

COMMENTS AND OPINIONS

Finasteride, 1 mg (Propecia), Is the Optimal Dose for the Treatment of Men With Male Pattern Hair Loss

In the Commentary "Study of the Food and Drug Administration Files on Propecia: Dosages, Side Effects, and Recommendations" published in the March 1999 issue of the ARCHIVES, Frankel¹ challenges the decision by the Food and Drug Administration to approve finasteride, 1 mg (Propecia; Merck & Co Inc, Whitehouse Station, NJ), for the treatment of men with male pattern hair loss. Frankel argues that the dose of Propecia is "far higher than the level measured as necessary for inhibition of the conversion of testosterone to DHT [dihydrotestosterone]," based on serum and scalp DHT levels we measured in balding men treated with finasteride for 6 weeks.^{2,3}

While the scalp DHT study was designed to demonstrate the biochemical efficacy of the drug at the target tissue over a broad dose range, that study was followed by a 6-month clinical dose-ranging study to fully characterize the dose-response relationship of finasteride in men with male pattern hair loss, using clinically relevant end points. In the clinical dose-response study, the 1-mg dose demonstrated significantly better efficacy compared with the 0.2-mg dose based on hair counts ($P = .04$, 1 mg vs 0.2 mg at month 3) and by an expert panel review of standardized clinical photographs ($P = .02$, 1 mg vs 0.2 mg at month 6).^{2,4} At month 6, the expert panel rated improvements in hair growth in 52% of patients receiving the 1-mg dose, compared with only 38% of patients who received 0.2 mg.⁴ Consistent trends in the data up to 12 months in a blinded extension to the dose-response study supported the superiority of the 1-mg dose.^{2,4} Also in agreement with the superior efficacy of the 1-mg dose, serum DHT was suppressed more with the 1-mg dose than with the 0.2-mg dose (median $\pm$ SE percent decrease, $-68.5\% \pm 1.4\%$ vs $-61.2\% \pm 1.7\%$, respectively, at month 6; $P = .002$, 1 mg vs 0.2 mg).⁴ Frankel concluded incorrectly that the difference in clinical efficacy at month 6 between the 1-mg and 0.2-mg dose groups was not significant because their values "overlapped statistically at the 95% confidence level."¹ This is a common mistake that has long been highlighted in both the statistical⁵ and nonstatistical^{6,7} literature. Frankel goes further and recommends that men with male pattern hair loss take the lower (0.2-mg) dose of finasteride, a dose that is suboptimal and is neither approved nor available to patients.

In contrast with the other concerns raised by Frankel, the safety profile of finasteride is well understood and is based on extensive, long-term clinical trial data and marketed experience with finasteride, 5 mg (Proscar; Merck & Co Inc), since 1992, as well as over 5 years of clinical trial experience with Propecia. The product label for Pro-

pecia identifies the low incidence of adverse events reported by a few men taking the drug in controlled clinical trials, and long-term data demonstrate that there is no increase in adverse events with continuing therapy.⁸ The data on semen parameters show that median ejaculate volume decreased by 0.3 mL (-10.9% ; 95% confidence interval, -18.9% to 4.3%) in Propecia-treated subjects, but there was also a decrease of 0.2 mL (-7.8% ; 95% confidence interval, -25.5% to 3.9%) in placebo-treated subjects^{8,9} and a between-treatment group difference of only 0.03 mL (1%; 90% confidence interval, -10.4% to 13.1% ; $P = .92$).⁹ No significant difference between treatment groups was observed for any other semen parameter.⁹ These controlled clinical trial data, as well as extensive preclinical studies in multiple animal species and clinical observations in men with genetic type 2 5 α -reductase deficiency, support the conclusion that there is no effect on male fertility with Propecia. Lastly, the product label for Propecia instructs physicians how to adjust the measured serum prostate-specific antigen level in men taking Propecia to compensate for the effect of finasteride.⁸ This simple adjustment has been demonstrated to preserve the sensitivity and specificity of the test in the detection of prostate cancer.¹⁰

Frankel stated that he was unable to find additional information in the medical literature, based on a MEDLINE search of the term *Propecia*. This is likely because the brand name of a drug is not generally used in scientific publications. A search of the term *finasteride* would have revealed several articles of interest, including the results of the multicenter phase 3 pivotal trials with finasteride, 1 mg, in 1553 men¹¹ as well as an independent, comprehensive review of finasteride in the treatment of men with male pattern hair loss.¹² Regardless, the documents obtained by Frankel under the Freedom of Information Act² provide ample evidence, based on efficacy and safety, to support the selection of the 1-mg dose of finasteride for the treatment of men with male pattern hair loss.

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Finasteride in a 1-mg Dose Is Safe and Effective

As an investigator and contributing author of studies on finasteride and male pattern hair loss,¹ I am writing in response to the commentary by Frankel² published in the March 1999 issue of the ARCHIVES. In his commentary, Frankel raises concerns about the dosage, long-term adverse effects, and costs of Propecia (finasteride, 1 mg). It is appropriate to raise and publish opinions about controversial issues. Commentaries, however, are not held to the same rigorous scrutiny and high scientific standards as peer-reviewed articles.

Frankel asserts that the 1-mg dose is unnecessarily high and, therefore, unnecessarily expensive, arguing instead that the data would support a lower 0.2-mg dose. His conclusion about the appropriate dosage, based on data from a 6-week trial examining the effects of finasteride on serum and scalp dihydrotestosterone (DHT), is erroneous. A separate 6-month clinical dose-ranging study was specifically performed to assess the effects of finasteride on hair growth using end points relevant to hair growth rather than effects on serum and scalp DHT. This longer study clearly demonstrated the superiority of the 1-mg dose of finasteride in end-point measurements of hair growth, including hair counts, expert panel global photographic assessments, and subjects' self-assessments of improvements, with trends of superiority extending to 12 months in a follow-up extension study.¹ Simply stated, clinical efficacy with the 1-mg dose was superior to the 0.2-mg dose. Certainly the scalp DHT measurements are relevant, but basing an argument regarding optimal dosage on scalp DHT levels alone is incomplete because the issues are more complex and may relate to the need to reduce additional sources of DHT from the serum or from within the hair follicle itself. Equally important, the safety profile of the 1-mg finasteride dose was similar to that of the 0.2-mg dose.

The low incidence of adverse effects and excellent tolerability of finasteride has been borne out in the extensive long-term clinical trials of finasteride at the 1-mg and 5-mg doses in humans,^{3,4} and safety data are also supported in extensive preclinical animal studies.⁵ Some of the clinical studies with finasteride for the treatment of men with male pattern hair loss have been ongoing for as long as 6 years, allowing those of us involved with these studies to observe our subjects over a long period. It has been my ex-

perience that not only is finasteride a useful drug in the treatment of male pattern hair loss in men, but it is also well tolerated and remarkably free of adverse effects. As years pass, benefits continue to accrue in terms that may not be reflected in increasing hair counts (hair density) but rather in terms that can be measured in continued improvement by the global photographic assessment, and by the more subjective but no less important parameters of patient satisfaction: the quantity and quality of hair to cover the scalp is improved, and hair density is being preserved. For most of my subjects, this has been more than adequate reason to continue participating in studies far beyond the initial study requirements.

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7-5 by '05

More than 25 years ago, the starting date of most hospital internships was advanced from July 1 to June 24. This allows physicians 1 week after their internship ends on June 23 to move to the location of their residencies that start on July 1.

Unfortunately, we in dermatology have not embraced this policy for our postresidency fellowships. Most fellowships in dermatosurgery, dermatopathology, etc, begin at 8 AM on July 1. This causes unnecessary stress. Residents must either request time off at the end of their residency or travel overnight to reach their fellowships on time.

I propose that each fellowship director achieve 7-5 by '05. By this, I mean that postresidency fellowships will begin on July 5 by the year 2005.

One way to achieve this is to notify your fellowship applicants that they will be expected to participate for one extra day. If each of the next few fellowship classes does this, 7-5 by '05 is easy to achieve.

An even easier method is to schedule Monday, July 3, 2000, as a vacation day. After your fellow leaves on June 30, you will enjoy a 4-day holiday weekend (Saturday, July 1 through Tuesday, July 4) and, beginning then and thereafter, your fellow will start on July 5 and finish the following July 3. Concerns about difficulties paying an employee who does not start on the first of the month are groundless, as any one of various arrangements easily solves such issues.

So all fellowship directors, remember the cry, "7-5 by '05." Your fellows and their residency programs will thank you.

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Physicians' Responsibility for Medical and Surgical Dermatology

I would like to offer my thoughts regarding Lynch's editorial¹ and subsequent letters to the editor²⁻⁴ concerning the demise of medical dermatology.

During the first week of medical school, the doers and thinkers, the surgeons and internists were already being distinguished in the anatomy laboratory. The gadgeteers, doers, and dissectors were enthralled with the mechanics of the scalpel and forceps, while the thinkers, talkers, and philosophizers were reading the text, memorizing every list, and extolling the wonderments of all this knowledge.

The readers and thinkers became medical dermatologists and, I hope, raised the science to a higher level in the last 40 years. They solved difficult cases, attended meetings, discussed various therapies, and enjoyed their status as astute physicians. The dissectors became surgeons and specialized their craft. The 2 groups meet, but they are at different ends of the philosophical spectrum. One group is not better than the other; the groups approach the science of medicine in different ways. Usually, surgical subspecialists do not want to do the work of medical dermatologists and vice versa.

Now, the academic dermatologists are being asked to train the surgeons. Both residents and trained dermatologists have to be trained by outside physicians to keep pace, save face, and make money. However, trained surgeons view self-taught surgical dermatologists as not entirely trained: since they never pulled the retractors in an abdominal case for 6 hours, they did not pay their dues. Also, many medical dermatologists in private practice have financial difficulty and try to become surgeons, performing only minor procedures. I hope there are only a few surgeons who fail and are unable to master the gadgets.

Lewis H. Lapham,⁵ the editor of *Harper's Magazine*, and a gentle modern-day H. L. Mencken, loves to shoot holes in the balloons of pomposity and monetary rhetoric. Perhaps in response to comments about money in the dermatology literature, he wrote:

[E]very now and then I come across a wandering idealist intent upon saving an orphan or a whale, but mostly I meet people to whom the fervors of social protest seem superfluous or quaint. They don't talk about changing the system, only about the means of improving their access to it, and they smile with their mouths but not their eyes. Impatient with metaphors and bored by sentiment, eager to advance the token of their lives around the Monopoly board of the standard American success . . .⁵

Why do we believe that lower compensation for medical care is fixed in stone? These parameters are al-

ways in flux. I believe that it is difficult for physicians who are thinkers from the first week of medical school to change completely into doers in the middle of their careers. We must all maintain the practice of medical dermatology. We must be superior medical dermatologists and surgeons. Otherwise, we become dermatologic surgeons on the periphery of medicine. We also become uncaring medical practitioners if we stay away from dermatologically ill patients. If we relinquish the practice of medical dermatology, it cannot be retrieved from the new caregivers. In addition, we must discuss our financial well-being. We just might find ourselves crushed by an avalanche of disapproval from our patients, insurance companies, and the institutions of medicine if we continue plying our trade only for monetary reasons.

A majority of today's physicians take responsibility for those who come to be healed. Nuland⁶ stated in a recent commentary that by accepting the Hippocratic oath physicians consecrate their lives to the care of the sick. He believes that many physicians are sustained for decades by the belief in their hallowed duty. We are duty bound to care for the sick and troubled patient, not just to make people beautiful. Nuland's commentary is taken out of context because the tone of his article argues against assisted suicide. Physicians in many other fields are grappling with major philosophical and medical dilemmas.

We must be exemplary in our knowledge of medicine and medical dermatology in particular. We must show that we care about the well-being of our ill patients.

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Wound Measurement Made Truly Simple by Point Counting

In the article by Kantor and Margolis,¹ high correlation coefficients are reported comparing wound size estimates using width, length, length $\times$ width, an ellipse model, and computer-aided planimetry. However, since measures of association are used instead of a measure of agreement, high correlation coefficients are to be expected.²

Unfortunately, leg ulcers are almost never rectangular. Occasionally, they are round or oval, but very often they are irregularly shaped or even multilocular, in which cases the types of measurements proposed are meaningless. Instead, I would recommend simple point counting for estimating the area of wounds or ulcers.³ This method, using a square lattice grid on a transparent foil, yields remarkably accurate results regardless of

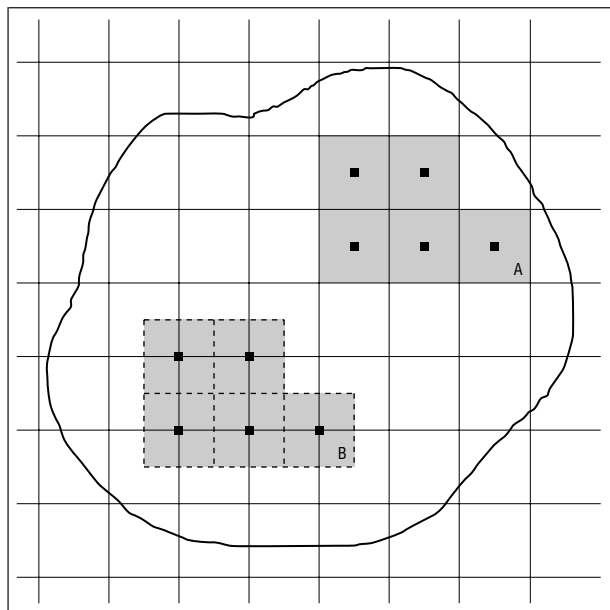


Figure 1. The principle of point counting: instead of counting the squares (A) within the bounded area, the crossover points of the square lattice grid (B) might be used as a substitute, since each crossover point might be regarded as representative of 1 square of the grid.

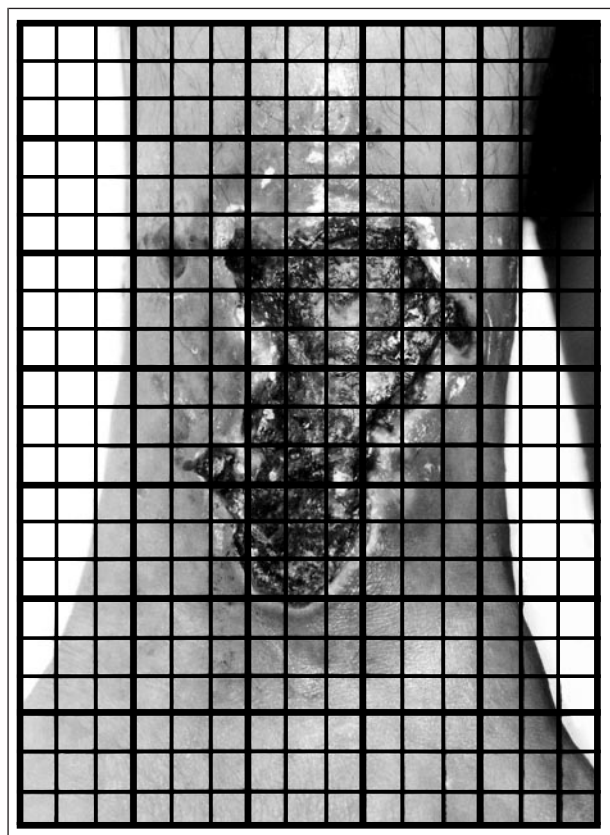


Figure 2. Irregularly shaped leg ulcer, superimposed with a square lattice grid of 1-cm squares. Thus, 1 crossover point represents 1 cm². Since 42 points are counted on the ulcer, its area is 42 cm².

the shape of the area to be measured (**Figure 1**).⁴ Since point counting is so simple and cheap, and its precision is comparable to that of computer-aided planimetry,⁴ it is ideally suited for the daily work of accurately recording the sizes of lesions (**Figure 2**). The same grid al-

lows the practitioner to estimate the irregularity of the lesion.³

In determining the sizes of skin lesions, the practitioner must remember that the area of only a few simple geometric figures, such as a circle, can be correctly described by just 1 linear parameter. Thus, using "diameters" to describe the areas of irregularly shaped lesions will inevitably result in inaccuracies and is inimical to evidence-based medicine.

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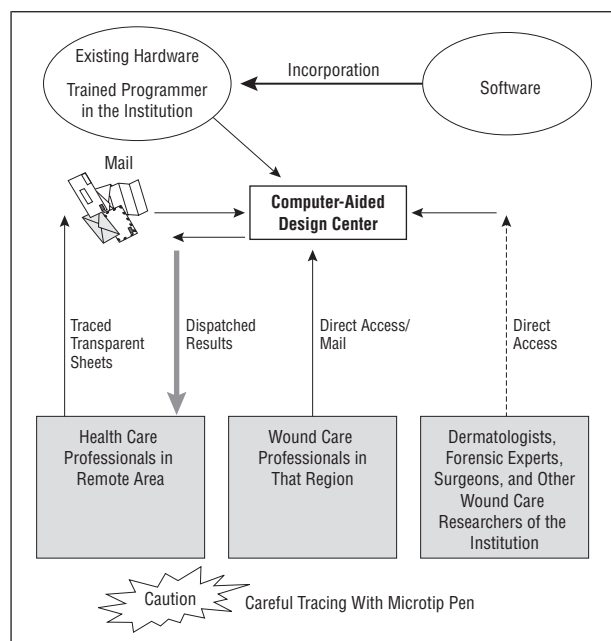
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Computers or Simple Wound Measurements: When Greek Meets Greek, Then Comes the Tug-of-War!

The title proverb, "When Greek meets Greek, then comes the tug-of-war," is from the novel *The Rival Queens* by Nathaniel Lee (1655-1692) and refers to any contest between 2 sides of equal strength. As illustrated in the present article, computers can be as accessible and economical as simple wound measurement techniques.

I read with interest and appreciation the article by Kantor and Margolis,¹ who compared computer-based planimetry with simple wound measurements. They have concluded that computers are high-technology methods of wound measurement, suitable only for clinical research and not accessible to health care providers. Hence, they conclude that computers are unsuitable for routine use in the clinical setting. Recently, however, our own research in Manipal, India, on cutaneous lesions and wound measurement with computer software^{2,3} has revealed that computers may be used to measure irregularly shaped ulcers with precision and rapidity, avoiding both wound contamination and patient discomfort.

We also found that advanced computer software can be made economically accessible to health care providers through the process illustrated in the **Figure**. Clinicians in remote areas can mail transparent sheets on which the wound has been traced to the nearest computer center³ and obtain the results. Tracing errors can be minimized by careful tracing with a microtip pen. Because a trained computer programmer operates the software, the clinician need not undergo extensive technical training. Also, because irregularly shaped ulcers of any origin and anywhere on the body can be measured by computers,³ health care specialists, forensic experts, or surgeons not under one roof, as well as all other clinicians in that re-



Advanced computer software made accessible and economical to health care providers.

gion involved in wound care, can share the technology at a central location, making it more economical and maximizing its generalizability. Forensic experts, for example, can document the area and perimeter of wounds with precision and produce this data conveniently as expert evidence³ because the dimensions of the traced wounds can be stored on a floppy disk.

Further, by incorporating only the software used in measuring the wound dimensions (computer-aided design software [eg, Auto CAD Release 14; Auto Desk Inc, San Rafael, Calif]) into the existing computer hardware of medical institutions or research centers, expense is minimized; no money need be spent on additional computer hardware.

Computer-aided wound measurement is accurate, reproducible, sensitive, flexible, standardized, informative, and meets the standard parameters of wound measurement put forth by Wysocki.⁴ It meets all uniformity and consistency requirements both in the clinical setting and for research. Both accessible and economical, computer-aided wound measurement compensates for the shortcomings of simple wound measurement.

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In reply

We agree with Dr Kanthraj that computer-based wound measurement is not necessarily inaccessible to physicians, and we agree that computers are a very useful adjunct to the health care system in general. The purpose of our article¹ was not to malign the use of computer-based wound measurement, but rather to investigate whether simple wound measurements often used in clinical practice, such as the length and width of a wound, reflect the computer-based planimetry used in clinical trials. As such, we did not intend to imply that computer-based wound measurement is inaccessible by definition, but rather that the realities of the health care system coupled with the relatively slow rate of physician adoption of novel technologies present a situation in which computer-based planimetry is used only rarely by anyone other than wound care specialists. Moreover, even if computer-based wound measurement did not involve high costs, the inconvenience of scanning a wound tracing (or sending one in to a centralized center, as suggested by Kanthraj) is not insignificant. Finally, wound assessment is ideally accomplished in real time; a 1-day or 1-week lag between physical measurement and knowledge of the wound size would not allow the physician to provide the patient with immediate feedback regarding the size of the wound and its relative change in size from the previous measurement. This delay would also require physicians to reenter data in a chart.

Given this reality, we investigated whether the wound measurements used by clinicians on a daily basis reflect those measurements gleaned from the sophisticated computer software used in clinical trials. The question of whether computer-based wound measurement should be adopted more widely is a separate one; however, because simple, inexpensive, and fast wound measurements closely approximate those done using computer technologies, barring an as-yet undetermined advantage to computer-based measurements, simple wound measurements are more than adequate for most patients in most health care settings.

Finally, while the actual method of wound measurement—whether computer based or otherwise—is important, the question of interobserver and intraobserver variability in these measurements is of even greater concern. Unless a patient sees the same physician or other health care provider on each visit, it is likely that the wound will be measured by different individuals at the time of each office visit. This is of special concern when conducting clinical trials in which data from numerous patients are examined and analyzed statistically. Despite Kanthraj's suggestions regarding the use of a microtip pen, computer-based planimetry has not been shown to reduce interobserver and intraobserver variability in wound measurement.²

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Congenital Cutaneous Defects in Co-Twins

Léauté-Labrèze et al¹ describe an infant survivor of a monozygotic twin pair with resulting aplasia cutis congenita (ACC) as a possible complication caused by the dead fetal twin. Unfortunately, the authors did not present electron microscopic or immunomapping findings of either the areas of bilateral absence of the skin or of the perilesional bulla of the patient. Photographs of this case (patient 1) along with the history of perilesional bulla and subsequent milia formation suggest a diagnosis of Bart syndrome.

In their discussion, the authors state that their presumed diagnosis, ACC, "should be distinguished from . . . other types of ACC (associated with epidermolysis bullosa)." Without providing the appropriate electron microscopic or immunomapping studies, this distinction cannot be made.

Congenital localized absence of the skin (CLAS) has been associated with virtually every form of epidermolysis bullosa.² While patients with Bart syndrome may present at birth with blistering and localized absence of the skin, spontaneous healing occurs within the first several months. These children may otherwise have normal growth and development.

Ultrastructural findings of the areas of CLAS have suggested that these lesions are merely a manifestation of in utero epidermolysis bullosa erosions, and not a separate entity such as ACC. Most likely, these areas of CLAS represent large erosive lesions induced in utero by physical mechanisms.² This hypothesis explains why CLAS lesions occur almost exclusively on unprotected areas like the skin of the lower limbs, buttocks, extensor surfaces of the forearms, and midline scalp. These are the very sites affected on patient 1 presented by Léauté-Labrèze et al. I believe that if appropriate ultrastructural studies had been done on this patient, a diagnosis of Bart syndrome might have been made.

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In reply

We thank Dr Kanzler for his interesting remarks about our article "Congenital Cutaneous Defects as Complications in Surviving Co-Twins." Despite the lack of electron microscopic and immunomapping studies with our first patient, we think that the correct diagnosis is still ACC type 5, and not Bart syndrome.



Aspect of the skin in patient 1 at age 7 years showing mild atrophic scars.

First, ACC type 5 is a recognized entity associating multiple, symmetric areas of ACC in a neonate surviving a dead co-twin.¹ Also, Bart syndrome is now recognized as a subtype of dominant inherited dystrophic epidermolysis bullosa.^{2,3} Skin fragility is noticeable even in adulthood. Our patient had no familial history of epidermis bullosa, and she had neither skin fragility nor mucous membrane involvement. At age 7 years, the cutaneous defect caused by neonatal ACC was nearly healed without major scarring or milia (**Figure**). She is now 10 years old and has no sign of epidermis bullosa. Genetic counseling has not been formally requested, but we have indicated that her disorder is sporadic.

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The American Academy of Dermatology Should Not Endorse Product Sales From Physicians' Offices

Dr Miller¹ has succinctly stated the opinion of many dermatologists who, despite these days of falling incomes secondary to managed care, still consider the sale of nonprescription products unethical and a conflict of interest. Indeed, this may represent the opinion of the silent majority of dermatologists. As expected, not everyone is of this opinion, and in fact there is a very vocal and well-organized group of dermatologists who promote these practices. Each physician should certainly conduct his/her practice as they see fit. But because there is such controversy over these issues and legitimate arguments for and against, it would be unwise for our specialty to officially endorse either view.

There is currently a resolution before the board of directors of the American Academy of Dermatology, generated in the advisory council, that declares it is "ethical" to sell nonprescription items in the office. The group that engineered this resolution cleverly combined it with one that endorses the sale of prescription products, a practice that is traditional in some areas. If this resolution is passed by the board of directors, it would be forwarded to the American Medical Association as our specialty's official position on the sale of nonprescription items. This is supposed to make us more competitive with the plastic surgeons who have already endorsed a similar stand. Two wrongs do not make a right. No vote can make a conflict of interest ethical.

When the resolution was debated in the advisory council, there were many who spoke in its favor. No one spoke against it except Dr A. Bernard Ackerman and myself. And yet, when the vote was taken, the resolution was passed by the slimmest of majorities. The vote was so close that a head count had to be taken. This indicates that while many physicians are against the sale of nonprescription items, they are hesitant to speak their minds probably because of peer pressure. One wonders what would have been the outcome if the vote had been by secret ballot.

It is time for those of us who are against such a resolution to make our opinions known to our colleagues. It would be an insult to the many dermatologists who voted against that resolution and who agree with Drs Miller, Ackerman, and myself for such a resolution to go forward. At the very least the Academy should remain neutral on this matter. That way, those who wish to sell items may do so of their own free will without restraint, and those of us who find such practices abhorrent are not burdened with a very objectionable official policy.

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Effectiveness of Photopheresis in Sézary Syndrome

We read with interest the article by Fraser-Andrews and colleagues¹ and think that analysis of their data requires qualifying comments. Conclusions drawn are based on the failure to demonstrate statistically significant differences between patients with Sézary syndrome (SS) treated with extracorporeal photopheresis (ECP) ($n = 29$) and 2 groups of patients treated without ECP ($n = 15$). However, the statistical power to detect such differences, if present, was small, given the low number of subjects. Thus, their results that relative to the combined non-ECP group, ECP-treated patients had their risk of dying cut nearly in half (hazard ratio, 0.56) and median survival time extended 150% (39 vs 26.5 months) were not statistically significant. Owing to the 4-fold degree of uncertainty in the death hazard ratio, we ask the authors to provide the confidence interval for the median survival time of their ECP-treated group, as the upper limit may be as high as the median survivals of ECP-treated patients reported by us and others (60-100+ months) and thus may not be statistically significantly worse, as implied in their report.

It is essential to emphasize that this report was not a randomized study. Important differences may exist between ECP and non-ECP groups. Data on prognostic factors, eg, white blood cell counts, Sézary cell counts, CD4/CD8 ratio, absolute CD8 counts, staphylococcal infection, or evidence of transformation to high-grade lymphoma, are lacking. The one discussed prognostic indicator, lymph node abnormalities, suggests that the ECP-treated group had worse disease, with 12 (41%) of 29 ECP-treated patients having nodal lymphoma compared with only 4 (27%) of 15 in the non-ECP group. In the ECP-treated group only 2 (7%) of 29 patients showed dermatopathic changes, whereas in the combined non-ECP group, 2 (13%) of 15 patients showed this better prognostic indicator. Because of their importance to survival, we ask whether similar differences existed between the patient groups regarding other critical prognostic indicators.

Additionally, we suggest that ECP therapy was not optimized: (1) Only 3 patients received ECP as primary therapy. Thus, patients with an inability to respond to up to fifth-line treatments were preferentially placed in the ECP group as presumably successful treatments were not abandoned for ECP. (2) Eleven of 29 ECP-treated patients received fewer than 8 treatments. We^{2,3} have shown that if patients have achieved a 50% reduction in skin disease by the eighth course, they are likely to be long-term survivors. By this criterion 38% of the reported patients were not given adequate trials of ECP. If each course is cited as 2 treatments (as indicated in the "Methods" section), only 11 patients met this criterion. Of these, 7 (64%) are still alive. (3) Three ECP-treated patients who died were given concomitant systemic steroids, and others were given prior chemotherapy, which for prolonged periods can substantially suppress the cellular immune response essential to effective ECP therapy.

Fraser-Andrews et al suggest that inclusion in previous studies of patients who were not erythroder-

mic, or did not have identifiable clonal circulating T cells, or both, skewed the results toward apparent benefit of ECP. Data have been presented demonstrating greatly improved survival in ECP-treated erythrodermic patients with cutaneous T-cell lymphoma (CTCL) with circulating clones.³ Southern blot findings were positive in 13 of 14 patients with SS and 1 of 2 patients with erythrodermic mycosis fungoides. The remaining patient with SS had 80% of CD4⁺ cells lacking CD7 expression and a positive Sézary cell preparation finding (15%-89%), suggesting a false-negative finding on the Southern blot. It should also be noted that although suggested in the report from Fraser-Andrews et al, the presence of a circulating clone to diagnose SS is not universally accepted.

In summary, we suggest that the failure of Fraser-Andrews and coworkers to demonstrate a significantly improved survival rate for patients with SS treated by ECP derives from inadequate statistical power and treatment regimens that diminish the likelihood of successful ECP therapy. We also question whether treatment groups were balanced for important prognostic indicators. We agree that a randomized trial would be desirable. We disagree that the "control" groups used in their study provide any advantage over other historical controls used by previous groups that suggest efficacy of ECP. Indeed, the results presented for the non-ECP groups tend to support the notion of 30-month median survival for patients with SS not treated with ECP.

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In reply

We are delighted that so many different groups from North America and Europe agree with our conclusions that a randomized trial would be desirable to assess the efficacy of photopheresis in CTCL.¹ Unfortunately, our recent efforts to establish an international trial have been unsuccessful. Our intention was to report our experience of photopheresis in a large series of patients with SS in which the diagnosis has been supported by molecular analysis of T-cell receptor genes. We have also compared the response data and median survival figures in this group with those results in patients for whom photopheresis was not available.

Although the Cox regression analysis suggests no significant difference in median survival time between those patients treated with ECP and those without, we accept that these results are based on small numbers of patients, which is precisely why we have suggested a randomized trial. However, our median survival figure for patients treated with ECP is 39 months, which is still considerably lower than previously published uncontrolled studies. It is also inappropriate to compare the upper limit of the confidence interval of the ECP-treated group with the overall median survival time of patients reported by other groups. Our data are based on one of the largest series of ECP-treated patients with CTCL in whom a specific diagnosis of SS has been established. Some previous reports have included patients with different stages of mycosis fungoides, which inevitably could affect survival figures.

Our median survival figures were corrected for both age and Sézary cell count. In their letter, Stevens et al suggest that our ECP-treated group had a worse prognosis because 41% had nodal lymphoma compared with only 27% in the non-ECP-treated groups. However, these figures are incorrect because 15 ECP-treated and 9 non-ECP-treated patients did not have lymph node biopsies performed, and it is well established that biopsy specimens of clinically normal peripheral lymph nodes in CTCL can show histologic evidence of lymphoma. Indeed, this would be much more likely in patients with SS as opposed to early-stage mycosis fungoides. The actual relevant figures from our study are that 12 of 14 lymph nodes in ECP-treated patients and 4 of 6 lymph nodes in non-ECP-treated patients showed lymphomatous involvement, which is equivalent to figures of 85% and 67%, respectively. However, these figures are too small to allow a meaningful comparison. Second, polymerase chain reaction-based analysis of all lymph nodes, including the samples showing dermatopathic changes, revealed evidence of a T-cell clone.

It is suggested that our ECP therapy was not optimized. We accept that previous immunosuppressive therapy or chemotherapy could potentially impair the cellular immune response generated by ECP, but most of the literature on photopheresis consists of studies of patients who had a variety of prior therapies, including Edelson's² original study. It was this cohort that provided the data for a median survival time of 60 months in the article subsequently published by Heald et al.³ It is also clear from the literature that some studies report the use of ECP in patients in whom there has been a considerable delay between diagnosis and treatment. In particular, the average time from diagnosis to treatment in the study by Gottlieb et al⁴ was 30 months. This is equivalent to the median survival time of patients with SS⁵ and indicates a strong element of selection bias. It is also argued that 11 of our ECP-treated patients did not have an adequate trial. We have reported all our data on ECP-treated patients regardless of whether they had an adequate preliminary course because this would potentially skew the results toward a good prognostic group. For example, 5 of these 11 patients either developed progressive disease or died after the initiation of ECP, and to exclude these patients would falsely improve our median survival time.

Stevens et al⁶ have published an abstract that is said to demonstrate greatly improved survival in ECP-treated erythrodermic patients with CTCL with proven circulating T-cell clones. However, this abstract reports only response data at 5 months rather than overall median survival time.

In conclusion, we believe that a randomized study assessing the efficacy of photopheresis in CTCL is urgently required. Indeed, such a study would clarify issues raised by previous studies and this correspondence while ultimately providing an acceptable consensus for the clinical use of photopheresis in CTCL.

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VIGNETTES

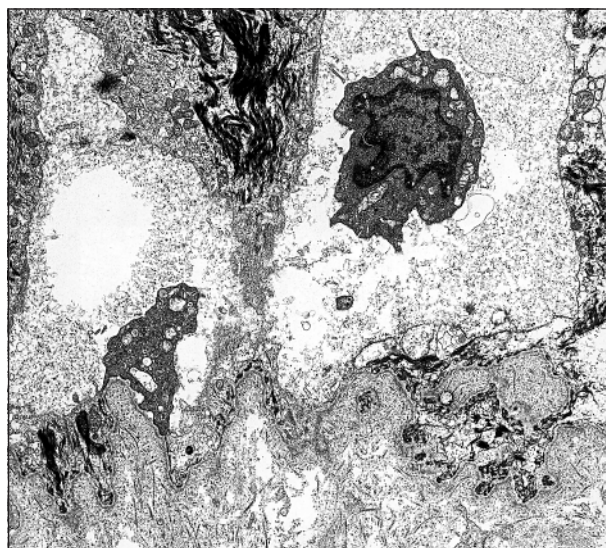
Two Familial Cases of Epidermolysis Bullosa Simplex Successfully Treated With Tetracycline

Little effective therapy is available for epidermolysis bullosa simplex (EBS), despite considerable knowledge of the basic disease defects. Recently, we observed that tetracycline treatment in 2 patients with EBS produced substantial improvement.

Report of Cases. *Case 1.* In 1995, we saw a 36-year-old white man with EBS, Dowling-Meara type, for follow-up examination and treatment of acne. One of us (R.W.P.) had observed him since 1962; the diagnosis was confirmed by electron microscopy (**Figure**). The patient's condition had improved with time, and he was applying only bacitracin zinc and polymyxin B sulfate (Polysporin; Glaxo Wellcome, Research Triangle Park, NC) ointment to erosions and 2.5% hydrocortisone cream to erythematous areas. Examination revealed scattered erosions and multiple bullae on the feet and hands, with many coalescing erosions on the inner thighs, surrounded by reticulated hyperpigmentation. Multiple acne papules were present on the chest and back.

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The patient was given tetracycline, 500 mg orally twice a day, for acne. Within 4 days, he noted that the EBS lesions were significantly improved. Later, he increased the tetracycline dosage to 500 mg orally 3 times a day. At 7 months' follow-up a single linear crusted lesion was noted on the left inner thigh. Three small healing blisters were present on the feet; none were present on the hands. Reducing the tetracycline dosage to 500



Electron micrograph shows the basal layer cytolysis characteristic of epidermolysis bullosa simplex (original magnification $\times 8000$).

mg orally twice a day resulted in multiple recurrent blisters and papules on the hands and feet 1 week later. One week after resuming the use of tetracycline, 500 mg orally 3 times a day, marked improvement was noted, with decreased formation of blisters and decreased skin fragility. A second dosage change to tetracycline, 500 mg orally twice a day, in 1997 produced a similar disease exacerbation. With much improved quality of life, the patient can now exercise regularly and walk long distances without disabling blister formation.

Case 2. A 64-year-old repairman, the father of the patient, had been hospitalized during much of his childhood for a blistering disorder diagnosed elsewhere as EBS. Although the disease had improved gradually, he had constant blisters on his hands and occasional blisters on his feet. Examination revealed multiple blisters on the fingers of both hands. Treatment with tetracycline, 500 mg orally twice a day, produced significant improvement in a few days. On examination 2 months later, he reported decreased skin fragility and noted more rapid blister resolution. No blisters were present on the hands. He refused to reduce the dosage and reported only rare blisters with continued treatment despite heavy manual work.

Comment. In EBS, mutations present in the genes for K_5 and K_{14} produce disturbances in intermediate filament assembly¹ that are linked to the clinical and histological findings. The antibacterial activity of tetracycline could prevent bullae superinfection, leading to quicker resolution of symptoms. However, suppression of the formation of new bullae was observed in both patients, suggesting that tetracycline use may modify the pathologic changes linked to the keratin abnormalities. Some patients with mild disease show no K_5 or K_{14} gene mutations¹; therefore, other defects in EBS pathogenesis might respond to treatment with tetracycline.

Tetracycline is an anti-inflammatory agent^{2,4} and may prevent tumor necrosis factor α release and secondarily inhibit destructive effects of lipopolysaccharides.⁵ In the treatment of EBS, tetracycline may modulate the enzyme activity that controls matrix degradation and thereby reduce bullae formation.

We hope that this report will stimulate further evaluation of tetracycline administration in other patients with EBS and generate new investigations into the pathogenesis and mechanisms of treatment effects in this disease.

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Multivariate Analysis in Alopecia Areata: Risk Factors and Validity of Clinical Forms

In 1965, Ikeda¹ proposed the following clinical classifications of alopecia areata (AA): "common AA," "atopic," "prehypertensive," and "mixed" or "combined" types. In 1995, Colombe and colleagues² defined 2 clinical-evolutionary types of AA: long-standing patchy AA and long-standing alopecia totalis and alopecia universalis, by genetic studies.

We designed a transversal and descriptive-associative study to define (1) the general profile of patients with AA, (2) the influence of sex, familial, and personal backgrounds on the disease, (3) the current validity of the classic and up-to-date classifications, studying in depth the stability of atopy as an independent clinical form, (4) the variables or cluster of symptoms that could be used as severe prognostic markers, and (5) the quantified risk of some variables in the development of alopecia totalis or universalis.

To examine these hypotheses, 110 patients with an active episode of AA were included at random in this study, which was carried out at our department of dermatology between 1995 and 1997. A detailed protocol, regarding familial and personal background histories of AA and other dermatoses, clinical features, evolutionary aspects, and biochemical and immunological studies, was recorded for each patient.

Sociodemographic profile showed a male-female ratio of 1.1:1. Family members of patients had AA in 22.8% of cases and vitiligo in 12.9% of cases. Personal psychopathological backgrounds were found in 76.5% of patients and 22.5% had atopy. Alopecia areata outbreaks were attributable to emotional stress in 52.1% of cases. The onset of alopecia occurred in 47.9% of the patients before 15 years of age, 25% had AA for more than 10 years, 58.8% had an isolated lesion, and 29.4% had alopecia totalis or universalis. Nail changes were found in 29.4%, as pitting and trachyonychia. Antithyroglobulin and antimicrosomal antibody results were only positive in 2.4% and 7.1% of cases, respectively. The main CD4-CD8 ratio was 1.76, although 25% of patients had a ratio over 2.00.

Using univariate associative statistics, vitiligo family histories were related with a more extensive spread of alopecia ($P = .008$) and AA backgrounds with nail changes ($P = .03$). Risk factors for developing severe forms of alopecia were early onset ($P < .001$) and nail changes ($P < .001$) (**Table**). Many patients with disease onset in early childhood had family members with AA ($P = .03$). Atopic patients did not show any significant difference in any considered variables. Two "dimensions" were determined by correspondence factorial analysis: the clinical form-nail changes as cluster variables and stress as a trigger factor of the outbreaks. The

Univariate Study of the Spread of Alopecic Scalp in 110 Patients and Its Association With Other Variables*

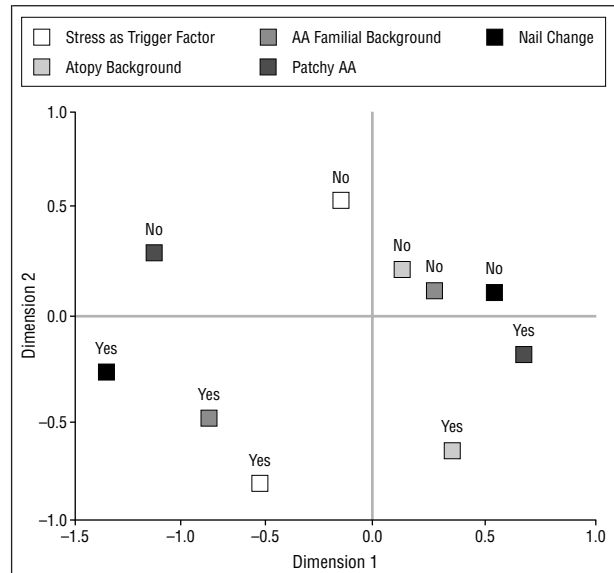
	Mean (SD)	Test	P
Sex			
Male	2.38 (1.34)	ANOVA	.50
Female	2.20 (1.21)		
Atopic background			
Yes	2.44 (1.37)	ANOVA	.57
No	2.24 (1.25)		
Vitiligo background			
Yes	2.33 (1.52)	ANOVA	.94
No	2.28 (1.27)		
Psychopathological background			
Yes	2.40 (1.29)	ANOVA	.10
No	1.92 (1.17)		
Atopic familial background			
Yes	2.32 (1.33)	ANOVA	.86
No	2.28 (1.25)		
AA familial background			
Yes	2.65 (1.30)	ANOVA	.12
No	2.19 (1.25)		
Vitiligo familial background			
Yes	3.15 (1.21)	ANOVA	.008†
No	2.17 (1.24)		
Infectious trigger			
Yes	2.31 (1.30)	ANOVA	.82
No	2.24 (1.25)		
Stress as trigger			
Yes	2.04 (1.19)	ANOVA	.15
No	2.40 (1.28)		
Age of onset	...	Kruskal-Wallis	<.001†
Nail changes			
Yes	3.10 (1.18)	ANOVA	<.001†
No	1.94 (1.16)		

*ANOVA indicates analysis of variance; AA, alopecia areata; ellipses, not applicable. Alopecic spread depends on vitiligo family backgrounds, age of onset, and nail changes. Alopecia spread is rated as follows: 1, 0% to 25% of the scalp; 2, 26% to 50%; 3, 51% to 75%; and 4, 76% to 100%.

†Data of significant difference.

other subgroup of closely high-related variables—patchy form, no nail changes, nonatopy, no family history, and stress as a trigger factor—was called *benign syndrome* (**Figure**). The most determining variables of the totalis or universalis forms were, again, age of onset (9.51 times less risk for every 10 years of life) and nail changes (8.44 times higher for the patient with nail disease), by forward logistic regression study.

The general profile in our study is essentially in agreement with other investigations,³⁻⁵ although there are logical differences in relation to the access to the specialty clinics in different countries. Clinical aspects and course and prognostic factors did not seem to be influenced by sex. Some backgrounds were related to certain clinical and course features, as in the association of vitiligo family history with extensive alopecia and AA family history with nail changes. These data support the theory that there is a genetic link among the families with AA, which includes other dermatologic or autoimmune diseases such as vitiligo.³ Other prognostic markers for extensive or totalis and universalis forms repeatedly were nail changes and early onset by univariate and multivariate analysis and logis-



Quantification of the categories of alopecia areata (AA). Dimensions 1 and 2 were determined by correspondence factorial analysis.

tic regression study. These results were similar to those obtained by Colombe and colleagues.²

According to our data, the “heterogeneous AA syndrome” is characterized by the 2 clinic-genetic subgroups of Colombe and coworkers² (in accordance with the “benign subtype” and the “bad prognostic subtype” disclosed by our correspondence factorial analysis) rather than by the 4 classic clinical forms of Ikeda. Atopic patients were not different in background, clinical course, and analytic characteristics compared with those not having atopy. These data question the validity of atopy as an independent clinical subtype and, consequently, the traditional classification of Ikeda.¹ This result is shared with Sharma.⁴ Multivariate statistical techniques showed, as characteristics of the “bad prognostic subtype,” the presence of the disease in the family history, nail changes, and early onset of the alopecia. According to our logistic regression study, the risk of the evolution to alopecia totalis or universalis depends mainly on the age of onset and the nail changes.

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High Prevalence of Cutaneous Reactions to Interferon Alfa Plus Ribavirin Combination Therapy in Patients With Chronic Hepatitis C Virus

Interferon alfa plus ribavirin combination therapy for patients with chronic hepatitis C virus (HCV) may be a better treatment option than either drug alone given its potential benefit and reduced incremental toxicity profile.¹ The aim of this study is to describe clinical and histological features of cutaneous reactions to interferon alfa plus ribavirin combination therapy in patients with HCV.

Patients and Methods. Included were 33 patients with HCV who received interferon alfa plus ribavirin combined therapy. The diagnosis of chronic HCV was based on elevated aminotransferase levels, detection of serum HCV-RNA by polymerase chain reaction, and liver histological findings.

Twenty-seven patients had been previously treated with interferon alfa monotherapy, and 6 had had no treatment. The 33 patients were treated with 3 mU of interferon alfa-2b subcutaneously 3 times a week combined with 1000 to 1200 mg of ribavirin daily for 24 weeks.

As a control group, we included 35 age-matched patients with HCV treated with 3 mU of interferon alfa alone, given subcutaneously 3 times a week for 6 to 12 months under the same baseline conditions. None of the patients in the control group was included in the combination therapy group.

The skin and mucous membranes were normal before treatment in all of the patients in both groups. After starting therapy, the patients were evaluated by clinical and laboratory assessment once every 2 weeks until week 8, and every 4 weeks thereafter during the study protocol.

Written informed consent was obtained from all patients. Protocol was approved by the ethical committee in accordance with the 1975 Declaration of Helsinki.

Results. Cutaneous adverse reactions, often of a lichenoid type, were more frequently observed in patients receiving the combination therapy (11/33 [33.4%]) than in patients receiving interferon alone (2/35 [5.7%]) ($P = .001$). One of the patients receiving the combination therapy developed lichen planus during follow-up, 4 months after discontinuing the treatment. In 6 of 11 patients, all cutaneous adverse effects were fully reversed during the course of the therapy. One patient had to temporarily discontinue treatment because of cutaneous adverse effects. The clinical and histological features of the skin lesions are described in the **Table**. In the control group, 2 patients had clinical features of lichenoid eruption.

Comment. Preliminary studies have suggested that treatment with ribavirin in combination with interferon alfa improves the therapeutic response in patients with HCV.¹ While the exact mechanism of action of ribavirin remains to be investigated, the drug is well tolerated.²⁻³ Recently, a report noted severe local cutaneous necrosis during treatment of HCV with interferon alfa and ribavirin.⁴ Nevertheless, adverse skin reactions with the combination therapy are reported infrequently. We hypothesize that some synergistic effect between interferon and ribavirin may exist, since during the combination therapy an increase in cutaneous toxic effects occurred vs patients receiving interferon alone ($P = .001$). Close clinical observation of patients treated with this combination therapy is recommended.

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Cutaneous Lesions and Histological Findings in 33 Patients Treated With Interferon Alfa Plus Ribavirin Combination Therapy*

Patient No./ Sex/Age, y	Skin Lesion	Histological Diagnosis	Interval Before Developing Skin Lesions, mo
1/M/30	Eczema (arms, legs)	Subacute psoriasiform dermatitis	4
2/M/39	Rash (arms, legs, back)	ND	2
3/M/36	Eczema (arms, legs)	Eczema psoriasiform	1.5
4/M/32	Malar erythema	ND	4
5/M/30	Malar erythema	ND	1
6/F/53	Lichenoid eruption (arms, legs, back)	ND	1
7/M/37	Rash (legs)	ND	2
8/F/55	Lichenoid eruption (arms, legs, back)	Lymphocytic dermatitis nonspecific	3
9/M/33	Lichenoid eruption (arms, legs, back)	Lymphocytic dermatitis nonspecific	1
10/M/33	Lichen planus (hands, legs, mouth, feet)	Lichen planus	9
11/M/34	Eczema (legs)	Eczema	1.5

*M indicates male patient; F, female patient; and ND, not done.

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Hepatitis C Virus Infection in Cutaneous Polyarteritis Nodosa: A Retrospective Study of 16 Cases

The etiology of cutaneous polyarteritis nodosa (PAN), a skin-limited vasculitis, is unknown.¹ Hepatitis B viral infection is clearly associated with systemic PAN, but not with cutaneous PAN,² suggesting different etiopathological mechanisms for these diseases. Recently a role for hepatitis C virus (HCV) in PAN has been debated.³⁻⁶ The aim of this study is to evaluate the prevalence of HCV infection in a cohort of patients with cutaneous PAN.

Subjects and Methods. All cases of cutaneous PAN seen between 1993 and 1997 in 3 hospital departments (16 medical records) were retrospectively reviewed. The final diagnosis was based on 3 criteria: (1) necrotizing vasculitis of medium-sized arterioles in the deep dermis and/or in the hypodermis; (2) benign long-term course; and (3) absence of systemic involvement. Hepatitis C virus serologic tests were performed at the first clinical manifestations. Positivity was assessed either by an enzyme-linked immunosorbent assay second-generation test (Ortho HCV ELISA Test System, second generation; Ortho Diagnostic Systems, Raritan, NJ) confirmed by a 4-antigen immunoblot assay (Chiron RIBA HCV Test System, second generation; Abbott Laboratories, Emeryville, Calif), or by 2 different enzyme-linked immunosorbent assay third generation tests (Asym HCV, version 3.0; Abbott, Les Ulis, France; Monolisa Anti HCV Plus; Sanofi Diagnostic Pasteur, Marne la Coquette, France).

In HCV-positive patients, active viral replication was studied in blood serum samples by reverse transcriptase polymerase chain reaction (Amplicor HCV kit; Roche Diagnostics, Neuilly/Seine, France) as previously described.⁷ In addition, clinical data and biological and immunological tests were collected to compare characteristics of HCV-positive and HCV-negative patients. Statistical tests included χ^2 tests and confidence interval calculation.

Results. Hepatitis C serological findings were positive for HCV in 5 of 16 patients tested. Reverse transcriptase polymerase chain reaction analysis findings were positive for active replication in the 3 patients tested in the HCV-positive group. Hepatitis B surface antigen results were negative in all cases, whereas 3 subjects tested

positive for anti-hepatitis B surface and anti-hepatitis B core antibodies, indicating a former hepatitis B infection. One HCV-positive patient was coinfectd by the human immunodeficiency virus type 1. Comparison between HCV-positive and HCV-negative subjects showed that HCV-positive patients had (1) a less severe disease than HCV-negative patients (segmentary edema, 0 of 5 vs 8 of 11 [$P < .01$]; pain in lower limbs, 6 of 11 vs 1 of 5 [$P = .19$]) and (2) a greater incidence of type 3 cryoglobulinemia (3 of 5 vs 0 of 10 [$P = .006$]) and hypocomplementemia (2 of 5 vs 1 of 11 [$P = .14$]). Antiphospholipid antibodies were detected in 5 patients, but no significant difference was observed between HCV-positive and HCV-negative patients.

Comment. Our data show a high frequency of HCV infection in patients with cutaneous PAN (5 of 16 [31.2%] cases) compared with the European prevalence (0.3%-0.6%)⁸ and with a group of patients observed for systemic vasculitis (60 patients with lupus erythematosus and 13 with Wegener granulomatosis) during the same period in one of our departments (1 case of 73 [1.6%]).⁹ In all 5 patients, HCV contamination had preceded symptoms of cutaneous PAN. Carson et al⁵ noticed that PAN related to HCV was likely to have a cutaneous involvement, a hypocomplementemia, and a more benign course. Furthermore, in a retrospective study of 408 patients infected with HCV, a cutaneous PAN was present in some cases.⁶ In addition, systemic PAN is rarely associated with HCV.⁴

In our study, hepatitis B surface antigen was not associated with cutaneous PAN, which is in accordance with previous publications.² A pathogenic role of human immunodeficiency virus could be discussed in 1 patient, but human immunodeficiency virus does not usually associate with PAN. Three HCV-positive patients had positive test findings for mixed cryoglobulinemia, and there-

Comparison of Clinical Characteristics and Laboratory Test Results of HCV-Positive and HCV-Negative Patients With Polyarteritis Nodosa*

Characteristic	HCV-Positive Patients	HCV-Negative Patients
Livedo	4/5 (80)	9/11 (81)
Nodules	4/5 (80)	7/11 (63)
Segmentary edema	0	8/11 (72)
Severe algia	1/5 (20)	6/11 (54)
Sedimentation rate	5/5 Normal (100)	6/11 Slightly high (54)
Hypocomplementemia	2/5 (40)	1/11 (9)
Antinuclear antibodies	5/5 Negative (100)	2/11 Positive (18)†
Antiphospholipid antibodies	2/4 Positive (50)	3/9 Positive (33)
Cryoglobulins	3/5 Positive (60)	9/9 Negative (100)
HBs antigens	5/5 Negative (100)	11/11 Negative (100)
Anti-HBs antibodies	1/5 Positive (20)	2/11 Positive (18)
HCV polymerase chain reaction	3/3 Positive (100)	Not tested
Human immunodeficiency virus	1/5 Positive (20)	11/11 Negative (100)

*HCV indicates hepatitis C virus; HBs, hepatitis B surface. Data are given as number of patients with the indicated result/number of patients tested (percentage).

†A titer higher than 1/100 is considered positive.

fore, some cutaneous PAN could be a manifestation of HCV-positive associated mixed cryoglobulinemia. Another mechanism could be complement activation via immune complexes containing viral antigens, as suggested by the presence of hypocomplementemia in 2 of 5 HCV-positive patients (**Table**).

In conclusion, whereas systemic PAN is often associated with hepatitis B viral infection, cutaneous PAN may be sometimes related to HCV. Only a small number of patients were observed in our study, however. To confirm this association, studies with a greater number of patients with this uncommon condition are warranted, as well as the detection of viral RNA in cutaneous lesions.

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Individual Variations in Allergic Contact Dermatitis From Urushiol

Clinical observations on the time course of allergic contact dermatitis from urushiol have been made by early investigators.¹⁻³ The onset of the eruption occurs most often within 24 to 48 hours after exposure to the antigen, and rarely as early as 5 to 6 hours or as late as 8 to 15 days. The duration of the reaction is its most variable feature, lasting from days to weeks. Untreated, the eruption can last 3 to 6 weeks.⁴ These historical observations have not distinguished clearly between previously sensitized subjects and first-time responders. The purpose of this study was to extend these observations by documenting individual variations in the course of experimentally induced allergic contact dermatitis from urushiol in previously sensitized adults.

Patients and Methods. After approval from the institutional review board, 40 male and female subjects aged 26 to 57 years (mean age, 42 years) with a documented history of allergic contact dermatitis to poison ivy or poison oak were entered into the study after informed consent was obtained. None of the subjects was immunosuppressed. They were prohibited from applying a topical steroid or other medication to the test site.

Ten microliters of urushiol extract (1:100 in ethanol; Miles Inc, Spokane, Wash [no longer commercially available]) was placed on a filter paper disk in a Finn chamber (Epitest Ltd Oy, Tuusula, Finland) and allowed to dry for 5 to 10 minutes.⁵ A patch was applied to the forearm of each subject and secured with 2-in Scanpor tape (Norgesplaster A/S, Aksjeselskap, Finland). After 4 hours, the patch was removed and the site was washed with liquid detergent and water. The site was assessed 4 hours after antigen application and again on days 1, 2, 4, 7, 9, 14, and 21.

The severity of the reactions were graded according to a scoring scale ranging from 0 (no reaction) to 7+ (erythema, edema, vesiculation, and ulcerative breakdown). For each subject, the times to exhibit the onset, peak, and resolution of the reaction were noted. Resolution was defined as no visible or palpable reaction remaining. The intensity of the reactions was also noted. Statistical comparisons were performed using a correlation coefficient with the Fisher r to z test. P values were given significance at a level of .05.

Results. The onset of the reactions ranged from 4 hours to 4 days (mean onset, 1.0 day). Four subjects experienced onset by 4 hours and 29 subjects by 24 hours after patch placement. Peak reactions occurred from 1 to 14 days (mean, 7.0 days) later. Fourteen subjects (35%) had the peak reaction at 9 days or later. The earliest resolution of reactions occurred at 14 days. Twenty-four subjects (60%) had resolution by day 21. Of the 16 subjects still exhibiting a reaction at 21 days, 14 had macular erythema, 1 had a 2+ reaction, and 1 had a 3+. The latter subject had a peak reaction of 6+ on day 7, which faded to 1+ by day 14. On day 18, she experienced a flare at the patch site, which became 3+ by day 21.

The maximum severity of the reactions ranged from 2+ to 7+. Twenty subjects (50%) had a maximum severity of 6+ or 7+. There was a positive correlation between the maximum severity of the reactions and the intensity during the first 96 hours ($P = .003$). Maximum severity also correlated with the duration of the reactions ($P < .001$), with severe reactions taking longer to resolve. Maximum severity did not correlate with the times of onset or peak of the reactions. There was no correlation between age of the subjects and onset, peak, duration, or severity of the responses.

Comment. This study documents the range of individual variations in allergic contact dermatitis from urushiol in previously sensitized adults. The variations in reaction time and severity most likely represent differences in underlying immune responses between individuals. Considering the complexity involved in the pathogenesis of allergic contact dermatitis, it is not surprising to see variations in individual clinical responses.

Lejman et al⁶ found that older subjects have delayed onset, diminished peak, and prolonged duration of allergic contact dermatitis to urushiol. We did not find correlations between age and any of the parameters in our study, where the maximum age was 57 years. The

study by Lejman et al compared subjects aged 18 to 25 years with subjects aged 65 to 84 years. Perhaps modifications of the clinical response in allergic contact dermatitis with age begin after the sixth decade.

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Correction

Error in Byline. In the vignette titled "Two Familial Cases of Epidermolysis Bullosa Simplex Successfully Treated With Tetracycline," published in the August issue of the ARCHIVES (1999; 135:997-998), Carla Retief, MD, should have been listed as the senior author.