Dermatology Research Within the Department of Defense

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Dermatologists in the US Department of Defense have made numerous research contributions over the past several decades. This article focuses on research performed during the past few years. Space does not permit a complete discussion of all research activities of the numerous Department of Defense investigators, and this review concentrates on the work of a few physicians who have made an impact in 4 areas of dermatologic research.

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Laser Research

An active duty Navy dermatologist serving at the Naval Medical Center in San Diego, CAPT E. Victor Ross, MC, USN, is an authority and pioneer in laser medicine and its applications for the treatment of skin disease.

Pseudofolliculitis barbae (PFB) is a malady of special importance to the military community because active duty service members are expected to be closely shaven. Ross and colleagues[1,2] have studied the use of a long-pulsed Nd:YAG laser in the treatment of dark-skinned patients with PFB. In the first phase of the study, the investigators used 3 light doses of the Nd:YAG laser to treat an area on the thighs of their subjects. The treatment resulted in an approximately 40% hair reduction after 90 days. In the second phase of the study, the beard area in patients with PFB was treated, with a 7-fold reduction in lesion counts in the treatment sites as compared with the control sites (Figure 1). Ross and colleagues demonstrated that the Nd:YAG laser was a safe and effective option for reducing hair and subsequent papule formation in patients with PFB.[1,2] This modality is now widely used at military medical facilities.

Ross and colleagues[3] also recently explored the use of lasers in the treatment of acne vulgaris. Using a rabbit ear model, they treated test areas with a 1450-nm laser with cryogen spray cooling. This treatment modality produced short-term thermal alteration of sebaceous glands with epidermal preservation. The investigators then demonstrated the same phenomenon using ex vivo human skin specimens. The method was subsequently tested on acne lesions on the backs of patients, achieving a statistically significant reduction in lesion count on the treated side as compared with the normal side. In this study, side effects were minimal and transient.[3]

Using a live pig model, Ross and colleagues[4] compared the effects of the CO_2 laser, Er:YAG laser, dermabrasion, and dermatome. In this study, the CO_2 laser resurfacing produced short- and long-term wound contraction that was greater than that induced by purely ablative methods, even for the same total depth of injury. The Er:YAG laser, however, produced wound contraction profiles similar to those seen with mechanical wounding. The researchers concluded that the initial collagen contraction and thermal damage caused by the CO_2 laser modulated wound healing.[4]

The CO_2 laser has often been described as an aggressive resurfacing tool, whereas the Er:YAG laser has had a reputation as a tool for superficial resurfacing. To determine if a CO_2 laser could be used for "gentler" resurfacing, Ross and colleagues[5] performed a side-by-side comparison of the CO_2 and Er:YAG

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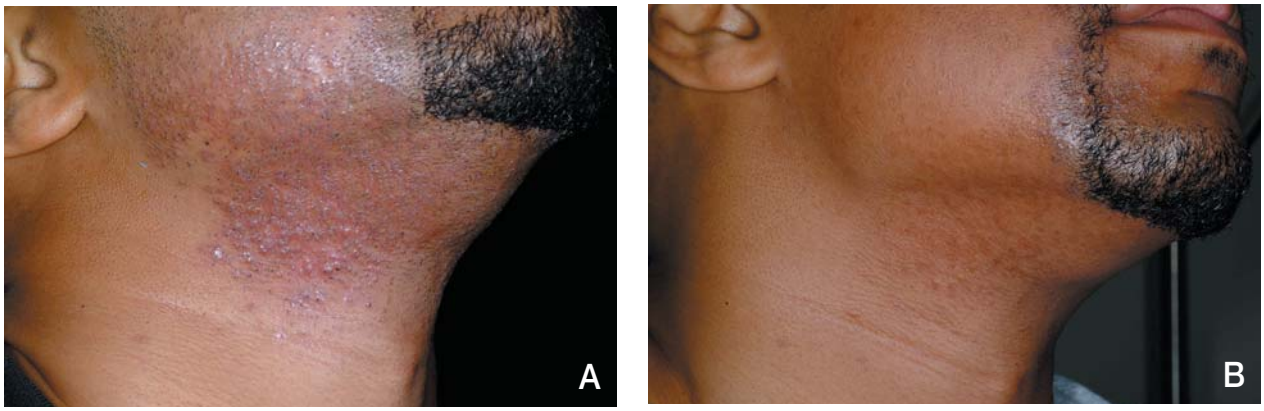

Figure 1. Patient with pseudofolliculitis barbae before (A) and after (B) treatment with the long-pulsed Nd:YAG laser.

lasers, applying the treatment to the periorbital and the perioral regions of their subjects. One side was treated with a pulsed CO_2 laser and the other side with an Er:YAG laser. Biopsies were obtained before treatment, immediately after treatment, and 3 or 6 months after treatment to evaluate the acute level of injury and subsequent degree of fibroplasia. The investigators found no statistically significant differences between the lasers with respect to hyperpigmentation and wrinkle reduction. They concluded that when CO_2 and Er:YAG laser parameters are set to create equivalent immediate postoperative histologic results, healing and cosmetic improvement also were equivalent. Therefore, a pulsed CO_2 laser can be used with one pass to mimic a moderately aggressive Er:YAG laser treatment.[5]

Ross and colleagues are among the pioneers of so-called nonablative skin remodeling with the laser. In one study, they attempted to achieve subsurface skin renewal by using a 1450-nm laser in combination with dynamic cooling.[6] With this modality, thermal damage was largely confined to the dermal zone where most solar elastosis resides. Results of the treatment showed improvement in wrinkle severity on the treated side compared with the control side.

Basic Science Bench Research

The Department of Dermatology at the Uniformed Services University has been performing bench research for several decades (Figure 2). John Stanley, MD (now Chairman of the Department of Dermatology at the University of Pennsylvania), and Kim Yancey, MD (now Chairman of the Department of Dermatology at the Medical College of Wisconsin), began much of their work on blistering disorders while they were at the Uniformed Services University.

In 1999, the Sulzberger Laboratory for Dermatologic Research was established at the Uniformed Services University, with Thomas Darling, MD, PhD, as its director. One of the long-term objectives of the Sulzberger Laboratory is to elucidate the genetic and molecular basis of cutaneous tumors in patients with inherited tumor syndromes. Darling's current studies focus on tuberous sclerosis complex (TSC) and multiple endocrine neoplasia type 1 (MEN1).

Patients with TSC possess inactivating mutations in the *TSC1* or *TSC2* genes that predispose to the development of skin and internal tumors. Although it had been shown that loss of the second normal allele results in the formation of kidney tumors in TSC patients, it was not known whether "2 hits" also were involved in the formation of skin tumors. To overcome problems created by the cellular heterogeneity of these hamartomatous tumors, Darling and colleagues used fluorescence in situ hybridization, a technique that allows inspection of individual nuclei for a second hit. The investigators demonstrated that TSC angiofibromas, periungual fibromas, and shagreen patches showed allelic deletion of the *TSC2* gene, indicating the presence of neoplastic cells in these tumors.[7] By culturing TSC skin tumors, Darling and coworkers were able to test for abnormalities related to loss of function of the *TSC2* gene. Cultured cells showed hyperphosphorylation (activation) of specific proteins involved in stimulating cell growth.[8] Rapamycin, a drug currently being tested in clinical trials for the treatment of TSC kidney tumors, inhibited this hyperphosphorylation, suggesting potential new medical approaches for treating TSC skin tumors.

Darling and colleagues at the National Institutes of Health found that skin tumors similar to those seen in TSC patients, including angiofibromas and collagenomas, developed in patients with MEN1.[9] These tumors showed allelic deletion of the *MEN1* gene[10] but not of the *TSC1* or *TSC2* genes (Darling

and Wang, oral communication, April 2004). To identify the location of the neoplastic cells, clusters of cells were microdissected, and the DNA was tested for loss of heterozygosity at the MEN1 locus. The genetically altered cells were located in perivascular clusters in angiofibromas[11] and in perifollicular stromal cells in collagenomas.[12] Further studies are underway to determine how these small clusters of cells are able to induce abnormal proliferations of surrounding cells.

Darling was also part of a group studying the clinical manifestations of the Birt-Hogg-Dubé syndrome.[13] The investigators were the first to report the association of the syndrome with kidney neoplasms. This finding is of great practical relevance to patients with the syndrome and to the physicians caring for them.

Figure 2. The Uniformed Services University, Bethesda, Maryland.

Dermatopathology

My colleagues and I recently conducted studies that have answered some very basic questions about the pathology of hair disease. One might think that information as fundamental as normal hair density would have been established long ago. In fact, this body of knowledge is incomplete, and most of it pertains to whites. In a retrospective study evaluating normal hair density in African Americans,[14] we found that average hair density is significantly lower in this population than in whites. Because the evaluation of hair disease hinges on accurate knowledge of "normality," these data will have a major impact on the interpretation of scalp biopsy specimens obtained from both African Americans and whites.

Knowledge of the causes and treatments of the various forms of scarring alopecia remains in its infancy. Some of our current work aims to elucidate the most common form of scarring alopecia in the African American population. Central centrifugal scarring alopecia (CCSA) is the current designation for this condition, replacing older terms such as hot comb alopecia and follicular degeneration syndrome. Findings of 2 retrospective studies evaluating the clinical and histologic features of central centrifugal scarring alopecia in men and women have greatly advanced our knowledge of the condition.[15,16] In all patients, the disease begins on the center of the crown or vertex, expanding over many years in a centrifugal fashion (Figure 3). The degree of inflammation varies considerably between persons. Premature desquamation of the inner root sheath (Figure 4) has been found to be a marker for very early disease and may prove to be important in the pathogenesis of the condition. Other histologic features are also characteristic of CCSA (Figure 5). Because treatment of CCSA is usually effective, recognition of the clinical and histologic features

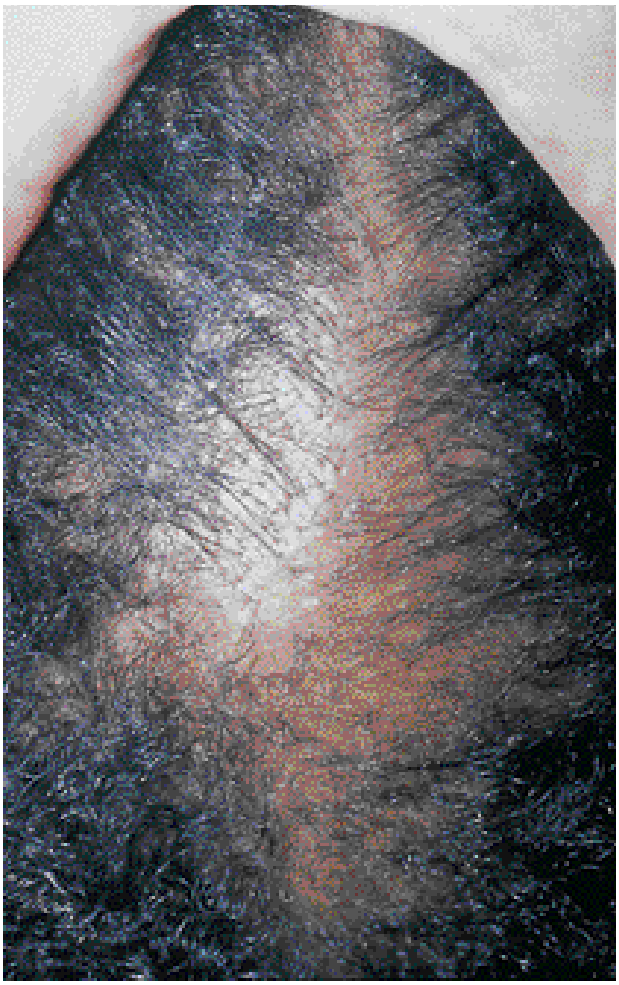

Figure 3. Typical example of central centrifugal scarring alopecia in a woman with slowly progressive disease. Clinically, this condition can be confused with androgenic alopecia.

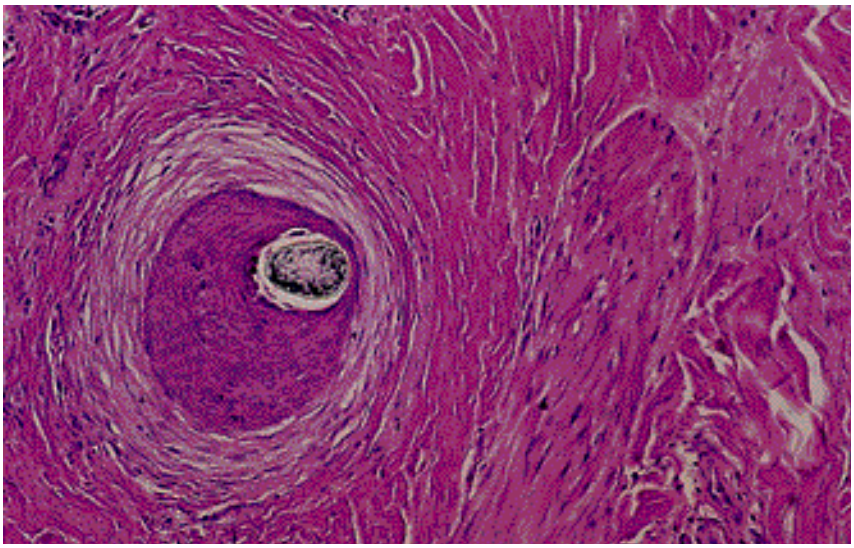

Figure 4. Biopsy specimen from a patient with central centrifugal scarring alopecia showing a follicle demonstrating premature desquamation of the inner root sheath (H&E, original magnification ×200).

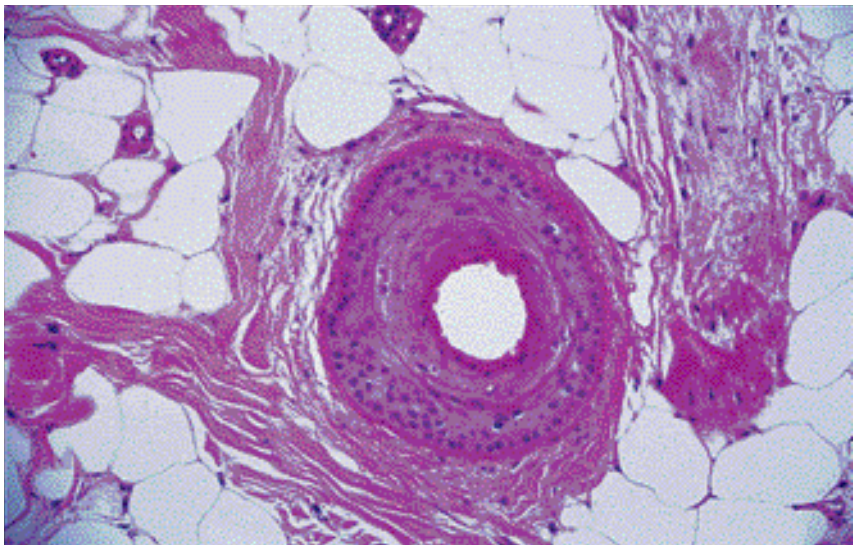

Figure 5. Biopsy specimen from a patient with central centrifugal scarring alopecia showing a follicle with eccentric epithelial atrophy and perifollicular lamellar ("onion skin") fibroplasia (H&E, original magnification ×200).

allows for early intervention and the prevention of progressive hair loss. In the past, some patients with indolent CCSA were diagnosed with pseudopelade, and those with fulminant disease were said to have folliculitis decalvans. Clinical manifestations of these conditions appear to overlap.

Additional work also has helped clarify the histopathologic features of acne keloidalis. Earlier descriptions of the pathologic features of acne keloidalis have focused on the hypertrophic scarring and highly inflammatory disease that is characteristic of late-stage disease. My colleagues and I conducted a prospective study of the histopathologic features of very early disease.[17] The findings of this study suggested that acne keloidalis is a primary form of scarring alopecia and has many histologic features in common with CCSA. The occurrence of acne keloidalis and CCSA in the same person suggests that the conditions may have a related pathogenesis. The same treatments are equally effective for both conditions.

Teledermatology

MAJ Hon Pak, MC, USA, is one of a handful of pioneers studying the use of telemedicine in the care of dermatology patients. Pak's recent review article on teledermatology and teledermatopathology is an excellent overview of the state of the art and the science of this field.[18]

Dr. Pak designed the first store and forward teledermatology consultation system for the US military. Pak and colleagues conducted a sophisticated prospective study measuring the degree of diagnostic concordance between a dermatologic examination of a patient via the teledermatology consultation

system versus a face-to-face examination of the same patient by the same dermatologist.[19,20] This study was performed in the dermatology clinic of a tertiary medical center. More than 400 patients with routine skin problems were evaluated. The investigators found that the diagnostic correlation between teledermatology and in-person consultation was 70% complete agreement, 21% partial agreement, and 9% disagreement.[19] These diagnostic agreement rates are similar to those of previously published studies using interobserver comparisons. However, in the study the diagnostic certainty (confidence) level between the 2 groups was determined to be significantly different, and this difference held true in every category of skin disease ($P \leq .0001$).[20] Unlike some other studies, investigators found that there was a 10% higher rate of recommendation for biopsy by the teledermatologist as opposed to the face-to-face dermatologist. Despite the slight increase in the biopsy rate, the authors concluded that teledermatology is an effective method of delivering dermatologic care in the appropriate setting.

Pak and colleagues concluded that the use of store and forward teledermatology could reduce the number of visits to a dermatologist by 80% and that only 20% of patients require an in-person visit to a dermatologist for further evaluation. Of the 80% seen via teledermatology, 30% required no follow-up, and only 12.5% required an in-person visit to the primary care physician.[21]

Based on his extensive experience with teledermatology, Pak has been able to successfully deploy a teledermatology consultation system within a large and underserved military population covering a very large geographic area. Pak and colleagues are studying both the clinical and financial ramifications of the use of teledermatology on such a large scale.[22]

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