COMMENTS AND OPINIONS

Antipruritic Potency of Serotonin Type 3 (5-HT3) Receptor Antagonists—a Reply

We read with great interest the case report of Downs and Kennedy1 about the successful treatment of intractable palmoplantar pruritus with ondansetron. Because of our continuous research on pruritus and the action of serotonin type 3 (5-HT3) receptor antagonists, we think that there are major points that should be clarified.

First of all, palmoplantar pruritus is an unusual location and a descriptive term but is not a diagnostic and disease entity. This raises the question on the etiology of palmoplantar pruritus. According to the report, neurological examinations, including electroneurography and upper spine radiography, had not been performed. It is possible that the palmoplantar pruritus was caused by nerve compression, nerve alteration, or neuropathy. The report further lacks important information such as the occupation and hobbies of the patient, to rule out external factors. The medical history does not mention the patient’s prior external medications. Elderly patients often use vasoactive emollients and ointments, especially after having experienced vein thrombosis. Such therapeutics, applied by the patients themselves, sometimes cause contact dermatitis, which the authors might see excluded by the lack of skin lesions and the corresponding histological findings. Furthermore, topical agents such as those containing, for example, capsaicin, can lead to various skin sensations without specific skin lesions and histological findings. Unfortunately, there are no data on allergological examinations such as atopy screening (except for total IgE levels) and epicutaneous tests. Neither histamine, eosinophilic cationic protein, serotonin, nor 5-hydroxyindolacetic acid had been measured as a standard parameter in the peripheral blood. It seems that the authors did not consider an adverse drug reaction in their differential diagnosis. Drug-induced itching is usually of generalization, but localized varieties occur.2 The authors mentioned that the patient’s hands and feet appeared “healthy” so that “pruritus sine materia” would be the more appropriate term to characterize this type of pruritus. Altogether, we think that there are important data missing in this case report.

The nature of substances that mediate cholestatic and uremic pruritus are not completely known. It needs to be clarified that the mechanisms of action leading to the clinically observed antipruritic effect of 5-HT3 receptor antagonists in these types of pruritus are not understood. The first case reports on the antipruritic effect of 5-HT3 receptor antagonists3 encouraged us to investigate the antipruritic potency of a 5-HT3 receptor antagonist (tropisetron) under experimental conditions. In healthy volunteers, we could not verify an antipruritic effect of tropisetron on histamine- and serotonin-induced itch under experimental conditions.4 As our first results also pointed toward a major role of skin mast cells (which cannot be explained in more detail in this letter) we performed the same experimental design when skin mast cells were depleted before.5 Our study demonstrated that tropisetron does not affect histamine-induced itch but has a measurable effect on serotonin-induced reactions in mast cell–depleted skin.6 It would be interesting to know whether the histological examination of the patient’s skin showed any specific findings on skin mast cell number and function. Though we did not investigate the agent ondansetron in our studies, our data are comparable because pharmacokinetic differences among these drugs are unlikely to contribute to clinical differences in activity. Downs and Kennedy should consider that ondansetron seems to have weak antagnostic activities on 5-HT1b, 5-HT1c, and adrenergic and opioid receptors.

According to our results, there is no definitive explanation for the effectiveness of ondansetron in this type of pruritus. Besides the medication’s effects on the skin’s mast cells, antiserotonergic activity and influence on central nervous processing may be possible.

The most interesting aspect of this publication is that the patient has remained free of pruritus for 1 year. It remains a question whether it is sensible to apply ondansetron on a regular basis, considering the high cost and possible adverse effects of long-term medication.

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In reply

We appreciate the interest of Weisshaar et al in our case report.1 The answers to points they raise are as follows:

1. They request clarification of our designation “palmoplantar pruritus.” This is purely descriptive of itch limited to the volar surfaces of hands and feet, and was not intended to convey a disease entity.

2. Concerning neurology, the patient was thoroughly evaluated by a neurologist, and the results of a computed tomographic scan of the upper spine and brain were normal. Sensory evoked potentials were not done, however, and can be a useful investigation in a patient with a clinically normal nervous system.

3. Concerning factors that may indicate a contact dermatitis, her occupation was housewife, and she had no hobbies. There were no prior medications other than those stated in the case report. Without further evidence for contact dermatitis or urticaria, patch or prick tests were not considered relevant.

4. Concerning extensive allergological investigations, because the patient had no symptoms or signs or family history of atopic allergy and no elevated total IgE levels, these investigations were deemed unnecessary.

5. Measurements for histamine, eosinophilic cationic protein, serotonin, and 5-hydroxyindolacetic acid were not performed.

6. We are unaware of localized pruritus being a potential adverse effect of any of the patient’s preexisting systemic medication, and also point out that these medications were taken only during the winter. Her pruritic symptoms persisted all year.

7. The number and morphological appearances of mast cells in the skin biopsy specimen were not abnormal; no functional studies (in vitro or in vivo) were undertaken.

We found the account of the commentators’ previous experimental work and complementary case report very interesting. Our case report demonstrates that ondansetron has provided a sustained clinical benefit without adverse effects for a difficult management problem of localized pruritus and is worth considering in such situations.

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Sézary Syndrome, Cutaneous T-Cell Lymphoma, and Extracorporeal Photopheresis

The report by Fraser-Andrews et al1 of their experience with extracorporeal photopheresis (ECP) treatment of patients with leukemic cutaneous T-cell lymphoma (CTCL) who had previously failed treatment with systemic chemotherapy provides valuable information. Since most of the previously reported patients received ECP as an initial systemic therapy, the study patients of Fraser-Andrews et al differ in this quite important way from those whom we and other investigators have treated with this type of active immunotherapy. The median survival of 39 months for the patients in the study of Fraser-Andrews et al did not differ in a statistically significant manner from the median survival of 22 months for their historical control group, and was shorter than the 60 to 100 months in prior reports in which many of the best responders also had clear evidence of clonal malignant cells. The relatively poorer survival data of Fraser-Andrews and colleagues may result from their ECP recipients having been selected from those for whom systemic chemotherapy had not been adequate management.

The reason that we and others have long advised that ECP therapy for patients with CTCL precede immunosuppressive chemotherapy, rather than vice versa, is that the immunocompetence of the patient is prerequisite to the ECP response.2 In experimental models of ECP therapy, immunosuppression with corticosteroids completely prevented otherwise potent responses.3

Extracorporeal exposure of malignant cells to photoactivated methoxsalen massively increases their display of tumor antigens by increasing peptide processing and transport.4 The best CTCL responses to ECP occur in patients whose CD8 (cytotoxic) T-cell counts have not been suppressed by either prior chemotherapy or disease progression, probably because the CTCL-specific antigens5 are weakly immunogenic.

We enthusiastically concur with the suggestion of Fraser-Andrews et al that a multi-institutional, prospective, controlled study be undertaken of the efficacy of ECP for CTCL. Yet it would make little sense to spend several years and great expense conducting a trial of a therapy that would be outmoded by the time the trial concluded. The understanding of the mechanism of ECP has now matured to the point of permitting its logical improvements. At this time, ECP is a rapidly evolving technology, comprehension of its scientific basis finally driving its evolution. For the past 9 months, our group has been conducting a phase I clinical trial of an altered ECP approach that enhances the immunogenicity of the CTCL cells, while simultaneously augmenting numbers of dendritic antigen-presenting cells. If our results remain encouraging, we would be more interested in testing this method in phase III trials than the standard ECP method that it will hopefully replace.

The principal lesson learned from clinical responses to ECP is that selective immunotherapy for patients with CTCL is possible when the capacity of the patient to respond to reinfused or “vaccinating” altered malignant cells remains intact. Sixteen years after the introduction of this treatment, scientifically based improvements of the immunotherapeutic method have finally become possible. It is those potentially improved descendants of ECP that will have sufficient promise to
Edelson suggests that prior treatment with chemotherapy might explain the failure of ECP treatment to affect survival in our patients with Sézary syndrome (SS). In fact, only 4 patients had been treated with high-dose chemotherapy such as fludarabine or pentostatin prior to starting ECP therapy. Most had received phototherapy (16 patients) or low-dose oral chemotherapy with chlorambucil (16 patients). This is still a popular first-line therapy with many dermatologists, and it seems highly likely that other studies of ECP also included patients who had been similarly pretreated. Indeed, in Edelson’s original study,1 28 of 37 patients had received systemic chemotherapy prior to ECP.

Edelson’s group has previously claimed that patients with CD8 counts below 0.15 × 10^9/L do not respond well to ECP. The mean CD8 count of our cohort prior to ECP was 0.25 × 10^9/L (range 0.01–0.56 × 10^9/L), which is only slightly lower than the mean CD8 count of our patients with SS at diagnosis (0.32 × 10^9/L). Thus, there is little evidence to support the view that chemotherapy has immunosuppressed our patients.

We do not deny that ECP may benefit patients with SS clinically, and in a minority of cases there may be a complete response. However, in our own studies we have not confirmed the observation that this depends on the initial CD8 count. However, our studies were confined to patients with a T-cell clone confirmed by genotypic analysis of the peripheral blood. We have observed that the CD8 count in patients with clonal SS is lower than in patients who fulfill the clinical criteria for a diagnosis of SS but do not exhibit a peripheral blood T-cell clone. It is this nonclonal group who might account for the predictive power of the initial CD8 count and the prolonged survival of patients in Edelson’s cohort.

Edelson also proposes selection bias as an explanation for our results, in that only those patients who failed other treatments were referred for ECP. This is a possibility, but selection bias could apply equally in the opposite direction, as discussed in our article. The only conclusion one can draw with certainty from this discussion is the need for a randomized study.

In his letter, Edelson seems to question the need for a randomized study of ECP, but enthusiasm for a particular therapy is no substitute for scientific rigor. As Zackheim and coauthors pointed out in a recent review of cutaneous T-cell lymphoma, “Randomised control trials (RCT) are needed in CTCL as they are in many other disease areas. If one wishes to have an unambiguous result in the evaluation of therapeutic efficacy, there is no substitute for a carefully performed RCT.”

In a review of 6 medical therapies, each subject to multiple therapeutic trials with historical as well as randomized controls, 79% of the 56 studies with historical controls found the experimental therapy to be superior, whereas only 20% of the 50 studies with randomized controls agreed. In the context of CTCL, some of the studies reporting prolonged survival with ECP have not even confined their analysis to SS, but have included patients with cutaneous patch- or plaque-stage disease. Investigators faced with a lack of response to ECP in patients with CTCL now advocate the use of ECP plus interferon alfa or, as in Edelson’s case, immune enhancement using tumor-specific peptides and dendritic antigen-presenting cells. With the advent of cytokine therapy such as interleukin 2 or interleukin 12, the number of combinations could be extended indefinitely, but does not override the need to test scientifically the efficacy of ECP itself against a standard chemotherapy regimen such as methotrexate.

Over the past 2 years, we have tried to establish such a study but have been unsuccessful despite the support of the president of the International Society for Cutaneous Lymphoma and the chairman of the European Organization for Research and Treatment of Cancer Cutaneous Lymphoma Group. Therakos, the company that provides ECP equipment, has little interest in such a trial because it already has Food and Drug Administration approval for the use of ECP in CTCL treatment.

Over a decade has passed since Edelson’s seminal article was published in the New England Journal of Medicine, and the lack of any randomized study of ECP therapy for CTCL is increasingly difficult to justify.

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**Randomized Trials and Scientific Methods**

We enjoyed the article by Smolle et al.\(^1\) that discussed a randomized clinical trial of homeopathy for warts. We strongly agree with the statement in their introduction that “...scientific methods are valuable tools for distinguishing helpful alternative medical methods from superstition and quackery.”

Scientific methods do not necessarily require a randomized trial. We can argue that sometimes a randomized trial is harmful. When a trial is performed, a test of statistical significance is done, such as a t-test. The standard in clinical medicine for a statistically significant result is a P value less than or equal to .05. Accepting a P value of .05 means that there is a 1 in 20 chance that a therapy without merit could be shown to be significant. One way to decrease the likelihood of getting a spurious result is to limit trials to topics that have a potentially medically explainable result. Is there even a scientifically defensible hypothesis for the therapeutic basis of homeopathy? Have any basic science experiments ever shown that the chemically pure water used in homeopathy is different from normal water?

A trial of a therapy with no medical basis is dangerous because by chance alone the trial could suggest that the therapy is effective. A potentially false-positive trial of a novel therapy may be followed by a second trial using a large number of patients. The likelihood that the second, larger trial would also give a false-positive result is low. But what about the interval between the trials? How many patients would spend their money and time chasing an ineffective therapy? Further, some alternative medicine practitioners and customers may choose to look at only “positive” studies. These problems could be avoided by limiting randomized trials to therapies that have a rational physiological explanation.

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**Careful Evaluation Needed of “Alternative” Claims**

The November 1998 issue of the *Archives* on alternative medicine and dermatology (November 1998) certainly is thought provoking. I would like to add my opinion to the discussion. In the enthusiasm and excitement over alternative approaches to medical care, I believe it is important to maintain the perspective of the past. In the prescientific era of medicine, treatment was frequently ineffective if not harmful. Infections, injuries, periodic epidemics of communicable disease, and other medical maladies, with few practical treatments, contributed greatly to human suffering and death. Adoption of the scientific method and the biological model of disease has led to the great triumphs of medicine in combating disease, promoting wellness, and extending the human life span. We must guard against the adoption of unproven remedies based solely on folklore, tradition, or anecdotal reports of success. Unfortunately, some of the articles within the issue on alternative medicine present anecdotes, opinions, and unreference statements and conclusions without challenge or editorial comment.

The discovery of new approaches to promoting wellness and combating disease is among our highest goals. So-called alternative treatments must be tested in well-controlled, properly designed studies. Those that convincingly demonstrate benefit are perhaps best not thought of as alternative therapies but rather simply as therapies that add to the armamentarium of medicine. There should be no bias against unconventional thinking, but rather an expectation that the utility of new techniques can be validated. Several of the articles within the special issue on alternative medicine do exactly that.

When new therapies appear to work without an understanding of their biological or physical mechanisms of effect, research to uncover these mechanisms of action may be very helpful in designing even more effective techniques. When it is difficult or impossible to construct a hypothesis for a mechanism of action for a therapy that is consistent with the current understanding of the physical laws by which the universe is governed, one must expect a particularly high level of proof. Marcello Truzzi has written, “...when such claims are extraordinary...we must demand extraordinary proof....”

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**Randomized Trial of Aromatherapy: Successful Treatment for Alopecia Areata**

The randomized trial of “aromatherapy” for alopecia areata by Hay et al.\(^2\) in the “Alternative Medicine” theme issue in the *Archives* is illustrative of several basic principles. Although the treatment resulted in a statistically significant improvement, I have questions about their initial randomization. The only statement on randomization procedure is, “Eighty-four patients were randomized into 2 groups by the aromatherapist.”\(^3\) There is mention neither of the technique used to randomize the patients nor of disease duration, which is a major predictive factor in alopecia areata.\(^2\) It must be remembered that approximately half of adult patients with recent onset of patchy alopecia areata have spontaneous remission within the first year. Thus, the reported re-
sults could easily be accounted for by differences in disease duration.

Assuming the treatment is effective, what conclusions does one make? No doubt some will take this as evidence that aromatherapy is valid, and “alternative medicine” is both a valid and important tool for the complete clinician. However, the logical response is to determine which of the botanicals is biologically active, isolate the active material, and standardize it. A large percentage of our medications come from botanicals, and it is no surprise that essential oils contain active moieties. The finding of active materials in essential oils does not justify random application of good smells based on unproven claims. Derivation of pharmaceuticals from botanicals is hard science and has no room for the vague, irrational claims of practitioners of “alternative medicine.”

Many other subjects touched by alternative medicine are amenable to scientific analysis, without validating the alternative medicine approach. Mind-body connections are real, and a subject for neurology, neuroimmunology, neurochemistry, and psychiatry. Much of alternative medicine is distinguished only by its lack of basis in rational thought, gullibility, and a lack of skepticism.

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In reply to Professor Kalish’s questions, patients were interviewed in a dedicated clinic for the study. After consent, evaluation and photography were performed, identical instructions were given by the aromatherapist, and randomization was carried out by giving every alternate subject the active treatment (alternating with placebo base oil/no essential oils). Thus there could be no selection bias; treatment was both random and blind. Table 1 details disease duration in active and control groups.

Disease severity was classified by the McDonald-Hull and Norris’ 4-point scale, as described in the article. The initial assessment of the disease severity in the 2 groups is outlined in Table 2.

We do not deny the frustrating unpredictability of this disease and constructed the study with statistical advice on power, numbers, and methodology anticipating the skepticism that would be met if we did find a significant effect. Any study can produce a false-positive conclusion and verification in further studies is desirable; but our results demonstrate that this therapy was successful. In Britain, patients are only referred to a dermatologist after seeing a generalist. Generally, British dermatologists are likely to review more severe cases than those of our colleagues in the United States. The photographic illustration we showed was one of several showing a degree of improvement we would not have expected by chance.

We agree entirely that this does not validate claims that aromatherapy is effective in other therapeutic areas. As with Chinese herbalism, some alternative therapies have a history and tradition. Over hundreds of years practitioners may have gained wisdom from trial and error in identifying active botanicals. We have found references from 100 years ago documenting the use of oils similar to those used in this study for hair loss. The task of identifying the active constituent would be fascinating but likely too complex, and would require support from the pharmaceutical industry.

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Table 1. Disease Duration for Both Active and Control Groups

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<th>Disease Duration, y</th>
<th>Active Group, No.</th>
<th>Control Group, No.</th>
<th>Total</th>
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<td>19</td>
<td>29</td>
</tr>
<tr>
<td>5-9</td>
<td>15</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>&gt;9</td>
<td>18</td>
<td>13</td>
<td>31</td>
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Table 2. Disease Severity Measured on the 4-Point Scale

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<th>2</th>
<th>3</th>
<th>4</th>
<th>Total</th>
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</thead>
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<td>9</td>
<td>22</td>
<td>0</td>
<td>42</td>
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<tr>
<td>Control</td>
<td>9</td>
<td>6</td>
<td>26</td>
<td>0</td>
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VIGNETTES

Oral Psoralen-UV-A for Systemic Scleroderma

Systeatic sclerosis is an autoimmune connective tissue disorder that is characterized by massive deposition of collagen in the skin and/or visceral organs. Attempts to treat the disease have included therapy with anti-inflammatory drugs, immunosuppressive agents, penicillamine, colchicine, calcitomin, retinoids, interferon gamma, and extracorporeal phototherapy.1 Recently, bath psoralen UV-A (PUVA) therapy was administered successfully to patients with circumscribed scleroderma and to a few patients with systemic sclerosis.2,3 Encouraged by this handful of positive reports, we examined whether standard oral PUVA therapy would
be an effective treatment for systemic sclerosis. Since there would be no need for special bath facilities, oral PUVA would be much easier to administer and offer to patients on an outpatient basis.

Patients, Therapy, and Methods. Four women (mean age, 58 years; age range, 44-73 years) with systemic sclerosis (mean disease duration, 3 years; range, 1-6 years) who had undergone progressive skin changes during the previous 6 months were treated with oral PUVA therapy after they had previously not responded to various treatment agents, including systemic steroids, calcitomin, and interferon gamma. Before oral PUVA therapy was begun, a 1-month washout treatment was administered where the patients had been treated with other therapy for systemic sclerosis. Each patient received 0.6 mg of 8-methoxypsoralen (8-MOP, Oxsoralen) per kilogram of body weight 1 hour prior to UV-A irradiation. The initial UV-A dose was 50% of the individual minimal phototoxic dose (range, 0.5-4 J/cm²). Psoralen UV-A was given 3 times weekly for 10 weeks, resulting in a mean cumulative dose of 70.5 J/cm² (range, 50.5-92.0 J/cm²). Two patients had to be switched from 8-methoxypsoralen to 5-methoxypsoralen (5-MOP, Geralen) because the 8-methoxypsoralen caused nausea. To evaluate the response to therapy, clinical scores were obtained for skin severity in 22 skin regions, joint motility, grip strength, and skin thickness (via 20-MHz ultrasonography). Also, skin biopsy specimens were taken immediately before and within 7 days after oral PUVA treatment. The biopsy specimens were processed, sectioned, stained with hematoxylin-eosin, and finally scored on a scale from 0 to 3 by a blinded observer (H.P.S) for 6 parameters (thickness of dermis, thickness of collagen bundles, width of spaces between collagen bundles, thickness of subcutaneous septa, presence of inflammatory infiltrate, and entrapment of eccrine glands), resulting in an overall histological skin assessment with a possible score ranging from 0 to 18.

Results. Whereas 3 of 4 patients reported an improvement of their subjective overall status and 1 patient exhibited stabilization of disease, the mean objective scores for skin severity, grip strength, joint motility, and skin thickness (via 20-MHz ultrasonography) before and after therapy did not differ significantly. However, the histological analysis revealed that oral PUVA treatment had ameliorated the histological skin score of all patients. The mean histological skin score was 6.3 before therapy vs. 3.0 after therapy (Wilcoxon test, P = .07).

Comment. The possible mechanism of action of PUVA in systemic sclerosis remains unclear at present. Psoralen UV-A may influence the course of disease by its local and/or systemic immunosuppressive effects. Alternatively, PUVA treatment, like UV-A treatment, may decrease the amount of collagen by directly inhibiting its synthesis and/or stimulating collagenase activity. The UV-induced production and release of cytokines such as tumor necrosis factor α or interleukin 6 may be responsible for decreased collagen synthesis. Perhaps singlet oxygen molecules induce the activity of matrix-metalloproteinases such as collagenase. Whatever the mechanism, our observation suggests that oral PUVA therapy may be an effective treatment for patients with systemic sclerosis who are undergoing skin changes, that further studies are clearly necessary to determine the significance of PUVA-induced amelioration of histological changes in the long-term clinical follow-up of patients with systemic sclerosis, and that more work in a greater number of patients with systemic sclerosis seems justified and desirable.

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Low and Irreproducible Methoxsalen Levels in Patients Receiving Photochemotherapy

Psoralen UV-A therapy (PUVA) is used for the treatment of psoriasis1 and cutaneous T-cell lymphoma.2 The efficacy may be related to the amount of drug present at the time of irradiation. From 1988 to 1996, 5274 blood specimens were collected from patients receiving photochemotherapy and analyzed by high-pressure liquid chromatography.3 Patients for whom at least 10 determinations were made (1029 determinations in 68 patients) were selected for detailed analysis. We show that it is not uncommon for patients to have very low levels of methoxsalen.

Patients and Results. Patients with similar parameters were categorized into 3 subgroups (Figure 1) corresponding to high (group 1), average (group 2), and low (group 3) methoxsalen levels. For group 1, the average ± SD methoxsalen level was 311 ± 218 ng/mL; for group 2, 201 ± 132 ng/mL; and for group 3, 118 ± 86 ng/mL. Figure 1 most clearly illustrates the differences between the 3 cluster groups because it can be seen that even though the patients in group 3 ingested some of the highest doses of methoxsalen, their blood levels were the lowest. The average ingested doses were 44, 46, and 50 mg, respectively. In group 1, only 3 of the measured levels corresponded to ingested doses greater than 60 mg; for
group 2, 41 mg; and for group 3, 83 mg. When the average plasma level–ingested drug ratio is computed, the bioavailability in group 1 was found to be more than 3 times that for group 3 (7.5 compared with 2.4).

Figure 2 shows chronological patterns of methoxsalen levels for representative patients from each of these groups. Although the average methoxsalen level in group 1 is much higher than for groups 2 and 3, there were still many instances of low or 0 values. Foremost among our observations is that there is a high frequency of low and perhaps suboptimal levels of the drug at the time of therapy: 1369 (31.7%) blood methoxsalen levels were lower than 50 ng/mL, and of these, 976 were lower than 20 ng/mL. Second, we have observed substantial variations in patient chronological profiles over months and years (Figure 2). An analysis of the pattern of methoxsalen levels of 1 patient (data not shown) placed that patient in group 3. However, a closer inspection showed that the 21 analyses could be divided into 2 groups (specimens 1-7 and 8-21). Two very different averages resulted (211 ± 117 and 22 ± 32, respectively). This kind of result indicates the value of periodically determining methoxsalen levels rather than relying on a single random measurement that may not be representative of typical methoxsalen bioavailability in a particular patient.

Comment. Familiarity with the patient’s methoxsalen plasma profile may provide an explanation for the lack of response to therapy. These variations have been attributed to food ingestion, metabolic disposition, and vasodilating drugs (for a discussion, see Gasparro, and references therein). Attempts to eliminate or minimize variations in psoralen blood levels have had limited success. One method of ensuring the delivery of methoxsalen to the target tissue in patients with psoriasis has been the implementation of bath delivery. While logistically more involved and less convenient than oral ingestion, this approach has been widely implemented in Europe. Other approaches have included supposi-
ries, topical application, and intravenous infusion (for a discussion of these issues see Gasparro,2 chapter 2 and references therein). Knobler et al5 formulated a sterile aqueous solution of methoxsalen for direct injection into the leukocyte/plasma fraction collected during the initial phase of photopheresis.5

Variations in methoxsalen levels highlight the need to establish a patient’s pattern of methoxsalen levels. While bath PUVA has been used in Europe, logistical issues have limited its implementation in the United States. Thus, for patients with psoriasis there seems to be no alternative to oral ingestion. For photopheresis, however, of these alternate routes, the direct injection of a methoxsalen solution into the collected lymphocytes is feasible. Finally, it is important to note that while no level of methoxsalen has been related to therapeutic efficacy, it would seem prudent to aim for reproducibility.

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**Bath Psoralen-UV-A Therapy for Persistent Grover Disease**

In 1970, Grover described a novel disease characterized by the sudden onset of intense pruritus and disseminated papules on the trunk. It has a typical histological picture, manifests predominantly in white men older than 40, and is frequently self-limited. However, in some patients the disease persists for several months or years, and therefore the original name, transient acantholytic dermatosis, has been abandoned in favor of Grover disease.3

Although a benign course of Grover disease responds to appropriate skin care and topical corticosteroids, treatment of persistent disease frequently remains unsatisfactory, and a standard therapy is still missing. Relief may be obtained by systemic treatments with either isotretinoin, corticosteroids, or relatively high doses of methotrexate.1,2 The etiology remains unclear, but it is well established that Grover disease may be provoked by UV exposure, ionizing radiation, heat, and sweating.3 Most interestingly, Paul and Arndt4 reported provocation of Grover disease during oral psoralen–UV-A (PUVA) therapy and clearing following continuation of oral PUVA, suggesting that Grover disease may be a photosensitive dermatosis responsive to photochemotherapy. Bath PUVA therapy is an important alternative to oral PUVA. For most indications it is at least as effective as oral PUVA but avoids most of the adverse effects.5

**Report of Cases.** Three patients with persistent Grover disease received bath PUVA therapy (Table). Despite the long-standing disease, all patients’ symptoms cleared completely with 10 to 37 treatments (Figure 1 and Figure 2). Bath PUVA therapy was performed as described4 and complete remission of pruritus and skin eruptions was achieved in all 3 patients (Figures 1 and 2). No relapse was observed within more than 1 year. Histological samples from a previously involved skin area were reassessed 6 months after bath PUVA therapy with no pathologic findings.

Comment. Despite careful treatment, Grover disease does not resolve in some patients.3 Systemic corticosteroids,
vitamin A derivatives, or other immunosuppressive agents may be effective in these patients, but relapses are frequent after the drug therapy is discontinued. As oral PUVA therapy achieved complete clearance of skin eruptions and pruritus in a single patient, and its usefulness has been suggested in reviews,4,6 we investigated the efficacy of bath PUVA therapy. The results suggest that this mode of PUVA treatment, which is almost devoid of the adverse effects associated with oral PUVA and which induces sensitivity to UV-A for less than 1 hour,5 is an important therapy for persistent Grover disease.

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Effects on Human Epidermis of Chronic Suberythemal Exposure to Pure Infrared Radiation

We have characterized the chronic effects of near infrared radiation on human epidermis in vivo and want to compare this with the alterations reported to occur after UV irradiation.

Patients and Methods. We studied 8 normal healthy volunteers (4 men, 4 women, age range 28-39 years; skin phototypes I through III) with no history of skin disorders and minimal solar damage.

An infrared lamp (Hydrosun 500; Hydrosun Medizintechnik GmbH, Germany) with single-output band (620-1370 nm) and an irradiance of 440 mW · cm⁻² was used. Irradiance between 250 nm and 400 nm is 0.0034 mW·cm⁻², but from 250 nm to 340 nm is only 0.00045 mW·cm⁻², 10⁶ less than the main infrared band; 9.5 minutes' irradiation at 30 cm is equivalent to a 1-hour exposure to a typical solar spectrum (ASTM).¹

Irradiation of buttock skin for 9.5 minutes produced no pain and was administered randomly to either the left or the right side daily for 6 weeks, excluding weekends. The 10 × 10-cm area irradiated was masked using a 15-mm-thick wooden board. A skin temperature increase of 2.6°C was measured during irradiation, resulting in a typical skin temperature of 33.4°C.

Assessments were made 1 day after the last irradiation. Skin roughness was assessed by stylus profilometry of silicone rubber “negative” replicas of the skin. DIN standard roughness parameters Ra (arithmetic mean height of surface profile) and Rz (mean of maximum peak to valley height from 5 equal sections of the profile) were measured in triplicate using 4.8-mm scans.

Four-millimeter punch biopsy specimens were taken from irradiated and unirradiated sites. One half of each biopsy specimen was for standard (hematoxylin-eosin) histology, the other for frozen section and histochemical studies. Using image analysis under light microscopy, the mean epidermal thickness (MET) was determined from a minimum of 5 fields across each specimen. Using cryostat sections, activity of glucose-6-phosphate dehydrogenase (G6PD) enzyme staining in granular layer (optical density units) and G6AUC, area under curve of G6PD epidermal distribution (arbitrary units), were measured.

### Characteristics of Nonirradiated and Irradiated Skin Samples

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>Sites, Mean (SD)</th>
<th>Within Subject Differences, P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonirradiated</td>
<td>Irradiated</td>
</tr>
<tr>
<td>Ra, µm</td>
<td>13.2 (3.2)</td>
<td>15.5 (4.9)</td>
</tr>
<tr>
<td>Rz, µm</td>
<td>61.1 (11.9)</td>
<td>69.7 (19.9)</td>
</tr>
<tr>
<td>MET, µm</td>
<td>57.82 (14.0)</td>
<td>63.7 (12.1)</td>
</tr>
<tr>
<td>G6PEAK</td>
<td>1.29 (0.5)</td>
<td>1.62 (0.4)</td>
</tr>
<tr>
<td>G6AUC</td>
<td>19.61 (6.6)</td>
<td>24.53 (6.2)</td>
</tr>
</tbody>
</table>

* Ra indicates arithmetic mean height of surface profile; Rz, mean peak to valley height; MET, mean epidermal thickness; G6PEAK, density of glucose-6-phosphate dehydrogenase (G6PD) enzyme staining in granular layer (optical density units); and G6AUC, area under curve of G6PD epidermal distribution (arbitrary units).

Buttock skin sample from volunteer 6, stained for glucose-6 phosphate dehydrogenase enzyme. Left, Irradiated site. Right, Nonirradiated site.
phosphate dehydrogenase (G6PD) enzyme was measured.² Using a suitable narrow bandwidth filter (597 nm, 43.5-nm bandwidth), the activity of the enzyme was assessed by taking the peak optical density (a measure of granular layer staining), and by integrating the stain density over the whole of the epidermis. Within-subject differences were tested using the parametric paired t test and the nonparametric Wilcoxon matched pairs signed rank test.

Results. Summary results are given in the Table. The mean epidermal thickness from irradiated sites was 5.8 µm (SD, 8.7 µm) thicker than the nonirradiated sites. Both the peak (granular layer) and the total (area under optical density curve) staining of G6PD enzyme were significantly higher in irradiated sites, with an average difference of 0.33 (SD, 0.46) optical density units and 4.92 (SD, 6.4) arbitrary units, respectively. The Figure shows typical sections from irradiated (left) and nonirradiated (right) specimens. Irradiated sites had significantly greater roughness than the control sites by both the Ra and the Rz parameters.

Comment. A significantly thicker epidermis was found in irradiated skin than in nonirradiated skin in this study. Glucose-6-phosphate dehydrogenase is an enzyme that is found in the cytoplasm of cells, and an increase in its activity has been found to be a marker of UV damage.² It is found in nonirradiated epidermis as a band of reaction product in the granular layer with only a small amount of activity in the malphigian and basal cell zones. In irradiated epidermis, this band spreads throughout the epidermis showing an increased activity down as far as the basal layer (Figure, left).

Cytochemical changes in G6PD activity have also been reported in solar keratoses and in preneoplastic and neoplastic epithelium in both rat and human tissue. It seems possible therefore that metabolic changes, such as the increase in G6PD activity seen here after infrared irradiation, are sensitive markers of early epidermal damage and are not specifically related to UV radiation.

The higher roughness parameters suggest that some damage has been inflicted on the irradiated sites. This could be caused by the increased production of epidermis, or a disruption in normal desquamation.

Definite signs of epidermal response to damage have been detected, so it seems that the pure infrared irradiation regimen used is capable of inducing skin changes, even in the absence of a notable increase in skin tissue temperature. In particular, the level of the enzyme G6PD was considerably elevated after the mild but pure infrared irradiation regimen. It is believed that this is a new finding and merits further investigation.

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