without cutaneous alterations in skin texture.

Patients and Methods. We used the frequency-doubled Q-switched Nd:YAG laser (Continuum Biomedical Inc, Livermore, Calif), which has a pulse duration of 5 to 7 nanoseconds, a wavelength of 532 nm, a pulse repetition rate of 10 Hz, and a spot size of 3 mm. Local anesthesia using 60% lidocaine tape was placed on the affected part 1 hour before laser irradiation. After laser irradiation, 0.12% betamethasone valerate ointment containing 0.1% gentamicin sulfate was applied for 3 days. All subjects had labial lentigos with atopic dermatitis. No


Results. Laser treatment removed labial lentigos in all patients after 1 or 2 treatments at an average energy fluence of 1.5 J/cm². All patients had no recurrence of lentigos until an average of 8.25 months. The laser treatment showed no adverse effects, including hypopigmentation or scars (Figure 1 and Figure 2).

Comment. The frequency-doubled Q-switched Nd:YAG laser has a dual wavelength of 1064 nm (which removes black ink tattoos, traumatic tattoos, and dermal melanosis) and 532 nm (which has been used for epidermal pigmentation). Compared with the ruby laser (wavelength, 694 nm) and alexandrite laser (wavelength, 755 nm), the frequency-doubled Q-switched Nd:YAG laser at a wavelength of 532 nm has a higher melanin absorption rate and lower melanin penetration. It has a pulse duration of 5 to 7 nanoseconds, which is the shortest among all lasers in clinical use today. Therefore, the frequency-doubled Q-switched Nd:YAG laser is expected to cause fewer adverse reactions. Various causes of labial lentigos have been reported, such as contact cheilitis from lipsticks or toothpastes as well as Peutz-Jeghers syndrome and Addison disease. However, Fujisawa et al reported that in 10 (47.6%) of 21 subjects, the causes of labial lentigos were not found by patch testing. They reported that in 8 (38.5%) of 21 subjects labial lentigos were associated with atopic dermatitis. Ishikawa et al reported that 59 (56%) of 106 patients had a combination of labial lentigos and atopic dermatitis. In atopic dermatitis, the lips are markedly dried and scaled, and the mucous membrane is damaged as the lips are rubbed and abraded, presumably inducing pigmentation. Because recently atopic dermatitis has been increasing throughout the world, we expect that these types of cases will increase.

There are many patients with labial lentigos who wish to have them removed for aesthetic reasons. However, labial lentigos of irregular shapes with a diameter of 5 mm or larger, which usually develop on older people, have the possibility of being lentigo maligna and should be treated carefully. Our study shows that the frequency-doubled Q-switched Nd:YAG laser at a wavelength of 532 nm can be used safely and effectively to treat labial lentigos.

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Expression of β-Catenin, a Key Mediator of the WNT Signaling Pathway, in Basal Cell Carcinoma

I

nactivation of the patched (PTCH) gene seems to be responsible for the genesis of basal cell carcinoma (BCC). The PTCH protein forms a complex with another membrane-bound molecule, smoothered (SMO), and is an important component in the SMO/hedgehog signaling pathway. Binding of PTCH to SMO represses the SMO signaling pathway, but when hedgehog is bound to PTCH, the PTCH protein seems to undergo a conformational change that leads to activation of the SMO pathway. Activation can also occur if PTCH is inactivated by loss of heterozygosity and/or mutation. Activation of the pathway results in transcription of downstream target genes. These targets may include mem-

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bers of the transforming growth factor β, bone morpho-
logic protein, and WNT protein families, as well as PTCH itself.2

β-Catenin is a multifunctional protein that plays a role in both cell adhesion and gene transcription. The role of β-catenin in adhesion has been well es-
established in the skin,3 but it is not known whether it also functions in the skin as a transcriptional regu-
lator in the nucleus. Recent studies have revealed the striking role for β-catenin in the WNT signaling path-
way.4 Activation of the WNT pathway can lead to nuclear translocation of β-catenin, and since WNT genes seem to be downstream targets of the SMO sig-
signaling pathway, we hypothesized that an indirect con-
sequence of SMO signaling in BCCs might be activa-
tion of the WNT pathway and nuclear localization of β-catenin.

We therefore investigated the expression of β-catenin in 195 formalin-fixed BCCs, using immuno-
histochemical analysis (Figure) to assess the role of β-catenin in these tumors. Immunohistochemical analysis was performed as previously described,5 using a polyclonal anti-β-catenin antibody (Santa-Cruz Bio-
technology, Santa Cruz, Calif), which detects nuclear localization associated with mutations in exon 3 of β-catenin.

Basal cell carcinomas showed a heterogeneous pattern of β-catenin membrane and cytoplasmic staining within individual tumor masses. β-Catenin positivity was prominent at the periphery of some tumor masses, es-
pecially in the solid subtype of BCCs. None of 195 BCCs examined showed nuclear translocation or an increase in the cytoplasmic accumulation of β-catenin. The findings did not support our hypothesis that activation of smoothened signaling as a consequence of PTCH inac-
tivation may ultimately result in translocation of β-catenin to the nucleus following activation of the WNT path-
way. β-Catenin is located at the membrane and in the cytoplasm in BCCs, but we found that it always shows less intense membrane staining in the tumor than in the adjacent normal epidermis. This indicates that the tu-
more cells have less cell-to-cell adhesion than normal basal cells. Hence, β-catenin seems to play a role in BCCs as a cell adhesion molecule but is not involved in nuclear signalling.

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Should Dermatologists Go Public?
A Skin Cancer Screening Campaign at Recreation Centers

Skin cancer screening has been initiated in many countries.1 Such programs can find a ready target population in individuals who frequent public baths. These individuals are frequently exposed to UV radiation and are usually in a state of dress that allows whole-body examination to be done more quickly. Thus, we decided to conduct a screening campaign that would attract people at public recreation areas to assess the acceptance of such a campaign.

Methods. In July 1998, we visited 3 large recreation centers in Styria, Austria. A total of 344 individuals (159 female, 185 male; mean age, 36.1 years; age range, 7 months to 89 years, Figure) were screened for skin cancer and data were collected on anamnestic, phenotypic, clinical, and sun-related risk factors. The individuals had complete skin examinations and were asked to answer a comprehensive questionnaire regarding different risk factors and their acceptance of the campaign.

Results. Forty-five subjects (13%) were referred to local dermatologists for surgical treatment of lesions suggestive of skin cancer or a precursor lesion. Eighteen (40%) of these 45 individuals with suggestive skin lesions were not planning to visit a physician in the next 6 months, and 28 (62.2%) had never had a skin examination before. The distribution of the different risk factors...
is given in Table 1. Ninety-seven subjects (36.5%) had 4 or more risk factors. Remarkably, in this group 47% of the clinically suspicious lesions were diagnosed. The questions and answers concerning the acceptance of the campaign are summarized in Table 2.

Comments. The usefulness of screening campaigns for skin cancer is controversial. On the one hand, skin cancer seems to be an ideal target for screening programs because it is easily detectable, and early therapy is simple and effective. On the other hand, the mortality of skin cancer is low, and the costs of general screening programs are high. Therefore, the broad consensus is that screening should be focused on those persons at high risk.2

We initiated a small focused screening campaign at 3 public recreation centers. The acceptance of our campaign by the subjects we screened was very high. Indeed, 72% of them preferred the campaign to a visit to a physician. In 53% of the cases, the subject had not been planning to have a skin examination but decided on the spur of the moment to take advantage of the opportunity for a free skin examination. More male than female subjects participated, a remarkable piece of datum, since men have a higher risk of developing malignant melanoma but are usually underrepresented in most screening campaigns.3,4

Of course, in planning further screening campaigns at public recreation centers, many limitations of this study should be avoided: (1) there must be follow-up of subjects having suggestive lesions and subjects with a high individual risk; (2) any clinical diagnoses of suggestive lesions must be histopathologically proven; (3) cost-effectiveness must be calculated; and (4) other locations suitable for screenings must be considered.

These caveats aside, we believe that organizers of skin cancer screening campaigns should remember to take the “Willie Sutton” approach, as applied by Weinstock and Rossi,5 to primary prevention. Just as Willie robbed banks “because that’s where the money is,” screening campaign organizers should target public beaches, baths, and recreation centers because that’s where those at risk for skin cancer due to UV light exposure often go to get their sun.

Table 1. Distribution of Anamnestic, Clinical, Phenotypic, and Sun-Related Risk Factors for Skin Cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No. (%) of Subjects</th>
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</thead>
<tbody>
<tr>
<td>Anamnestic (n = 288)</td>
<td></td>
</tr>
<tr>
<td>Family history of skin cancer</td>
<td>20 (6.9)</td>
</tr>
<tr>
<td>History of skin cancer</td>
<td>11 (3.8)</td>
</tr>
<tr>
<td>Change in a skin lesion</td>
<td>58 (20.1)</td>
</tr>
<tr>
<td>Phenotypic (n = 288)</td>
<td></td>
</tr>
<tr>
<td>Blond/red hair</td>
<td>87 (30.2)</td>
</tr>
<tr>
<td>Blue/gray eyes</td>
<td>131 (45.4)</td>
</tr>
<tr>
<td>Ephelides</td>
<td>93 (32.2)</td>
</tr>
<tr>
<td>High sun sensitivity (skin type I or II)</td>
<td>104 (36.1)</td>
</tr>
<tr>
<td>Clinical (n = 318)</td>
<td></td>
</tr>
<tr>
<td>&gt;50 Nevi</td>
<td>29 (9.1)</td>
</tr>
<tr>
<td>&gt;10 Atypical nevi</td>
<td>34 (10.6)</td>
</tr>
<tr>
<td>Numerous solar lentigines</td>
<td>87 (27.3)</td>
</tr>
<tr>
<td>Sun-related (n = 288)</td>
<td></td>
</tr>
<tr>
<td>&gt;10 Sunburns</td>
<td>75 (26)</td>
</tr>
<tr>
<td>At least 1 sunburn with blisters</td>
<td>76 (26.3)</td>
</tr>
<tr>
<td>Use of sunscreen always</td>
<td>162 (56.2)</td>
</tr>
<tr>
<td>Use of sunlamps/sunbeds</td>
<td>64 (22.2)</td>
</tr>
</tbody>
</table>

Table 2. Questions and Answers Concerning the Acceptance of the Screening Campaign in 288 Responders*

<table>
<thead>
<tr>
<th>Question</th>
<th>Answers</th>
<th>Mean Age, y</th>
<th>Male (n = 161)</th>
<th>Female (n = 127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is this the first examination of your moles?</td>
<td>Yes: 194 (67)</td>
<td>37.6</td>
<td>114 (71)</td>
<td>80 (63)</td>
</tr>
<tr>
<td>No: 94 (33)</td>
<td></td>
<td>42.0</td>
<td>47 (29)</td>
<td>47 (37)</td>
</tr>
<tr>
<td>Without today’s campaign, would you have had your moles examined?</td>
<td>No: 153 (53)</td>
<td>38.1</td>
<td>89 (55)</td>
<td>64 (50)</td>
</tr>
<tr>
<td>Yes by a general physician: 54 (19)</td>
<td></td>
<td>42.7</td>
<td>29 (18)</td>
<td>25 (20)</td>
</tr>
<tr>
<td>Yes by a dermatologist: 81 (28)</td>
<td></td>
<td>38.5</td>
<td>43 (27)</td>
<td>38 (30)</td>
</tr>
<tr>
<td>How did you like this screening campaign?</td>
<td>As pleasant as a visit to a physician: 79 (27.4)</td>
<td>39.7</td>
<td>43 (27)</td>
<td>36 (28)</td>
</tr>
<tr>
<td>Less pleasant than a visit to a physician: 1 (0.3)</td>
<td></td>
<td>48.0</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Why did you like this screening more than a visit to a physician? (more than 1 answer possible; n = 208; male, n = 107; female, n = 91)</td>
<td>No waiting time: 137 (66)</td>
<td>37.6</td>
<td>80 (68)</td>
<td>57 (63)</td>
</tr>
<tr>
<td>No sick certification: 93 (45)</td>
<td></td>
<td>39.2</td>
<td>53 (50)</td>
<td>40 (44)</td>
</tr>
<tr>
<td>No journey to and from: 71 (34)</td>
<td></td>
<td>39.1</td>
<td>39 (36)</td>
<td>32 (35)</td>
</tr>
<tr>
<td>To have to change while bathing: 34 (16)</td>
<td></td>
<td>33.6</td>
<td>25 (23)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Other reasons: 17 (8)</td>
<td></td>
<td>50.3</td>
<td>10 (9)</td>
<td>7 (8)</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are number (percentage).
This study was supported by a grant from the Österreichische Krebshilfe, Steiermark, Austria.

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Onychomycosis Treated Until the Nail Is Replaced by Normal Growth or There Is Failure

In our opinion, the tested regimens for the use of current antifungals in the treatment of onychomycosis are not optimal for the clinical use of these drugs and also are misleading with respect to efficacy. A flurry of letters in the literature indicates that our concerns are shared.

There is a difference of opinion about whether orally administered drug enters the nail bed and overlying nail plate through the entire area of the nail bed or is incorporated into these structures in their individual matrix regions and then moves distally. In either case, however, the assumption that the nail bed maintains fungistatic or fungicidal properties after a fixed period of treatment that is shorter than the time required to replace the entire toenail by normal growth has not been demonstrated in these large studies.

In our own office practice, we treated 20 consecutive patients with total nail bed culture positive for *Trichophyton rubrum* onychomycosis using 200 mg of oral itraconazole twice a day for 1 week of every month, for 11 or more months, until the mycotic nail bed had been completely replaced by new nonmycotic nail bed. We treated the next 20 patients with 250 mg of oral terbinafine hydrochloride daily for 1 week of every month, following the same protocol as above.

All patients were examined monthly for evidence of proximal extension of the nail bed lesion beneath a reference notch that had been cut into the overlying nail plate of the target nail to mark the proximal limit of the nail bed lesion at the beginning of treatment. Any proximal extension of the lesion during treatment was a treatment failure. In compliance with the informed consent agreement, these patients were removed from the study.

There were 5 failures in the 20 patients treated with itraconazole, 3 after 1 month of treatment and 2 after 6 and 7 months, respectively. In the 20 patients treated with terbinafine, there were 2 failures, 1 after 1 month of treatment, and 1 after 6 months. The remaining 33 patients continued to respond until the mycotic nail bed had been replaced by a normal nail bed (11 to 13 months after starting treatment). Potassium hydroxide analysis and culture findings were negative for organisms. These patients were recorded as cured. The cure rates of 75% (itraconazole) and 90% (terbinafine) exceed those reported in the large studies, and the relative efficacy of the 2 drugs is compatible (although it may not be statistically significant in this small sample).

We recommend this method of treatment and evaluation for office use and studies of efficacy as being more rational in terms of the normal growth dynamic of the nail and nail bed, and more precisely interpretable with respect to cure and failure.

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The “Wobble Sign” in Epiluminescence Microscopy as a Novel Clue to the Differential Diagnosis of Pigmented Skin Lesions

Epiluminescence microscopy (ELM) is a noninvasive technique for the diagnosis of pigmented skin lesions (PSLs).1-3 Epiluminescence microscopy criteria are all static criteria that can be evaluated for their presence or absence.3 We describe a new...
dynamic ELM approach and describe new dynamic ELM criteria.

Materials and Methods. During the ELM examination of any PSL, the ELM device can be maintained fixed at the surface of the skin. If the device is slightly moved horizontally, parallel to the surface, a dynamic approach is added. The lesion sticks to the ELM device and follows its movement. When there is a papular component, the superficial part of the lesion stays stuck to the ELM device (does not move) whereas the underlying skin structures dissociate from the superficial image. For training purposes this can be performed with a large papular dermal nevus (Figure).

Results. During the last 6 months we added the wobble test to our standard ELM examination using different ELM devices, and found that the wobble test can be performed with all of them. We examined a total of 162 PSLs (49% underwent histopathological examination [Table 1]) and found 3 different wobble patterns (Table 2): (1) The PSL behaves like the surrounding skin during the wobble test. Thus, the lesion moves en bloc with the surrounding skin, and no underlying stucture is dissociated from the static image. This occured mainly in flat macular lesions without a dermal component (Table 3). (2) The PSL follows the movement of the ELM device, leaving back the surrounding skin; the static image of the PSL itself is dissociated, and deeper structures having a fleshy consistency seem to move under the superficial component. Wobble pattern 2 occurred mainly in PSLs with an important dermal component such as dermal nevi and compound nevi with a dermal component (Table 3). (3) The PSL follows the movement of the ELM device, leaving back the surrounding skin, but the static image of the PSL does not change, because the stiff papular component cannot be dissociated from the surface of the lesion itself. Wobble pattern 3 occurred exclusively in seborrheic keratosis (Table 3).

Comment. The wobble test is easy to perform and provides additional information to the standard ELM examination, which is only a static examination. The additional data provided by a dynamic approach such as described in this study concern the overall spatial organization of the lesion, its behavior compared with the surrounding skin, and the behavior of the deeper dermal structures. The evaluation of these new ELM criteria provides new information on PSLs and might be a clue to the diagnosis of compound nevi with an important dermal component in the center of the lesion and a peripheral epidermal com-

Top, The dermal nevus as seen by epiluminescence microscopy (ELM): A, side view (neutral position); B, ELM view (neutral position); and C, ELM photograph (neutral position). Bottom, The dermal nevus as seen by ELM: D, side view (after wobble movement to the left); E, ELM view (after wobble movement to the left); and F, ELM photograph (after wobble movement to the left).

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ponent. Such lesions are benign but can be easily mistaken for dysplastic nevi or malignant melanoma. This is a pilot study that we consider only exploratory for purposes of any other extrapolation because it lacks many appropriate controls. The practical applicability of our observation, therefore, deserves further large-scale controlled studies.

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Joachim Krischer, MD
Jean-Hilaire Saurat, MD
Geneva and Lausanne, Switzerland


High-Fluence Modified Pulsed Dye Laser Photocoagulation With Dynamic Cooling of Port-wine Stains in Infancy

Lightening or partial clearing of port-wine stains (PWS) in infants has been demonstrated through photocoagulation with the pulsed dye laser (PDL) (wavelength, 585 nm; pulse width, 0.45 milliseconds; spot size, 5-10 mm; energy fluences, 4-8 J/cm²). It has been theorized that selective vascular injury could be further optimized by modifying the PDL to include a broader pulse width, a longer wavelength, and higher energy fluences through the use of dynamic cooling spray. In this pilot study we used a PDL with modified parameters in the treatment of infants with facial PWS to evaluate the safety and efficacy of this new device.

Materials and Methods. Sixteen infants younger than 12 months (10 girls, 6 boys; average age, 3.4 months) with facial PWS were treated at the Laser & Skin Surgery Center of New York following informed consent from their

Table 1. Distribution of Histopathological Diagnoses for Pigmented Skin Lesions*

<table>
<thead>
<tr>
<th>ELM Diagnosis</th>
<th>Histological Findings</th>
<th>Compound Nevus</th>
<th>Junctional Nevus</th>
<th>Dermal Nevus</th>
<th>Seborrheic Keratosis</th>
<th>Superficial Spreading Melanoma</th>
<th>Nodular Malignant Melanoma</th>
<th>Lentigo</th>
<th>Lentigo Maligna</th>
<th>Atypical Nevus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound nevus</td>
<td>38</td>
<td>19</td>
<td>13</td>
<td>...</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Junctional nevus</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Dermal nevus</td>
<td>46</td>
<td>10</td>
<td>...</td>
<td>10</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Seborrheic keratosis</td>
<td>38</td>
<td>16</td>
<td>...</td>
<td>...</td>
<td>16</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Superficial spreading melanoma</td>
<td>7</td>
<td>7</td>
<td>...</td>
<td>...</td>
<td>6</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Nodular malignant melanoma</td>
<td>1</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Lentigo</td>
<td>18</td>
<td>18</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>18</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Lentigo maligna</td>
<td>1</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Atypical nevus</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Ellipses indicate not applicable; ELM, epiluminescence microscopy.

Table 2. Description of the Different Wobble Patterns of Pigmented Skin Lesions (PSLs)

<table>
<thead>
<tr>
<th>Wobble Pattern</th>
<th>Consistency of PSL</th>
<th>Surrounding Skin</th>
<th>Deeper Structures</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Behaves like surrounding skin</td>
<td>Follows device</td>
<td>Behave like surrounding skin</td>
<td>Lentigo</td>
</tr>
<tr>
<td>2</td>
<td>Fleshy</td>
<td>Stays back</td>
<td>Stay back</td>
<td>Dermal nevus</td>
</tr>
<tr>
<td>3</td>
<td>Stiff, stare</td>
<td>Stays back</td>
<td>Not visible</td>
<td>Seborrheic keratosis</td>
</tr>
</tbody>
</table>

Table 3. Distribution of the Different Wobble Patterns for Different Epiluminescence Microscopy (ELM) Diagnoses*

<table>
<thead>
<tr>
<th>ELM Diagnosis</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Junctional nevus</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Lentigo</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Lentigo maligna</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Compound nevus</td>
<td>0</td>
<td>37</td>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>Dermal nevus</td>
<td>0</td>
<td>46</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td>Atypical nevus</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Superficial spreading melanoma</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Nodular spreading melanoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Seborrheic keratosis</td>
<td>0</td>
<td>1</td>
<td>37</td>
<td>38</td>
</tr>
</tbody>
</table>

* Unless otherwise indicated, data are number of lesions (percentage).
The modified pulsed dye laser (Candela; Sclero-laser HP, Wayland, Mass) included a 595-nm wavelength, a 1.5-millisecond pulse width, a 7-mm spot size, energy fluence of 11 to 12 J/cm², and dynamic cooling (tetrafluoroethane) spray 30 milliseconds prior to each laser pulse followed by a 30-millisecond postlaser pulse delay. An average of 3.2 treatments were performed at 3- to 6-week intervals with no adjunctive anesthesia except a topical cream eutectic mixture of local anesthetics (prilocaine, lidocaine; Astra Pharmaceuticals, Wayne, Tex) in 3 patients. The lesions were photographed digitally (Kodak 210; Eastman Kodak Company, Rochester, NY) under constant lighting, and the images were evaluated blindly by 3 of the treating physicians. Posttreatment improvement was assessed as a percentage of reduction in lesional color on a quartile scale in 25% gradient ranges of 0% to 25%, 26% to 50%, 51% to 75%, and 76% to complete clearing.

Results. Sixty-three percent of patients had greater than 75% clearing after an average of approximately 4 treatment sessions (Figure). Two infants showed less than 25% clearing and 14 of the 16 infants had partial areas of complete clearing. There were no atrophic or hypertrophic scars and no evidence of hypopigmentation or hyperpigmentation. Three patients developed a dermatitis after the third treatment session that was controlled with low-potency topical corticosteroids.

Comment. This preliminary study suggests that early intervention during infancy using a modified PDL with a longer wavelength, broader pulse width, dynamic cooling spray, and high-energy fluences can result in lightening or clearing of PWS with minimal risk of adverse effects. The 63% of patients with greater than 75% clearing in approximately 4 treatment sessions compares favorably with the 45% of patients with more than 75% lightening after 4 treatment sessions in a smaller study.1 These data also demonstrate significant improvement over the findings of van der Horst et al,2 who found an average improvement of 40% after 5 treatments in infants and children.

Multiple modifications of the PDL parameters have been used in this study without control for any of the variables. Thus, it is not clear whether all or some of the variables are contributory to the improved therapeutic results, although the changes in wavelength, pulse width, and higher energy fluences all either increase vascular injury or improve therapeutic outcome.3,5 The cryogen spray delivered prior to each laser pulse allows for the safe delivery of higher energy fluences by limiting the cooling to the epidermis while leaving the temperature of the PWS vessels unchanged.5 The spray is also responsible for an anesthetic effect, limiting the need for additional topical, local, or general anesthetics. If these results can be confirmed in larger studies, there is the potential for long-term benefits by limiting the probable ectactic growth of the cutaneous vessels as well as a psychological benefit from the lightening or removal of these facial malformations.

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able number of months or years. Particles designed to become soluble, to burn, to rupture, to bleach, or to be transported after activation by laser light or other external energy, might be made, tested, and approved by the Food and Drug Administration.

Years ago, I naively failed to anticipate that laser tattoo removal would inevitably lead to—more tattooing. This is sad, because I have never met a tattoo more beautiful than the skin onto which it was placed. With equal naivete perhaps, I suggest that we should continue to work on making tattoos safer and more removable than ever. Otherwise, what looks like sunlight at the end of this tunnel is surely the headlight of an oncoming train filled with unhappy, tattooed passengers.

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REFERENCES


Correction

Authors’ Names Omitted. The names of 2 authors were inadvertently omitted from the Vignette “Onychomycosis Treated Until the Nail Is Replaced by Normal Growth or There Is Failure” in the July 2000 issue of the ARCHIVES (136:940). The complete list of authors is as follows: Nardo Zaias, MD, Gerbert Rebell, MS, Martin N. Zaiac, MD, Miami Beach, Fla, and Brad Glick, DO, MPH, Margate, Fla.