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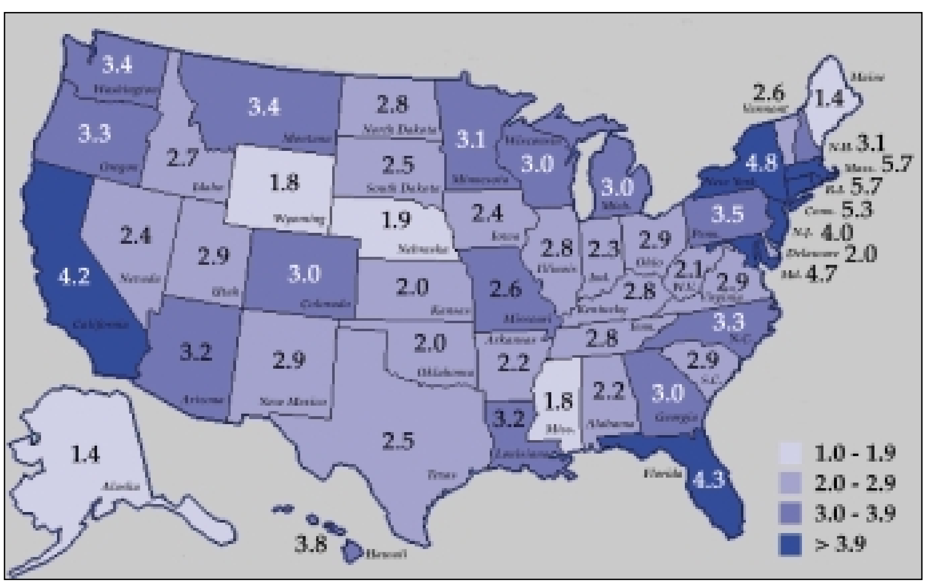
# DERMATOLOGY FOCUS™

*Also In This Issue*



## Dermatology Workforce— Emerging Data Portend Future Changes

Over the past 20 years, many dermatology workforce projections have forecast a disturbing oversupply. This mirrored the more general conviction that there was—or soon would be—a glut of physicians in the medical community, the cumulative result of federal measures that had begun in the early 1960s to increase the physician workforce and close the threatening gap projected for the near future. Financial supports were put in place to encourage physician training, and then restrictions were gradually eased for international medical graduates wanting to train and practice in the U.S. The rapid success in producing many more physicians eventually sparked predictions of oversupply—particularly in the specialties—by the century's end. A counterbalancing plan unveiled in 1994 included recommendations to persuade medical students to choose primary care over a specialty. And some states, such as California, legislated specific reductions in residency graduates across specialties. Various calculations of oversupply and needed reductions were based on generalized models that are now being found seriously flawed.




**Geographic density of dermatologists.** Active nonfederal dermatologists per 100,000 U.S. population by state, 2002. Data sources: AMA Masterfile and U.S. Census (Courtesy of Jack Resneck, Jr.)

*(Continued on page 2)*

## Focus on Research

### Pathophysiology of Acne—The Newest Insights

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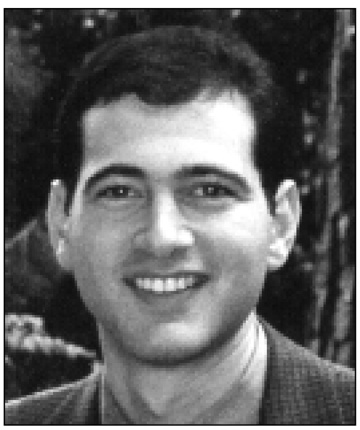
Acne vulgaris—the most common skin disease affecting adolescents—continues into adulthood for many. At least 85% of people in the United States report having suffered from it at some point in their lives, and it affects an estimated 40 to 50 million Americans at any given time. Although it is clear that acne arises from the interplay of four elements—overproduction of sebum by the sebaceous glands; overcolonization of the pilosebaceous unit by *Propionibacterium acnes*, a ubiquitous resident on the skin; hyperkeratinization of the upper follicle; and the release of inflammatory mediators into the skin—the underlying molecular pathol-

*(Continued on page 11)*

Similar concerns surfaced within dermatology as the annual number of graduates from residency programs doubled from 1965 (150 graduates) to 1983 (about 300). Although it has remained stable since then, vigorous arguments and anecdotes have painted this as too many or too few dermatologists. Regulatory agencies were making—or threatening—a reduced cap on residency programs despite only anecdotal evidence.

This is roughly the point at which Jack Resneck, Jr., MD (Department of Dermatology and the Institute for Health Policy Studies at University of California–San Francisco), and Alexa B. Kimball, MD, MPH (Department of Dermatology at Stanford University), began their research—first individually and then in partnership—to clarify and probe critical workforce issues in dermatology. In addition, they both serve on the Workforce Taskforce of the American Academy of Dermatology Association (AADA).

Resneck's interest in politics and policy predated his undergraduate degree in health policy, and he had worked in health policy research before starting medical school at UCSF. When California mandated a "drastic reduction of the number of specialists who were training in the system," he says, "I became involved with these issues locally, and then did a Fellowship in Health Policy Research after my residency." A renewed desire to become involved in health policy research brought Resneck to workforce issues.


Jack Resneck, Jr., MD

Kimball's concern arose during her post-residency Clinical Trials Fellowship at the NIH. Her appointment as the resident–fellow member of the AADA Workforce Taskforce exposed her to the diametrically opposed—and equally unsupported—views on workforce balance that characterized these meetings. "Some members were convinced that we were training way too many residents," she recalls. "Others insisted that we were not training enough. And *all* of their evidence was purely anecdotal. I realized right then and there that *we needed data*!" The experience galvanized her, and she began planning her first survey.

Once Resneck and Kimball met and discovered their common focus, they have been close collaborators ever since, with Resneck adding his policy focus and Kimball her epidemiologic perspective to their shared expertise in conducting and evaluating this kind of research.

## Resneck: Breaking New Ground

Resneck's first article, in October 2001, spelled out the inadequacy of standard parameters for assessment and prediction, identified difficulties in estimating optimal workforce size, and pointed to the reality of a shortage—not a surplus—in dermatology. He cautioned that "in an era when regulatory bodies are making more centralized decisions about residency training, dermatology itself must attempt to estimate and anticipate the future needs for the specialty. Simply allowing others to make decisions about the future size of the workforce based on outdated data risks an oversupply or undersupply, either of which will have detrimental effects on dermatologists and their patients." Most especially, continuing to train too few dermatologists threatens patient access to skin specialists and may affect the quality of care.

In addition to inadequacies built in to previous methods that estimate supply—constructed primarily around a standard head count—Resnick also pointed out that current forecasts were not taking into account such emerging factors as the suspected shift to earlier retirement, the different choices that women—a rapidly increasing presence in the dermatology workforce—make about work hours, or the increasing use of physician assistants. Most glaringly, the standard head count ignores geographic disparities between states. The number of dermatologists per 100,000 population in 1999 ranged from lows of 1.0 in Alaska, 1.3 in Wyoming, and 1.5 in West Virginia to highs of 4.9 in New York, 5.0 in Massachusetts, and 5.3 in Rhode Island. Certain cities—e.g., San Francisco, New York City, and Boston—have much higher ratios. (See map on cover for concentration by state for 2002.) Resneck also discussed flaws used to estimate future demand.

Resneck's revised calculations showed a current supply of dermatologists that averaged 3.3 per 100,000 population, but emphasized that, in reality, demand had already outstripped this. "The mailboxes of recent graduates were flooded with letters from recruiters and practices across the country, and a recent mailing from the AADA had listed 387 practices seeking clinical dermatologists—significantly beyond the 300 annual graduates looking for positions," he says. "Anecdotal evidence was suggesting that even cities with traditional surpluses were actually experiencing shortages. Academic centers and private practices were reporting difficulty in filling available positions, and wait times for dermatology appointments were getting longer." And Resneck pointed out that unacceptably long delays might serve as an effective indicator of workforce inadequacy.

"The challenges facing future workforce research are not trivial," he emphasized. "Existing models to estimate demand are imperfect, future demand is a moving target, and it is unclear how to deal with geographic maldistribution. As a specialty, however," he continued, "dermatology needs to explicitly address these issues with scientifically rigorous investigation. Failure to do so threatens action by outside regulatory bodies using outdated and possibly erroneous data."

Resneck's first joint effort with Kimball would continue this line of exploration.

## Resneck: Reimbursement Level Affects Access

Resneck's next study—published in January 2004—addressed concerns provoked by the 5.4% cut in Medicare physician payments implemented in 2002 coupled with the threat of further cuts. With longer appointment wait times already reflecting a relative shortage of dermatologists, he hypothesized that patients with lowered coverage would become more likely to experience appointment refusals, longer wait times, or both. "There was already clear evidence of poor access to care for patients with Medicaid," Resneck notes. "We wanted to see if this initial reduction of Medicare payment rates had begun to affect access to care."

Having determined that the ability to obtain timely appointments is a key measure of access, they surveyed dermatologists in 12 medium- and large-sized communities across the country to determine wait times for routine new-patient visits (communities representing a variety of geographic regions and health care markets). In early December 2002, dermatologists or their staff received a telephone query about the next available appointment for a hypothetical new patient with a randomly assigned insurance type—Medicaid, Medicare, or fee-for-service private insurance.

The responses to Medicare and to private insurance were generally equivalent. Acceptance of coverage was 85%

and 87%, respectively, with mean wait time 37 days except in “hot spot” communities, where Medicare payments were significantly lower than commercial payments. There, the rejection rate was somewhat greater and wait times a little longer. Access for patients with Medicaid was substantially less. Only 32% of the surveyed offices accepted Medicaid coverage, and when it was accepted, the typical wait for an appointment was 50 days—an increase of 34%. And in communities with atypically low Medicaid payments, this patient group faced even higher rejection rates and longer wait times.

In areas with a low concentration of dermatologists, wait times were generally longer and patients with government payors were somewhat more affected. Conversely, increasing local concentrations were associated with the opposing pattern. An unexplained surprise was the outlier status of Boston—with the highest concentration of dermatologists in this sample, yet exceedingly long wait times, and virtually no difference in wait time between Medicare and Medicaid.

Resneck regards this relationship between reimbursement and access to care as a useful measure for gauging the impact of changing economics, and dermatology reimbursement levels for specific insurance types. “When a system is stretched to its limits and there are no longer enough doctors to see all of the patients needing care, then reimbursement rate influences access. So patients with lower paying insurance are the ‘canary in the coal mine,’” Resnick observes. “And some access limitations in hot spots where Medicare payments are low relative to private insurers suggest that patients in these areas may be the first to experience effects if further Medicare payment cuts are made. The significant access problems for Medicaid beneficiaries may be a harbinger.”

Alexa B. Kimball, MD, MPH

## Kimball: Dermatology—Unique Specialty Workforce Economics

Kimball—in tracing the history of policy changes that created, and then tried to stem, the general oversupply of physicians—notes the irony that “in complex systems such as medicine, by the time a solution is fully in place, the nature of the original problem may have materially shifted.”

After describing the warnings and responses that had achieved a 50% increase in the number of medical schools and doubled the student population from 1960 to 1980, and the continued increase in both residency positions and the proportion of specialists, she pointed out that during the several-decade span in which these planned changes were materializing, unanticipated changes in the structure of medicine—primarily affecting demand or pricing—also occurred. Medicare, created in 1965, by 1990 was determining treatment guidelines for millions. Managed care was another unanticipated juggernaut. Although the first true HMO had appeared in 1972, it was not until acute concerns about cost containment preempted center stage in the early 1990s and opened the door that permitted them to flourish. Today, this is the majority of insured coverage. So by the early 1990s—with the responses to those late 1950s warnings in full flower and the supply of physicians booming—the spiraling costs of an altered economic environment were no longer hospitable to this greatly expanded medical community. The aggressive focus on cost containment turned to Medicare and the HMO, and other mechanisms as well, to reduce or control demand in many cases.

The first projections of a coming physician surplus in most specialty areas had actually appeared in 1980, and were supported by subsequent studies. By the early 1990s—when these projections had become the reality for many medical specialties—the medical community attempted to train more generalists “who could play a central role in managed care organizations.” The ratio improved only partially, and a significant percentage of newly graduating residents have difficulty in finding jobs they want, compensation levels have been flat or declining, and job satisfaction has been low.

Yet Kimball also found the opposite experience for dermatology residents. Rather than citing more positions available than graduates to fill them, and lengthening patient wait times, she approached this with a survey that would become an annual status-taking.

At her first Workforce Taskforce meeting, Kimball knew that “a large survey of the entire dermatology population is a very expensive proposition. But I had just taken the Board review course that most recent graduates sign up for, and I realized that the next session would provide a terrific and imminent survey opportunity—a captive population of recent graduates sitting with pencils in front of them. I could get the kind of information about their experiences that would enable me to start clarifying these issues.”

In 1999, Kimball carried out an anonymous survey with cooperation from the course sponsor and AAD staff. It was accomplished with minimal effort and expense and produced a response rate—from 65% to 80%—that far outstrips the return from mailed surveys.

In 1999, “only 9.8% of recent dermatology graduates experienced difficulty in securing a preferred position, and 6.9% in 2000,” Kimball says. New trainees had received an average of 6 job offers in 1999, and 5 in 2000. And a telephone survey of

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dermatologists in 2002 "found that waiting times for appointments exceeded the criterion cutoff times," she notes, "further evidence suggesting a high demand for dermatologic services."

## The Critical Factors

Kimball first examined four trends that "have both tightened the supply and increased the demand for dermatologists," and thus appear to be responsible for dermatology's preferential position compared to other medical specialties.

*Supply of new dermatologists:* Unlike the continued influx of residents in other specialties, dermatology had already stabilized by the end of the 1970s, before it had reached a saturation point, "most likely because—compared to inpatient specialties with significant in-hospital care—additional positions in dermatology were not viewed as having the same financial benefits," Kimball explains. Yet additional positions would be welcomed, as "the residency match in dermatology remains intensely competitive," she points out, "with high rates of candidates who do not match."

*Managed care and shifting health care systems:* Although managed care substantially reduced visits to specialists across the board, visits to dermatologists eventually began to increase after successful arguments were made—with legislative success in Florida and Georgia—to allow direct access. And in the broader picture, emerging evidence indicating that gatekeeping has become increasingly ineffective has opened up access to dermatologists and other specialists.

*Changing professional demographics:* The increasing percentage of women in the physician workforce is driving changes in workforce patterns, and the specialty percentage of women in dermatology is among the highest (along with obstetrics/gynecology, pediatrics, and rheumatology). Women are now approximately 25% to 30% of all practicing dermatologists, up from 5% 25 years ago, and as they now constitute over 50% of dermatology training program graduates, this figure will continue to climb. Kimball explains that their impact comes from the fact that "women work roughly 4 to 5 hours less per week than their male counterparts, a factor of approximately 10%." Thus their increase from 5% to 25% of practicing dermatologists currently reduces the dermatologist supply by 2% (i.e., [25 – 5] x 10%). With women now at least 50% of each graduating class, the equivalent number of full-time equivalents entering the workforce is decreased by 5%.

*Changing scope of practice:* Many of the increasing number of cosmetic procedures being performed by dermatologists are also done by plastic surgeons, yet the opposite supply patterns within these two specialties have created very different workforce profiles. In 1998, for example, difficulty in finding a desirable position after residency affected 44.30% of plastic surgeons and only 5.40% of dermatologists, while earning a salary equal to or higher than expected characterized 90% of dermatologists but only 52% of plastic surgeons.

Factors that may become additional determinants in the not too distant future include the increased demand for dermatologic services of an aging population, the increasing incidence of skin cancer in the U.S. population, and the rapidly growing use of Physician Assistants (PAs) by dermatologists, each of whom sees an average of 28 patients a day.

Summing up, Kimball cautions that "although the demand for services may continue to grow in this small area of medicine, the difficulties in projecting physician workforce require continued attention as the U.S. health care system continues its rapid evolution."

## Kimball: Gender and Parenting

With this increasingly high proportion of women entering dermatology, Kimball believed it important to identify any impact of gender, marital status, and parenting on work choices. She used the representative results from the 2002 workforce survey. The 191 respondents (109 men, 82 women) represented 54% of that year's entire pool of residency graduates plus 49 fellows. The mean male age was 33 years, almost two-thirds (64%) were married, and roughly one-third (37%) had children. The mean female age was 34 years, three-fourths (75%) were married, and almost one-half (47%) had children.

Although on average, men spent significantly more hours on patient visits per week than women (31 hours vs 26 hours), this difference virtually disappeared when the comparison was limited to men and women who were not parents, regardless of marital status (see Table 1 below). Comparing dermatologists with and without children made this clear. The 46 female parents spent *fewer* hours on average seeing patients than those who were not parents (24 vs 27). In sharp contrast, male parents spent *more* hours per week seeing patients than male dermatologists who were not parents (34 vs 29). Comparing parents, then, male dermatologists saw patients a greater number of hours than their female counterparts (34 hours vs 24 hours).

Highlighting these trends within the parent subgroup, 70% of the women and 11% of the men reported decreased work hours because of child care responsibilities. None of the women and 15% of the men reported an increase in work hours due to child care responsibilities. A multiple linear regression using the combination of gender and parenting to account for the differential in hours of patients seen per week closely approached significance ($P = .07$). (The significance level most likely reflects the small subgroup numbers rather than any inherent weakness in the relationship.)

These contrasting parent–gender patterns might reflect the fact that more of the male parents found themselves the sole wage earner and thus compelled to provide for the increased expenses of a family, while more female parents were financially able to reduce their work hours to remain at home part time with their children. And again, it might indicate that "as is true in many other careers, women are still carrying more of the child-rearing responsibilities," Kimball notes. "The take-home point from this observation," she says, "is that, although women work fewer hours, it is not the substantial difference that some in the specialty have insisted, and it appears to be tied in to the early years of raising a family."

An unexpected outcome of this survey was the observation that women were spending slightly more time than men in practicing medical dermatology (25 hours vs 22 hours).

Kimball described consistent results from a lengthy practice profile survey mailed in 2002 to almost half of the AADA membership. Kimball and Resneck had helped to design the survey. In contrast to recent workforce entrants, this AADA survey covered the entire working population, with 1,425 dermatologists responding (70% men and 30% women, with a mean age of 50 years).

**Table 1. 2002: Number of Respondents and Total Number of Hours Worked* Per Week**

| | Men Hrs – No. | Women Hrs – No. | *P*-Value |
|---|---|---|---|
| All | 40 (75) | 34 (97) | <.01 |
| Parents | 45 (26) | 32 (42) | <.01 |
| Nonparents | 38 (49) | 35 (55) | .42 |
| Married† | 44 (47) | 35 (67) | <.01 |
| Not married | 36 (26) | 35 (26) | .89 |

*Defined as the mean of the sum of hours spent seeing patients/week plus hours spent at other practice-related activities.

†The *P*-value when comparing the average total of hours/week worked by married and unmarried men was .06; the *P*-value when comparing the average total of hours per week worked by married and unmarried women was .88.

Although these women overall were seeing patients for significantly fewer hours per week than the men (28 vs 34), "women dermatologists older than 50 years see patients significantly more hours per week than women 50 years and younger," Kimball says, 31 hours versus 28. But it is unclear at this point," she adds, "whether this reflects getting past the childbearing and child-rearing years, or is attributable to generational differences."

## Resneck and Kimball: Exploring the Shortage

Kimball and Resneck's first collaborative effort was a more comprehensive assessment of the dermatology workforce shortage. Their database came from this 2002 AADA survey plus the combined results from Kimball's three surveys of recent training graduates (1999, 2000, 2002). Their most recent surveys included several surrogate measures of workforce adequacy that Resneck and Kimball had developed, i.e., mean wait time for a new patient, hiring search to expand practice, and use of physician extenders. Responses to questions addressing supply were calculated for the group, and then separately by state to detect any local patterns.

Of the AADA responders, just over half (52%) reported working in suburban areas, with fewer in urban (38%) and rural (10%) locations. Almost half (46%) were in solo practice, while 26% worked in 2- or 3-physician groups and 29% worked in larger group practices. A significant number had gone on for additional residency or fellowship training.

About half (49%) felt that their own area was undersupplied, 20% reported too many dermatologists, and 31% found a good balance. Not a single state contained a majority reporting too high a local supply. A local undersupply, however, was reported by the overwhelming majority in rural areas, in several midwest states (Kansas, Minnesota, Wisconsin), and in five states with small sample size (Maine, Vermont, New Hampshire, South Dakota, Delaware). Wherever undersupply was perceived, "the vast majority—90%—reported a need for more medical or general dermatologists," Kimball and Resneck say. Only 19% saw a need for pediatric dermatologists, and just a few cited the need for specialized surgical or cosmetic dermatologists. "Dermatologists' perception of supply correlated strongly with wait times for new patient appointments," Resneck says.

One-third of the AADA respondents were actively—but unsuccessfully—seeking to hire an additional dermatologist, and 10% were actually trying to fill two or more positions. "The mean duration of these ongoing searches was 16 months at the time of the survey," Resneck and Kimball report. And the mean new patient wait-time was 89% longer among those seeking associates (53 days) compared with those who were not (28 days). "Very large proportions of dermatologists in certain states were seeking associates," they add, including the majority of respondents in the moderate-to-large states of Minnesota, Wisconsin, Virginia, and Arizona. (The lowest percentages of dermatologists seeking associates—ranging from 6% to 19%—were in Missouri, Iowa, Washington state, Mississippi, and Texas.)

One-third of the AADA respondents were easing patient access by using physician extenders. Roughly 25% were using mid-level practitioners such as physician assistants and nurse practitioners, with the remainder including aestheticians and other nursing personnel. The use of physician extenders was particularly high in Florida, Georgia, Iowa, Minnesota, Tennessee, Illinois, and Oregon (from 43% to 49%). Resneck and Kimball note that despite the lack of earlier data, "these figures likely represent a dramatic increase." The Society of Dermatology Physician Assistants, which had 860 members as of June 2004, identified only 6 dermatology physician assistants (PAs) in 1993. The current number of certified PAs in the specialty is estimated at 1,200–1,500, and it is considered to be the fastest growing of all the smaller specialties.

Among the recent dermatology trainees, the vast majority regularly received more than one job offer, and

*(Continued on page 8)*

# Record Giving Highlights DF Annual Meeting

## State of the Foundation

*President Bruce Wintroub, MD, presided over his first Annual Meeting of the Dermatology Foundation in February. This official start of the DF's 40th anniversary year was marked by new records in contributions from dermatologists and corporations. Dr. Wintroub also unveiled plans for the upcoming DF Clinical Symposia* (held this past March 17–21), *inaugurating a new CME opportunity to gain the cutting edge of clinical progress.*

***Career Research Funding Sets Record.*** Since 1964, the year that the Dermatology Foundation came into existence, dermatologists and corporate partners "have built a generous tradition of giving," Dr. Wintroub said. "The result has been $32 million allocated to 1,350 research and career development awards over these four decades." Prior to 1989, these awards consisted of modest single-year fellowships and grants. For over a decade now, the focus has been multiyear awards with an annual stipend that has increased from $40,000 to $55,000. Total funds awarded for research have climbed above $3 million for the first time, providing a record 61 awards. This includes the newest funding category, the Medical Dermatology Career Development Award "created to address severe dermatologic disease and build the knowledge base of medical dermatology," Dr. Wintroub explained.

Amy Locke-Grant, Senior Product Manager at Genentech, Inc.,–a new Corporate Partner–accepts DF Corporate Honor Society Silver Benefactor Award from Jouni J. Uitto, MD, PhD, Chairman, DF Board of Trustees.

***Record Revenues and Members.*** More than $2 million was contributed by individual dermatologists. Corporate support totaled $2.3 million. Two-thirds of all Foundation members participated at the Leaders Society and *Annenberg Circle* levels, which reached a record combined roster of 1,386. Dr. Wintroub applauded the efforts of the 200 physician-volunteers who make the nationwide LS membership campaign such a resounding success. "The Leaders Society has become *the* most successful effort within those few medical specialties in which physicians support their own research and career development programs," he noted. By the Annual Meeting, the *Annenberg Circle* roster numbered 205 contributors who have made this exceptional $25,000 lifetime commitment to support the specialty's progress. In 2003, 66 people joined the *Annenberg Circle,* "a nearly 50% increase in a single year!" Dr. Wintroub enthusiastically announced.

"Our ability to celebrate 40 years of increasing success in building the careers of researchers, educators, and leaders throughout medical and surgical dermatology is the result of broad-based and generous support from both individual dermatologists and the corporate community. And, it is key to our ever-improving ability to offer our patients the best in dermatologic care."

***Burgeoning Corporate Support.*** Dr. Wintroub expressed appreciation for the substantial increase in corporate contributions. These annual contributions are invaluable for enabling funding for a number of important components that include "underwriting education programs and publications for practitioners, and building the careers of the most promising young investigators through the Foundation's Research Awards Program," he pointed out.

"The new *Clinical Symposia* is an excellent example of corporate support, and testimony to their respect for the specialty" Dr. Wintroub added. The 24 companies contributing support for this important new CME meeting are led by Stiefel Laboratories—which provided $100,000 for 2004 and $1 million overall—to fund the keynote Werner K. Stiefel Lectureship that will open the Symposia each year. An additional 10 companies contributed at the $50,000 level of sponsorship: 3M Pharmaceuticals, Allergan Skin Care, Amgen, Inc., Biogen Idec, Centocor, Inc., Connetics Corporation, Fujisawa Healthcare, Inc., Galderma Laboratories, L.P., Genentech, Inc., and OrthoNeutrogena.

## Recognition—Sandra Rahn Benz, DF Executive Director

On behalf of the Dermatology Foundation, Dr. Wintroub presented a special award to DF Executive Director Sandra Rahn Benz to celebrate her 25 exceptional years of commitment and dedication. "She has been instrumental in guiding the DF to its current status," Dr. Wintroub affirmed. "We are deeply grateful for these 25 years, and proud to give you this award."

Sandra Rahn Benz, Executive Director, is given special recognition award by DF President Bruce Wintroub, MD.

Ms. Benz said that "each and every one of you in this organization is very dedicated to the specialty—and that has made my job such a pleasure."

# DF Founder Eugene J. Van Scott, MD

## The Foundation's Role—More Crucial Than Ever

Dr. Eugene J. Van Scott—a founder of the Dermatology Foundation and still active in his chosen specialty—has been honored with the Dermatology Foundation's Distinguished Service Award, reserved for those whose dedicated and insightful leadership and service to the specialty have had a transforming impact. This Award was first given jointly, in 1989, to Thomas B. Fitzpatrick MD, PhD, and Irvin H . Blank, PhD, and in 1998 to Howard V. Dubin, MD. Now 40 years since his instrumental role in founding the DF, Dr. Van Scott reflected on the Foundation's beginnings and its current stature and substance beyond anything its founders ever envisioned, and turned an eye toward the future.

"The Dermatology Foundation actually began the day that Tom Fitzpatrick and Irv Blank came down from Harvard and Mass General to see me at the NCI to discuss Tom's concept for a new organization in dermatology," Dr. Van Scott recalled. "He was convinced that the welfare and future of dermatology depended upon continued good research, and the increasingly stiff competition for NIH funds had come to worry him. He envisioned an organization within dermatology dedicated to supplementing NIH funding by raising research money earmarked specifically for young dermatologists."

**"Without the Dermatology Foundation, dermatology itself would not be in the position of strength that it is today."**

Eugene J. Van Scott, MD

The three agreed that success would require the direct involvement of dermatology's influential leaders, especially "Donald Pillsbury at the University of Pennsylvania, who was the most important person in dermatology at that time," Dr. Scott said. Several years earlier Dr. Pillsbury, along with Kenneth Endicott—then director of the NCI—had secured substantial funding for a number of departments of dermatology throughout the United States—"though he was convinced that the country needed, and could support, only a dozen or so departments, and now there are well over 100!" Dr. Van Scott noted with a smile.

Drs. Fitzpatrick, Blank, and Van Scott successfully recruited some of the specialty's leaders for the new organization, including Donald Pillsbury as the first president, and the Dermatology Foundation formally came into being in 1964. Rounding out this group of 10 founders were Herman Beerman, MD, Robert R. Kierland, MD, Clarence S. Livingood, MD, J. Lowry Miller, MD, Wiley M. Sams, MD, and Marion B. Sulzberger, MD.

Reflecting on the Foundation's initial history, Dr. Van Scott finds that the first 15 to 20 years "were really on the order of a shakedown cruise before it emerged—with voltage and energy—as a significant force in the specialty." That crucial transformation reflected the DF's ultimate success in attracting a wide swath of dermatology's leadership. "Once this leadership grew to include visionary Trustees, imaginative grant application reviewers, and a perceptive continuing education faculty," he explained, "this in turn attracted inventive research-minded young people—who now, in their turn, are becoming the leaders of today."

Now, in addition to providing the research funding that was its original *raison d'être,* the Dermatology Foundation "has itself taken on the role of leadership," Dr. Van Scott points out. "It's akin now to an academy or an academic institution, with a visionary faculty in the form of its enlightened directors and collective membership. The DF provides leadership in looking at medical economics, in fostering research in new scientific paths of dermatologic relevance, and in the specialty's 'introspection.' Without the Dermatology Foundation," he continued, "dermatology itself would not be in the position of strength that it is today."

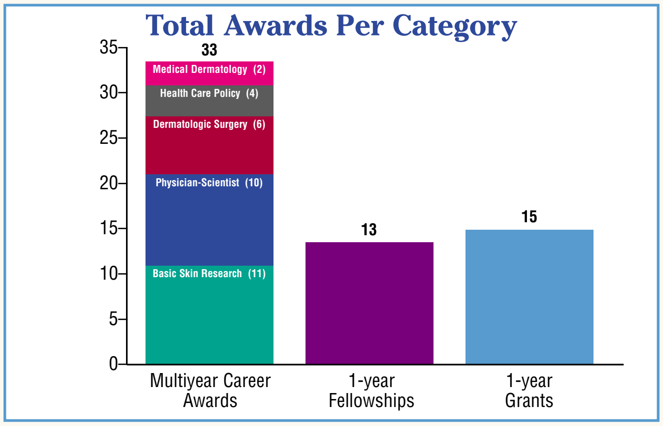
Dr. Van Scott expressed his deep satisfaction with a collateral factor that he feels has enhanced both the Foundation's rise to eminence and the prominence attained by the specialty today. "And that has to do with the importance of the skin itself," he said. "Time has shown that this interface between the organism and its environment is much more important than a simple protective envelope that keeps bad things out and the good things in. The recent awareness that the entire immune system tracks through the skin is now enabling the skin to provide great points of novelty and discovery that relate to the immune system in general."

Dr. Van Scott noted that "the problems of the skin are going to increase in importance in the next decade or so," pointing out that "the DF's mission for the future is to expand its current position of strength, particularly by extending the Career Development Awards program. The physician-researcher is especially important to dermatology now, as well as to medicine in general in the United States, and meeting this challenge is what lies with the Foundation now."

## DF Research Support—Expanding to Meet Dermatology's Future

Addressing the growing demands of the specialty, Dermatology Foundation members and corporate supporters provided funds for 61 specialty-enriching projects. Over $3 million was allocated to research award funding. A panel of 20 scientists objectively selected these projects from the large pool of award applications. The many valuable projects that had to go unfunded point to the urgent need for continued growth in DF support.

More than half of the 2004 awards support substantial Career Development Awards that provide $55,000/year for up to three years. New this year are two Medical Dermatology Career Development Awards, which address severe dermatologic disease and build the base of medical dermatology.




The one-year projects funded for 2004 include:

- 13 Fellowships: 1 in pediatric dermatology, 7 Dermatologist Investigator Research Fellowships, and 5 Research Fellowships.
- 15 Grants: 5 Patient-Directed Investigations, 6 Research Grants, 2 Ichthyosis Grants, 1 Dermatopathology Grant, 1 Program Development Grant.

many received four or more. Private dermatology groups attracted more than one-third. Close to half of the overall group reported the highest level of job satisfaction, and 10% or less were dissatisfied or very dissatisfied.

### Right-Sizing the Workforce

The number of dermatologists has grown far more quickly than the U.S. population, tripling over the three decades from 1970 to 2002 (going from 1.9 to 3.5 per 100,000). Yet after decades of controversy concerning impending surplus versus continuing shortage, at last "there is now considerable evidence confirming that we face an undersupply," Resneck and Kimball state. Graduates find a plentiful job choice, the number of dermatologists seeking associates is far greater than the number of trainees annually emerging from residency programs, and the lengthy wait times for new patients shown here—and validated by other studies—are considered excessive.

Kimball and Resneck identify causes on both the supply and demand sides of the equation. Tightening the supply side in dermatology, the AADA survey showed the average dermatologist working fewer days per week, anecdotal evidence supports a trend toward early retirement, and the existing supply is geographically maldistributed. (As recent trainees consistently rank location as the most important factor in job selection, this difficulty is likely to continue.) Demand has been increasing as the scope of dermatology practice has rapidly broadened, our aging population presents a greater frequency of skin problems, and many managed care organizations have begun to ease their gatekeeper policies—in part because of pressure brought by the dermatology community. "While this state of affairs may provide plentiful job choices for recent graduates," Resneck and Kimball observe, "a severe shortage of dermatologists threatens patient access to care and is likely to further increase the amount of medical and surgical skin care provided by non-dermatologists." They point out the troubling irony that "after years spent successfully convincing the public that dermatologists should be the primary caretakers of the skin, the field now finds itself unable to meet the demand it helped to generate."

The thorny question now confronting us becomes—how do we address this urgent need. Normally, imbalances in supply and demand are righted through price adjustments in the marketplace. The social considerations and ethics of health care prohibit unlimited play of these dynamics. In addition, our current managed care system has placed an artificial limit on price change. The supply of dermatologists is also determined by more than direct market forces. Despite an excess of applicants for training positions, the number is controlled by medical schools/hospitals (which in part involves its own market factors) and accreditation committees.

Resneck and Kimball note several ways—each with its own risks and difficulties—to fill this gap, "ranging from training more residents, incentivizing physicians to move to underserved areas or provide general/medical dermatologic care to more patients, and increasing the use of physician extenders and physicians with other training." Resneck emphasizes the need for care and thoroughness in reaching conclusions, as "the decisions made now have long-term impact. We're stuck with them for years and years. Failing to train enough people now is very hard to make up for later. Overcompensating and training too many will impact the entire professional life span of the people we train. And as the current workforce status is never static, those addressing these issues must remain attentive to rapid evolution of factors affecting both supply and demand in the U.S. health care system.

Dermatologists cannot postpone their response to this shortage indefinitely, Resneck and Kimball warn, "or the care of the dermatologic patient may ultimately be delivered by someone else."

### Suggested Readings


Jacobson CC, Nguyen JC, Kimball AB. "Gender and parenting significantly affect work hours of recent dermatology program graduates." *Arch Dermatol.* 2004; 140:191–6.

Resneck J Jr, Pletcher MJ, Lozano N. "Medicare, Medicaid, and access to dermatologists: The effect of patient insurance on appointment access and wait times." *J Am Acad Dermatol.* 2004;50:85–92.

Resneck J Jr, Kimball AB. "The dermatology workforce shortage." *J Am Acad Dermatol.* 2004;50:50–4. ■

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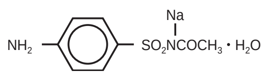


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Each gram of Plexion SCT,® (sodium sulfacetamide USP 10% and sulfur USP 5%) contains 100 mg of Sodium Sulfacetamide USP and 50 mg of Sulfur USP in a cream containing: Purified Water USP, Kaolin USP, Glyceryl Stearate (and) PEG-100 Stearate, Witch Hazel USP, Silicon Dioxide NF, Magnesium Aluminum Silicate NF, Benzyl Alcohol NF, Water (and) Propylene Glycol (and) Quillaja Saponaria Extract, Xanthan Gum NF, Sodium Thiosulfate USP, Fragrance.

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**CLINICAL PHARMACOLOGY**: The most widely accepted mechanism of action of sulfonamides is the Woods-Fildes theory, which is based on the fact that sulfonamides act as competitive antagonists to para-aminobenzoic acid (PABA), an essential component for bacterial growth. While absorption through intact skin has not been determined, sodium sulfacetamide is readily absorbed from the gastrointestinal tract when taken orally and excreted in the urine, largely unchanged. The biological half-life has variously been reported as 7 to 12.8 hours. The exact mode of action of sulfur in the treatment of acne is unknown, but it has been reported that it inhibits the growth of Propionibacterium acnes and the formation of free fatty acids.

**INDICATIONS:** PLEXION Cleanser, PLEXION Cleansing Cloths, PLEXION SCT and PLEXION TS are indicated in the topical control of acne vulgaris, acne rosacea and seborrheic dermatitis.

**CONTRAINDICATIONS**: Plexion Cleanser, PLEXION Cleansing Cloths, PLEXION SCT and PLEXION TS are contraindicated for use by patients having known hypersensitivity to sulfonamides, sulfur or any other component of this preparation. These PLEXION,® brand products are not to be used by patients with kidney disease.

**WARNINGS:** Although rare, sensitivity to sodium sulfacetamide may occur. Therefore, caution and careful supervision should be observed when prescribing this drug for patients who may be prone to hypersensitivity to topical sulfonamides. Systemic toxic reactions such as agranulocytosis, acute hemolytic anemia, purpura hemorrhagica, drug fever, jaundice, and contact dermatitis indicate hypersensitivity to sulfonamides. Particular caution should be employed if areas of denuded or abraded skin are involved.

**FOR EXTERNAL USE ONLY.** Keep away from eyes. Keep out of reach of children. Keep container tightly closed.

**PRECAUTIONS:** General - If irritation develops, use of the product should be discontinued and appropriate therapy instituted. Patients should be carefully observed for possible local irritation or sensitization during long-term therapy. The object of this therapy is to achieve desquamation without irritation, but sodium sulfacetamide and sulfur can cause reddening and scaling of the epidermis. These side effects are not unusual in the treatment of acne vulgaris, but patients should be cautioned about the possibility.

**Information for Patients:** Avoid contact with eyes, eyelids, lips and mucous membranes. If accidental contact occurs, rinse with water. If excessive irritation develops, discontinue use and consult your physician.

**Carcinogenesis, Mutagenesis and Impairment of Fertility** - Long-term studies in animals have not been performed to evaluate carcinogenic potential.

**Pregnancy Category C** – Animal reproduction studies have not been conducted with PLEXION Cleanser, PLEXION Cleansing Cloths, PLEXION TS or PLEXION SCT. It is also not known whether these PLEXION brand products can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. These PLEXION® brand products should be given to a pregnant woman only if clearly needed.

**Nursing Mothers** - It is not known whether sodium sulfacetamide is excreted in the human milk following topical use of Plexion Cleanser, Plexion Cleansing Cloths, PLEXION SCT or PLEXION TS. However, small amounts of orally administered sulfonamides have been reported to be eliminated in human milk. In view of this and because many drugs are excreted in human milk, caution should be exercised when these PLEXION brand products are administered to a nursing woman.

**Pediatric Use** - Safety and effectiveness in children under the age of 12 have not been established.

**ADVERSE REACTIONS:** Although rare, sodium sulfacetamide may cause local irritation.

**DOSAGE AND ADMINISTRATION:** PLEXION Cleanser: Wash affected areas once or twice daily, or as directed by your physician. Avoid contact with eyes or mucous membranes. Wet skin and liberally apply to areas to be cleansed, massage gently into skin for 10-20 seconds working into a full lather, rinse thoroughly and pat dry. If drying occurs, it may be controlled by rinsing cleanser off sooner or using less often.

**PLEXION Cleansing Cloths:** Wash affected areas with cleansing cloth once or twice daily, or as directed by your physician. Wet face with water. Wet cloth with a little water and work into a full lather. Cleanse face with cloth for 10-20 seconds avoiding eyes. Rinse thoroughly and pat dry. Throw away cloth. Do not flush.

**PLEXION SCT:** Use once daily or as directed by your physician. Wet skin. Apply in a film to entire face, avoiding contact with eyes or mucous membranes. Wait 10 minutes or until dry. Rinse thoroughly with water and pat dry.

**PLEXION TS:** Cleanse affected areas. Apply a thin film of PLEXION TS to affected areas 1 to 3 times daily, or as directed by a physician.

**HOW SUPPLIED:** Plexion,® (sodium sulfacetamide 10% and sulfur 5%) Cleanser is available in 6 oz. (170.3 g) tube (NDC 99207-741-06) and 12 oz. (340.2 g) bottle (NDC 99207-741-12). Plexion,® (sodium sulfacetamide 10% and sulfur 5%) Cleansing Cloths are available in boxes of 30 cloths (3.7 g) (NDC 99207-745-30). Plexion SCT,® (sodium sulfacetamide 10% and - sulfur 5%) is available in a 4 oz. tube (NDC 99207-744-04). Plexion,® (sodium sulfacetamide 10% and sulfur 5%) Topical Suspension is available in 30 g tube (NDC 99207-743-30).

Store at 15º - 25ºC (59º - 77ºF).

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References: 1. Data on file, MEDICIS® Pharmaceutical Corporation.

# Focus on Research

(Continued from cover)

ogy remains elusive, and existing treatment is far from ideal. Isotretinoin is useful in treating severe acne, but its well-known multiple side effects—the most serious being teratogenicity—make it far from optimal. Although antibiotics address *P. acnes*, the increasing presence of drug-resistant clinical isolates is diminishing their efficacy, and long-term antibiotic use has come under scrunity for possible serious health consequences well into the future.

Yet acne carries significant medical and psychological impact. The continued presence of multiple lesions, and the hyperpigmentation and permanent scarring that can result, diminish self-image and create social inhibitions, depression, anger, severe embarrassment, and anxiety. In 1999 (the most recent year with reliable statistics), acne alone accounted for 7.9 million doctors visits and for prescription medications costing approximately $1.2 billion, and millions more for over-the-counter treatments. Many adolescents with significant disease do not even consult a physician, perhaps due to the limited treatment options and their side effects.

The development of more effective treatments rests on advances in understanding the complex underlying molecular pathology of this skin disease, and thus identifying effective targets. Diane Thiboutot, MD, and Jenny Kim, MD, PhD, approach this from very different vantage points. Thiboutot's focus has been on understanding the sebaceous gland and the local relationship between androgens and sebum production. Most recently she has documented the steroidogenic nature of the sebaceous gland, and is exploring its clinical significance. Kim—with a PhD in immunology—is characterizing the innate immune response to *P. acnes* and its primary role in the destructive inflammatory response. She is also investigating novel antimicrobial treatments.

## The Sebaceous Gland

Early in her research, Thiboutot had concluded that "we really can't make any therapeutic advances until we learn more about the factors that regulate sebum production." She focused on androgen hormone metabolism in sebaceous glands "because we knew that androgens increase the glands' size and sebum secretion—and thus these hormones are important." Discovering normal serum levels for these androgens in acne patients prompted her realization that "hormone action in the skin, as in other endocrine target tissues, is regulated by local levels of steroid hormone, enzymes, growth factors, and cytokines."

She examined regional levels of two steroid-metabolizing enzymes—5α-reductase, which transforms testosterone into dihydrotestosterone (DHT), which in turn directly influences sebum production, and 17β-hydroxysteroid dehydrogenase (17β-HSD), which interconverts steroid hormones back and forth between weaker and stronger. She also began to pursue peroxisome proliferator-activated receptors (PPARs), determining that PPAR-γ is the predominant isoform in the skin. She is now exploring its function in the sebaceous gland.

## The Steroidogenic Nature of Human Skin

Most recently, Thiboutot decided to approach the sebaceous gland from a somewhat radical perspective—to see if it is actually capable of manufacturing steroids *de novo*. "The prevailing view has been that the steroidogenic tissues are limited to the adrenal glands, testes, and ovaries," she says. "We've always known that the sebaceous gland is capable of metabolizing existing androgen hormones, which are important in the development of acne. Our laboratory had characterized the two upstream enzymes 5α-reductase and 17β-HSD and another laboratory had characterized 3β-HSD, so it was clear that the skin is able to convert the androgen precursor DHEA—dehydroepiandrosterone—into androgens and estrogens," Thiboutot explains. "We had also learned from experiments in other laboratories as well as ours," she continues, "that the sebaceous gland can take the two-carbon fragment acetate and synthesize cholesterol from it. So the sebaceous gland demonstrated activity of all of the enzymes involved in the cholesterol biosynthetic pathway, and those for metabolizing steroid hormones. The key to making the steroid hormone itself," Thiboutot adds, "is the ability to convert cholesterol into a steroid. "And the enzymatic steps for accomplishing that crucial transition were the missing links." Although there was no direct evidence that they existed in the skin or sebaceous glands, several observations in the literature hinted at their presence.

In the mid-1990s, researchers at the University of Pennsylvania had discovered that the protein in charge of translocating cholesterol from the outer to the inner mitochondrial membrane, where steroid synthesis occurs, is present in the skin. This regulatory protein is *StAR—steroidogenic acute regulatory protein.* Much more recently, a cutaneous research laboratory in London found *steroidogenic factor-1 (SF-1)* in human skin. This orphan nuclear receptor (called an orphan because no ligand or activator molecule has yet been found) regulates the complete network of genes—from transporting cholesterol into the mitochondria, then for the succession of conversions, first to hormonal precursors, and then to the variety of androgens, estrogens, and progesterones—responsible for transforming cholesterol into hormones.

"At that point, it made sense to me that the cholesterol-converting enzymes must also be in the skin," Thiboutot says. "It was logical to expect that the key conversion enzymes weren't necessarily missing, but just had never been fully investigated."

## The Search for the Missing Link

The critical enzymes that Thiboutot would be searching for are members of the *P450 side chain cleavage (P450scc) system*—the system that catalyzes the initial step in steroid hormone synthesis once cholesterol is translocated to the inner mitochondrial membrane—and the enzymes that assist it. These assisting enzymes include the cofactors *adrenoxin* and *adrenoxin reductase*, generic electron transport proteins for all mitochondrial forms of cytochrome P450. Adrenoxin reductase picks up the electron and transfers it to adrenoxin, which passes it on to P450scc, which converts cholesterol to the precursor pregnenolone. The enzyme *P450c17 (P450 17-hydroxylase)* is essential for the intermediary conversion between pregnenolone and DHEA.

As freshly cultured sebaceous glands differentiate too rapidly to provide the large numbers of cells necessary for the biochemical assay that demonstrates an enzyme's activity, Thiboutot developed an immortalized human sebaceous gland cell line by transfecting sebocytes from normal facial skin of a healthy male with DNA encoding a viral oncoprotein. Once SEB-1 was established, and Thiboutot had thoroughly confirmed its sebaceous phenotype, she was ready to search human facial skin, human sebaceous glands, secondary cultures of human sebocytes, and SEB-1 sebocytes for the presence of the missing link steroidogenic proteins, and

(Continued on page 11)

# 66 Dermatologists Join *Annenberg Circle* in 2003

Nearly doubling the new membership total for 2002, 66 dermatologists made the major lifetime pledge to support research and training in their field by becoming members of the *Annenberg Circle* in 2003. This exceptional level of philanthropy is based on a lifetime contribution of $25,000, which can include up to $10,000 in accrued Leaders Society membership.

The Dermatology Foundation is honored to recognize the 205 members on the 2003 roster.

To join the ***Annenberg Circle,*** contact Joe Flint, Manager, Individual Giving, at *jflint@dermatologyfoundation.org*

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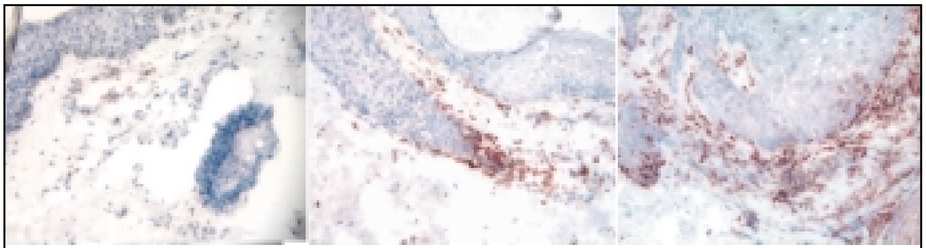
assess their activity in SEB-1 sebocytes. The human skin, sebaceous gland, and sebocyte cultures functioned primarily as parallel experiments for documenting the suitability of SEB-1 as a model for steroidogenesis in sebaceous glands.

Antibodies to P450scc, P450c17, adrenodoxin reductase, and SF-1 successfully localized these critical steroidogenic proteins in all of Thiboutot's preparations. In human skin, the three enzymes were present in sebaceous glands and ducts and hair follicles, and were particularly prominent in the more differentiated layers of the epidermis. These enzymes were also detected in the cytoplasm of both cultured and immortalized sebocytes. Antibodies to SF-1 pinpointed a perinuclear or nuclear localization. Identifying the proteins for all three enzymes and SF-1 in extracts from each sebocyte preparation confirmed the immunohistology data.

Now Thiboutot had to determine that these critical steroidogenic proteins are actually functional in these locations. She grew SEB-1 colonies, then added forskolin to half of them to stimulate adenylate cyclase release, which in turn induces steroidogenic enzyme activity. Then hydroxycholesterol—chosen as the substrate because it easily traverses the mitochondrial membrane without StAR, and thus can reach a sufficient concentration where needed—was added to each SEB-1 colony. The clear result was production of 17α-hydroxypregnenolone—"and the biochemical pathway from acetate through potent androgens was complete," Thiboutot says.

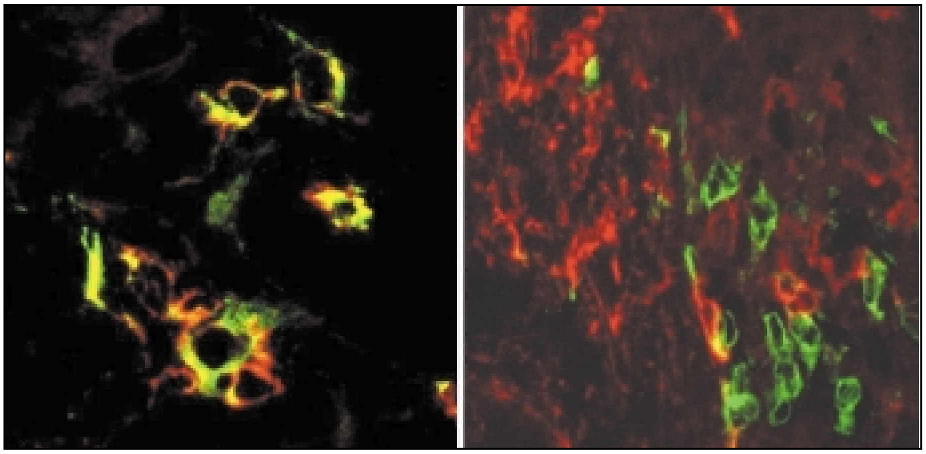
The cholesterol-converting enzymes in the skin "are present in much lower levels compared to ovarian or adrenal tissue," she adds, "but they are still there. These data suggest that human skin can function as an independent peripheral endocrine organ," Thiboutot points out. "Delineation of the steroid hormone biosynthetic pathway in the skin completes an essential step in advancing our understanding of how androgens mediate both the physiology and pathophysiology of the skin," she adds. "Now the challenge is in determining the functional significance of this pathway in normal and diseased skin. This will be particularly relevant to androgen-mediated diseases of the skin—such as androgenetic alopecia and hirsutism, as well as acne—where the potential exists for local enzyme inhibition as a therapeutic intervention."

Thiboutot points to the remarkable nature of this discovery, expanding yet again our concept of the skin's capabilities. "Over the past 15 years we have learned that the skin is a key organ of the immune system, is important in vitamin D metabolism and photoprotection, and is very active metabolically," she observes. "This is yet another piece of evidence that supports the importance of the skin in a variety of processes that were previously thought to take place only in a certain few specialized organs."



6 hours | 12–24 hours | 48–72 hours

**TLR2 expression in acne lesions.** Kinetics as the lesion evolves are revealed by monoclonal antibodies for TLR2. In early lesions (up to 6 h), a few rare $TLR2^+$ cells were detected. Between 12 and 24 h, $TLR2^+$ cells were much more numerous around the pilosebaceous follicles. In older lesions (48–72 h), still greater numbers were detected. (Reprinted with permission from *J Immunol.* See *Suggested Readings.*)



**$TLR2^+$ cells in acne lesions.** Using color immunofluorescence—red for TLR2, and green for CD14 (monocytes) or CD3 (T cells)—double-positive cells turn yellow when the two confocal images are superimposed. $TLR2^+$ cells near the follicular bulbar region clearly co-localize with $CD14^+$ monocytes/macrophages (*left*), but not with $CD3^+$ T cells (*right*). (Reprinted with permission from *J Immunol.* See *Suggested Readings.*)

## *P. acnes* and the Innate Immune System

Kim's interest in acne evolved tangentially from research toward the end of her PhD training in immunology. She was working in the laboratory of Robert Modlin, MD, Chief of Dermatology at UCLA, when awareness of the innate immune system as the first responder to microbial invasions—via the highly conserved pattern–recognition toll-like receptors first discovered in Drosophila—suddenly burgeoned in the latter 1990s. Modlin, who had been using leprosy and the immune response to *Mycobacterium leprae* as a model for elucidating different types of T-cell responses, discovered in 1999 that toll-like receptor 2 (TLR2) actually provided the initial recognition of this Gram-positive mycobacterium, which then activated adaptive immunity. "Being a dermatologist," Kim explains, "my interest was in the role of toll-like receptors in common skin diseases, and I wanted to look at acne in this context." She turned to the inflammatory response produced by the immune system's reaction to *P. acnes*.

Kim had been intrigued by a paper published in 1995 by B. R. Vowels, who was working in Jim Leyden's laboratory at the University of Pennsylvania. They had demonstrated that *P. acnes* induced human monocytes—from acne and non-acne subjects—to produce the proinflammatory cytokines IL-1β, IL-8, and TNF-α. They had also succeeded in blocking a substantial portion of this response by adding jimson lectin—which binds peptidoglycan, the predominant cell-wall component of Gram-positive bacteria—to the mix. This suggested that a peptidoglycan might be the soluble stimulating factor inducing monocytes to produce these inflammatory cytokines in response to *P. acnes*. The cytokine production that *P. acnes* induced in monocytes was also

## Leaders Society—
## Continued Growth Builds the Specialty

Each year the Dermatology Foundation—the specialty's unified, physician-based fund-raising and grant-making arm—increases its ability to fund important research projects. This success is the direct result of increased physician membership.

The DF owes a great deal to the 24 dermatologists in the volunteer campaign network who each enrolled three or more new Leaders Society members in 2003: **Rodney S. W. Basler, Ronald R. Brancaccio, Jonith Y. Breadon, Lawrence L. Bushkell, Alexander Chiaramonti, Lisa A. Garner, J. Blake Goslen III, Scott L. Gottlieb, Stephen D. Houston, Sewon Kang, Mary P. Lupo, Frederick A. Lupton, Darius R. Mehregan, Donald J. Miech, O. Fred Miller III, Eliot N. Mostow, Arthur R. Rhodes, Richard K. Scher, Jimmy D. Schmidt, Steven K. Shama, John R. Vydareny, John J. Voorhees, Jonathan S. Weiss,** and **Bruce U. Wintroub.**

inhibited by blocking the membrane molecule called CD14, known to be a monocyte membrane receptor for lipopolysaccharide (LPS). How it signalled was not understood, since CD14 lacked a cytoplasmic domain. Although the puzzle was solved with the discovery of TLRs, until Kim's research, the molecular mechanism underlying the ability of *P. acnes* to activate monocyte cytokine release remained unknown—although investigators began to suspect that it involved some sort of pattern recognition receptor.

Kim knew that activation of TLRs by a ligand can influence the immune response through at least four different pathways: the induction of cytokines, which directly activates the adaptive immune response; the induction of co-stimulatory molecules that influence adaptive immunity; a direct antimicrobial effect; or apoptosis and tissue injury. And she learned that several Gram-positive bacteria, including *Mycobacterium tuberculosis*, had recently been determined to activate monocytes via TLR2. Although *P. acnes* is a highly atypical Gram-positive bacterium, with unique cell wall features that include a distinctive peptidoglycan, she decided to see if recognition by TLR2 is the key to initiating the monocyte-produced cytokines that launch the inflammatory response in acne.

### Covering All the Bases

Kim carried out a series of highly coordinated studies—some in the culture flask, some in cells from genetically altered mice, and in some skin biopsies from patients with acne—all designed to explore a possible relationship between *P. acnes* and TLR2. Each one provided a building block to confirm TLR2 as the initiating step in the *P. acnes*-induced inflammatory response that is a critical component of acne.

To begin with, Kim used two cell lines—HEK 293, cultured from human embryonic kidney cells, and BaF3, a hematopoietic cell line—that do not express endogenous TLRs and are thus unresponsive to microbial TLR ligands. She engineered these two cell lines with the equipment enabling them to respond—the monocyte receptor CD14, and an endothelial leukocyte adhesion molecule (ELAM)—enhanced with the luciferase reporter gene—that responds to signals from NF-κB, which is required for several proinflammatory cytokine promoter activities. HEK 293 cells were also transfected with TLR2, while BaF3 cells were transfected with TLR4. NF-κB activity would occur only if the respective TLR recognized a microbial ligand. She successfully pre-tested each modified cell line with a known stimulus. Then when both cell lines were exposed to *P. acnes*, TLR2-transfected cells were found to demonstrate significant NF-κB activation. TLR4-transfected cells did not.

Because TLR2 cooperates with TLR1 and TLR6 in recognizing microbial ligands, Kim wanted to know whether TLR2 requires this collaboration for responding to *P. acnes*. In collaboration with Shizuo Akira's group from Osaka University in Japan, she used knockout mice for each TLR, obtained peritoneal macrophages from normal mice as well as each type of knockout mouse, exposed them all to *P. acnes*, then looked for release of the cytokine IL-6 as proof of TLR activation. *P. acnes* induced IL-6 release in the normal macrophages. The innate immune response pathway was also intact in mice lacking TLR1 or TLR6. Only the macrophages from mice missing TLR2 did not respond to *P. acnes*. Thus, TLR2 alone was found to be sufficient for mediating the response to *P. acnes*.

Kim then looked at IL-12 gene activation, because IL-12 is "one of the major proinflammatory cytokines produced by monocytes in response to Gram-positive organisms, and a pivotal cytokine in activating Th1 T-cell responses." After using a murine macrophage cell line to demonstrate that *P. acnes* induces activity of the IL-12 gene's promoter through a TLR2-dependent mechanism, "we determined whether the resulting cytokine protein production is also dependent on TLR activation," Kim says. She and her co-workers used various dilutions of *P. acnes* to stimulate primary human monocytes from normal donors, and measured both IL-12 and IL-8, which is involved in neutrophil chemotaxis. *P. acnes* induced the release of both cytokines in a dose-dependent manner. The experiment was repeated after adding blocking antibodies to TLR2 or to TLR4 to cell cultures 30 minutes before stimulation with *P. acnes*. Blocking TLR4 had no impact on IL-12 protein levels. But neutralizing TLR2 diminished cytokine production by 65%.

Once Kim had provided this extensive series of observations documenting the critical role of TLR2 in steps of the inflammatory response to *P. acnes*, she used monoclonal antibodies to analyze over 30 acne lesion biopsies from patients, looking for TLR expression as well as the presence of T cells and monocytes. $TLR2^+$ cells were detected on large ovoid cells within lesions, primarily in the inflammatory infiltrate around the perifollicular/peribulbar region. None were found in normal skin. Kim points out that "as the primary event in inflammatory acne involves the disruption of the follicular epithelium and colonization of the follicles with *P. acne*, with subsequent inflammatory reactions in the surrounding dermis, the detection in biopsied lesions of $TLR2^+$ cells in the perifollicular region provides indirect evidence that TLR2 activation contributes to the pathogenesis of acne, and suggests that these cells promote inflammatory responses at the site of disease activity." Looking at the kinetics of $TLR2^+$ expression (see photos on page 13), few such cells were seen in lesions biopsied within 6 hours after they had appeared. These $TLR2^+$ cells had become more numerous around the pilosebaceous follicles between 12 and 24 hours, and even greater numbers were detected in older lesions obtained between 48 and 72 hours. "We concluded that the infiltration of $TLR2^+$ cells is an early event in the evolution of acne lesions," Kim explains, "and that the frequency of cells expressing these toll proteins increases during the evolution of this disease."

In these same perifollicular areas, Kim also detected numerous cells expressing the monocyte CD14 molecule, and others expressing the T-cell marker CD3. She discovered that TLR2 co-localized only with the monocyte marker (see photos on page 13), suggesting that monocytes in acne lesions expresses TLR2, and thus are activated by it. This coordinates with the initial observation from Leyden's lab that *P. acnes* induces monocytes to release proinflammatory cytokines.

Kim notes that IL-8 and IL-12 are prominent in the cytokine profile associated with *P. acnes*. IL-8 attracts neutrophils to active lesions, and then their release of lysosomal enzymes may lead to rupture of follicular epithelium and further inflammation. IL-12 promotes development of Th1-mediated immune responses. Overproduction of these cytokines has been implicated in the development of tissue injury in certain autoimmune and inflammatory diseases, and Kim believes that there are strong parallels in the pathogenesis of acne.

## Immunologic Irony

Kim notes the irony that "recognition of microbial pathogens by cells of the immune system triggers host defense mechanisms to combat infection and prevent disease, yet these same pathways can also result in inflammation at the site of disease that leads to tissue injury." The defense mechanism itself can create disease. Such responses include the formation of immune complexes, the recruitment and activation of neutrophils and monocytes, the release of cytokines, and the release of degradative enzymes.

In this vein, "it is tempting to speculate that the inflammatory cytokine responses triggered by *P. acnes* and mediated by TLR2 are actually harmful by promoting inflammation and tissue destruction," Kim states. "Given these data, TLR2 is a logical target for therapeutic intervention designed to block inflammatory cytokine responses in acne, as well as other inflammatory conditions in which tissue injury is detrimental to the host."

## Therapy: Endogenous Antimicrobials

Because the inflammatory response elicited by *P. acnes* is thought to be pathogenic in inflammatory acne, this disease is often treated with oral antibiotics, such as tetracycline and erythromycin, which inhibit components of bacterial growth and replication. But these antibiotics have been a mainstay of acne treatment for over 30 years now, and the concern that this long-term, widespread use would produce resistant strains of *P. acnes* has now been realized. Oral antibiotics can cause other problems as well—vaginal yeast infections via destruction of the vagina's natural bacterial flora, gastroentestinal discomfort, discoloration of nonerupted teeth, and sensitivity to sunlight. For the more severe cases in which antibiotics have no therapeutic benefit, oral isotretinoin is often clinically effective but its side effects seriously compromise its overall utility. Kim stresses the need for a new category of acne-fighting drugs that are both effective in killing *P. acnes*, and nontoxic.

She has begun to develop a novel antibacterial agent that, so far, meets these requirements. She has taken it from the menu of endogenous antimicrobial peptides, which interact with the surface of microbes to form pores that result in membrane rupture and cell death. These endogenous antimicrobial peptides may also directly modulate host defense. And as they do not interfere with bacterial metabolism, resistance is less likely to develop. "Since the ideal treatment for acne vulgaris would be both antimicrobial and anti-inflammatory," Kim points out, "these antimicbrobial peptides hold promise as effective topical therapeutic agents."

Kim is working with granulysin, an antimicrobial peptide first discovered in human T and NK cells. It belongs to the group of saposin-like proteins, highly conserved for almost a billion years from amoebas to humans. "Studies in our lab," Kim comments, "have demonstrated granulysin's wide range of antimicrobial activity against bacteria, parasites, and fungi. And we have shown that by synthesizing smaller peptides from the full-length human granulysin, it is possible to correlate its antimicrobial activity with specific elements in the peptide structure."

Kim and her co-workers identified a small region of the granulysin peptide to be particularly effective at killing *P. acnes*. They began to modify its sequence slightly to optimize its efficiency in a sebaceous environment.

So far, *in vitro* studies showed granulsyin peptide to have both antimicrobial and anti-inflammatory activity against *P. acnes*, markedly inhibiting production of a wide array of inflammatory cytokines and chemokines, yet without toxicity to human monocytes or keratinocytes. Kim reports that her research group is working on improving the ability of these peptides to penetrate the full thickness of the epidermis and reach the pilosebaceous unit where *P. acnes* resides.

## Suggested Readings


Thiboutot D, Jabara S, McAllister JM, et al. "Human skin is a steroidogenic tissue: Steroidogenic enzymes and cofactors are expressed in epidermis, normal sebocytes, and an immortalized sebocyte cell like (SEB-1)." *J Invest Dermatol.* 2003;120:905–14.

Kim J, Ochoa M-T, Krutzik SR, et al. Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses." *J Immunol.* 2002;169:1535–41. ■

# DF Research Support—Reaching Into the Future

*The Dermatology Foundation—dedicated to building the research and teaching careers of medical and surgical dermatology's future leaders—furthers scientific and clinical progress by supporting significant research and anchoring the academic careers of gifted young investigators. Today's investments clearly have long-term impact on the specialty. The four investigative dermatologists discussed in this issue all received DF awards at critical points in their respective careers—including for much of the research presented here. They describe the critical impact of these funds.*

***Alexa B. Kimball, MD, MPH,*** Associate Professor in the Department of Dermatology at Stanford University is in her final year of a Physician Scientist Career Development Award for gene transfer research in junctional epidermolysis bullosa. "Finishing an NIH Clinical Trials Fellowship and joining Stanford, I needed start-up funding for the time and resources to pursue my academic interests," Kimball explains. "These career funds allowed me to develop the clinical procedures for a novel gene therapy approach and build a thriving clinical trials unit at Stanford. It was also my first real entry into the professional ranks of dermatology researchers," she adds, "and is enabling me to apply for outside funds." Kimball, who studies workforce issues as well, "remains incredibly grateful that the DF seeded both my work and my professional momentum."

***Jack Resneck, Jr., MD,*** Assistant Professor in the Department of Dermatology and the Institute of Health Policy Studies at UCSF, received a Dermatologist Investigator Research Fellowship in 2001 for his first specialty workforce study, then a Clinical Career Development Award in Health Care Policy that began in 2002 for examining dermatology workforce adequacy. DF funds "fill a crucial gap—that time after residency before young researchers are ready to qualify for major NIH grants. DF grants allow them to get their work moving forward. The importance of these funds in keeping young researchers in academics while they develop their projects cannot be overstated," Resneck points out.

***Jenny Kim, MD, PhD,*** Assistant Professor in the Division of Dermatology, David Geffen School of Medicine at the University of California, Los Angeles, won single-year grants in 1994 and 1995 for doctoral study projects. Then in 2002 she received both a one-year Research Grant and a three-year Clinical Career Development Award for her pioneering exploration of the immune response to *P. acnes.* Her initial immune response data enabled her to win an NIH K08 Award, which began at the end of the first Career Award year. "The DF awards allowed me to start my research career," Kim says, "by enabling me to develop experience and skills and then gain NIH funds."

***Diane Thiboutot, MD,*** Associate Professor in the Department of Dermatology at Pennsylvania State University, has documented the steroidogenic nature of the sebaceous gland. A 1991 Research Grant during her residency allowed her to purchase laboratory supplies to begin studying androgens in sebum. A mentored Research Fellowship in 1994, as a first-year junior faculty member, "allowed me to pursue my research interests—this time assessing 5-α reductase activity in isolated sebaceous glands." A 1995 Clinical Career Development Award for comparing steroid-metabolizing enzyme activities in sebaceous glands and keratinocytes from subjects with and without acne "guaranteed continued research time," Thiboutot says, "and the opportunity to garner preliminary data to apply for NIH funds." A K08 Award was followed by an NIH R01 Award for her studies on the regulation of human sebaceous glands. "Dermatology is very fortunate to have the DF," Thiboutot says. "I have recently joined the Annenberg Circle to help support our future dermatology investigators."

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