There is little disagreement that our health and medical care system is in need of fundamental reform. But what should be the first step? The National Health Council, an organization representing all segments of the health care community to improve the health of all people, believes meaningful reform must begin with patients and their families - empowering people to play an active role in promoting health, preventing disease and managing their own health care decisions. Further, the Council believes adoption of, and widespread access to, personal health information technology (PHIT) is the logical starting point. Among other things, PHIT enables the documentation of an individual’s complete, lifelong health and medical history into a private, secure and standardized format that he or she owns and controls, but yet is accessible to legitimate providers day or night from any location.

The Katrina disaster of 2005 drove home the need for PHIT. Paper files were no match for Katrina, and thousands of records were permanently destroyed. Among them were chemotherapy records for 80 evacuated children. Despite the need for precise timing and accuracy in the treatment of these young patients, doctors were left to guess. By contrast, and because of PHIT, 50,000 New Orleans VA Medical Center patients’ health records were spared and available online at the height of the hurricane. Beyond natural disasters, paper records present other problems. Each year, thousands die because of medical errors often associated with inaccurate information. About 7,000 perish annually due to prescription errors alone. Missing records also jeopardize safety. Not only do patients not have easy access to their own information, these records also are difficult or impossible for providers to obtain or share - particularly in emergencies. On a positive note, an American Hospital Association study indicates the mortality rates of the country’s top PHIT-enabled hospitals are 7.2 percent lower than average.

There is also the problem of waste. According to a RAND Health study, up to a third of health expenditures is wasted due to inefficiencies (approximately $600 billion in 2004). The good news, says RAND Health, is that PHIT savings could reach $162 billion in just one year - a windfall that could be used to broaden access to care. So how do we go from paper to PC? Again, the answer lies with patient and consumer demand. Research conducted by the NHC shows that once PHIT is explained to them, people quickly see the benefits: efficiency, effectiveness, timeliness and safety in the delivery of services. Further, individuals are willing to take action to secure these benefits. Over the next five years, in concert with member organizations and other partners, the Council will lead a coordinated effort called Putting Patients First® to educate, inspire and mobilize the patient community. The desired result is that demand from these millions of people will convince policymakers, health care providers, businesses and insurers to make PHIT a reality.

Myrl Weinberg, CAE
President, National Health Council
A VIEW FROM THE TOP

2005: A VERY SUCCESSFUL YEAR

Welcome to the first issue of the Quarterly for 2006. In 2005 we expanded our focus to include more patients outside the U.S. We sponsored our 2nd International Scientific Meeting. We assisted more patients in understanding their options and empowering themselves. We helped save lives.

We all remember what it was like when we started presenting with lesions – how difficult it was because of the itching or the pain, and not knowing what was happening. Every day the IPF is contacted by someone newly diagnosed who is feeling that way. I can’t begin to tell you how many people have told us that our personal touch has made a huge difference.

Our work is more than answering e-mails or phone calls. We are educating members of the medical community to help them better treat patients. We are advocating for better healthcare and research with our affiliates through events like our first Capitol Hill Day. We are providing information on clinical trials that may bring us better treatment and better care.

The only way we can continue our work is with your support. Because we are a rare disease, we don’t have the notoriety that many organizations have. We are competing with other small disease foundations for public and private money. The best way for us to continue to live our mission statement is by asking our base to make sure we remain a viable organization.

There are many ways to help. If you own a business and you usually give your customers gifts during the holidays, donate to the IPF on their behalf. Sign-up for a matching gift program with your employer, or designate the IPF when you donate to the United Way. We are now also taking vehicle donations, and when you shop online check out our shopping affiliation page - http://www.pemphigus.org/affiliates.html. You can order flowers, travel, or shop at WalMart online in the comfort of your home.

There are so many causes out there that are worthy of your support. We believe that people with pemphigus and pemphigoid are as important to the world as anyone else. We believe that your health and well-being matters too. We must continue to meet our goals and with your help we can.

$hop Online!
http://www.pemphigus.org/affiliates.html

The IPF now offers a shopper’s affiliation page on our site! We will be adding more merchants based on your feedback, feasibility, and program benefits for both you and the IPF. Merchants such as Amazon.com, WalMart, GiftBaskets.com, Easy Click Travel and others! We are excited to offer this service to you – services we all use, only now the IPF can receive a portion of your purchase towards our fundraising efforts. Look for “Shopping” on the navigation menu!
This inaugural letter comes with great pleasure, passion, and gratitude for the opportunity you have entrusted to me to lead the IPF and work with such a talented group of dedicated individuals on our Board of Directors and our Medical Advisory Board, and a number of dedicated staff leaders and active volunteers within the Foundation. Your Board of Directors met in November 2005 and, with the help of a consultant, developed an exciting and challenging strategic plan for the Foundation that will ensure its growth as the agency that advocates for education, information, support, research and training for all those affected by, or involved in the treatment of, Pemphigus and Pemphigoid.

This Growth Campaign for the IPF will require the hard work of many people, and the generous contribution of time and money. At this very moment we are working with a handful of individuals – “path finders” - who are willing and able to make a significant commitment to the IPF Growth Campaign. We likewise plan to attract commitments from commercial entities to contribute to the campaign. And, we need every person who has been touched by pemphigus or pemphigoid to also make – in addition to whatever they have done already – an additional donation to the IPF.

With a solid plan in place, and the financial resources to drive the plan, we fully expect that within three years we will have an IPF that is better in advocating for its constituents and more influential in contributing to the generation of new knowledge in the optimal diagnosis and treatment of pemphigus and pemphigoid.

In future Newsletters I will provide updates to all of our constituents on the measurable progress we are making, and in doing so gain your continued confidence that your Board is performing well as a steward of your trust and support. Look for details on our progress in future communications in each of the following strategic plan initiatives: Patient Support; Public Awareness; Research, Education and Advocacy; Management and Operations; and Fundraising.

Please make a generous contribution to the IPF that is above your usual level of giving and please indicate your donation is to support the IPF Growth Campaign.

Sincerely yours,

David A. Sirois, D.M.D., Ph.D.
President, Board of Directors
International Pemphigus Foundation
A NOVEL EXPLANATION FOR ACANTHOLYSIS IN PEMPHIGUS VULGARIS: THE BASAL CELL SHRINKAGE HYPOTHESIS

Jean-Claude Bystryn, MD, New York, New York and Sergei A. Grando, MD, PhD, Dscie Sacramento, California

The current explanation for suprabasal acantholysis in pemphigus vulgaris (PV) is that antibodies to desmoglein (Dsg) 3 and Dsg 1 block the function of these two adhesion molecules by steric hindrance or by altering their structure, causing keratinocytes to detach from each other. The restriction of acantholysis to the basal layer is explained by Dsg 3 being expressed predominantly in the deeper epidermal layers and Dsg 1 in the more superficial ones with the presence of one Dsg able to compensate for the lack of function of the other.

Accordingly, blisters occur only in deep epidermal layers in PV and only in superficial layers in pemphigus foliaceus because the presence of both adhesion molecules in the intervening layers compensates for the antibody-mediated loss of function of one or the other. This explanation is not fully satisfactory, as acantholysis does not appear to be triggered by loss of adhesion between desmosomes and its restriction to the basal layer in PV appears to involve factors other than Dsg compensation.

Here, we propose an alternate explanation for acantholysis in PV and its restriction to basal cell layer. First, it is that the binding of pemphigus antibodies to keratinocytes causes changes in their cytoskeletal structure with consequent partial collapse and shrinkage of the cells. Keratinocytes separate because they shrink more than they can be held together by desmosomes, not because of a primary defect in the function of desmosomes. Second, the shrinkage is limited to basal cells in PV because basal cells are less rigid and shrink more readily when their cytoskeleton is altered. Their cytoskeletal structure is affected to a greater extent by the signaling event, and/or different set of signaling event is triggered in basal cells.

The observations that support the alternate hypothesis we propose are summarized below.

ACANTHOLYSIS IS NOT TRIGGERED BY LOSS OF DESMOSOMAL ADHESION

Acantholysis between keratinocytes occurs first in areas where there are no desmosomes, not at the desmosomes where the separation should occur first if acantholysis was caused by blocking their adhesive properties. In fact, desmosomes appear to separate only late in acantholysis. Electron microscopy studies of early PV lesions clearly show that keratinocytes separate first in the interdesmosomal areas, at the time desmosomes are intact and still adhere to each other. In moderately advanced acantholysis that has progressed to a wide separation between adjacent keratinocytes, desmosomes still adhere to each other at the end of stretched-out sections of the cell membrane (Figure 1, page 10).

The cells appear to be pulling away from each other with the desmosomes trying to hold them together. Even in the final stage of acantholysis when keratinocytes are fully separated from each other, intact desmosomes with the two half-desmosomes still adhering to each other float in the intercellular space or remain attached to one keratinocyte while the adjacent cell has lost its half-desmosomes. Desmosomes do not stop adhering in pemphigus, rather they appear to be torn away from the cell surface while still adhering to each other.

THE RESTRICTION OF ACANTHOLYSIS TO THE BASAL LAYER IN PV DOES NOT APPEAR TO BE CAUSED BY DSG COMPENSATION

Acantholysis remains limited to basal cells in oral pemphigus, even though there is no expression of Dsg 1 in the oral mucosa or only a minor expression. In the absence of a compensatory adhesion molecule, acantholysis should involve all oral epidermal layers according to the Dsg compensation hypothesis. Acantholysis remains restricted to the basal cell layer in the approximately 50% of patients with PV who have both Dsg 1 and Dsg 3 antibodies. According to the Dsg compensation hypothesis, such patients should have acantholysis involving all epidermal layers as the adhesion properties of both molecules would be blocked. One cannot argue that the Dsg 1 antibodies are present in low and, thus, ineffective levels because their levels can be as high or higher than those against Dsg 3; nor that the anti-Dsg 1 antibodies...
There are two types of Federal disability programs – Social Security Disability (SSDI) and Supplemental Security Income (SSI). The definition of disabled is the inability to perform any type of work. The disability must also be anticipated to be continuous for a period of one year minimally.

In order to qualify for Social Security Disability (SSDI) you have to work a total of 40 quarters of on the books work over your lifetime. If you are between 20 and 30 years old, the requirement is somewhat less. Benefits you receive from SSDI will be based upon the length and amount of your earnings over a lifetime (with emphasis towards latter years of earnings). Benefits can range from as low as about $100 to approximately $1400 per month.

If you are not eligible for SSDI, you might be eligible for Supplemental Security Income (SSI). If your income earnings are no higher than $18,000 per year. If you are eligible for SSDI, but the money you will be receiving is less than the $579/month, SSI may make up the difference. For example – if when filing for SSDI, your eligibility is only $500 a month, SSI will make up the difference of $79.

Where you live can make the difference in the $579/month, SSI may make up the difference of $79. You are encouraged to schedule an appointment to take an application. Make an appointment if possible. It will save a lot of time. You can also call and make an appointment if phone if that is more convenient. Your basic information will be taken and a packet of forms will be sent to the local office. You are encouraged to document each transaction with the local office. You are encouraged to document each transaction with a person is illiterate)

There are four steps to apply for SSDI or SSI

**Step 1:** The first thing the worker will ask is: Are you working? Working is measured only in terms of the amount of money you make. For 2005, if you make less than $830.00 per month, you are not considered working.

**Step 2:** Do you have a medical impairment? This is determined by whether your level of disease has more than a minimal impact on your ability to do any single basic work activity.

**Step 3:** There are medical conditions that are so severe they would clearly prevent a person from working in any capacity. Pemphigus/pemphigoid* is included as one of the listed impairments (under bullous diseases), but merely having the diagnosis is not enough. If, however, a person with pemphigus is able to document their personal disabilities which are caused by their pemphigus/pemphigoid and are deemed unable to work because of those conditions, a favorable determination should be made. Complications from treatment of bullous diseases should also be considered as eligibility criteria.

Pemphigus/pemphigoid is not a skin disorder; rather it is an auto-immune disorder which manifests itself on the skin and/or mucous membranes.

**Step 4:** If a person is able to perform the work he/she has performed for at least 15 years, then they would not be eligible.

**Step 5:** If a person has been able to get to Step 4, then the burden of proof switches to the government to show that a person can perform other work besides their usual job.

The government will consider four factors:

a. A person’s remaining abilities both mental and physical

b. A person’s education – the higher the education, the more a person could adjust to other types of work (in practice, though, the only consideration is whether a person is illiterate)

c. Does the person have specific skills that he/she could not perform because of their diagnosis. For example, someone who works with the public but is taking large doses of immune suppressors could be at risk for further health complications as a result of working. Also, someone who has experienced complications from steroid treatments, such as osteoperosis or compression factors may no longer be able to perform jobs with strenuous physical demands.

d. Age – For anyone under 50, this is not applicable.

There are three ways to apply: in person, by telephone, or on the internet. If you go to the social security office in person, you could wait a long time to see an intake worker. Call 1-800-772-1213 to make an appointment if possible. It will save a lot of time. You can also call and schedule an appointment to take an application by phone if that is more convenient. Your basic information will be taken and a packet of forms will be sent to you to be completed and returned to the local office. You are encouraged to document each transaction with the local office. You are encouraged to document each transaction with the local office.
the Social Security office for your own records. Although you can fill out the forms through the Internet, they are not very user friendly. It is possible, but not recommended at this time.

If after this process you receive a denial, you have 60-days to file an appeal. You must file within that 60-day period or you would begin the process from the beginning if you choose to reapply. It is common for an application to be initially denied initially. We do recommend you file an appeal. If possible, find a medical social worker or a disability attorney to help you. A disability attorney’s fee will be withheld until the case is resolved. Any costs incurred will be the responsibility of the client.

Applying for disability can be a daunting experience. When you are diagnosed with a disease such as pemphigus or pemphigoid, not only do you now have to cope with the disease, but you also have to deal with the healthcare system as well. If disability insurance would improve your situation, you should apply. If you need an attorney’s help, you should find one.

There is a bill in Congress to eliminate the waiting period for Medicare. In the Senate the bill is S.1217 “Ending the Medicare Disability Waiting Period Act of 2005.” In the House of Representatives you can ask your representative to support HR 2869 which is the Houses’ companion legislation to Senate Bill S.1217.

With diseases like pemphigus and pemphigoid, the first two years (24 months) can be the most important and the most difficult. If Medicare were immediately available to those who are approved for disability, it could be lifesaving. Check our website for a more detailed account on Social Security Disability (http://www.pemphigus.org/pdfs/IntroToSocialSecurityBenefits.pdf).

...continued from SSKI/SSI, page 5

FUELED BY DR. SARAH BRENNER’S RESEARCH, A CHANGE IN DIET MADE ALL THE DIFFERENCE
A PV PATIENT’S SUCCESSFUL DIETARY CHANGES

by Laura Sigura

My disease began a year ago in February 2005, with a final diagnosis in August 2005. I was using Crest Whitestrips and during the two week treatment I erupted with four blisters. My gums became spongy that they bled and started to peel off easily. This did not go away. My dentist at the time didn’t know what it was from and claimed the whitestrips probably caused it, but it should go away. In June 2005 I developed blisters under one underarm and on my stomach, then also a vaginal blister. The gynecologist ruled out herpes and didn’t know what it was, and also said the others looked like pimples.

I found a new dentist in July 2005 who didn’t like what she saw in my mouth and when I told her about the other blisters she immediately stated I may have an autoimmune process. I went to an oral surgeon who confirmed her suspicion, but he sent me to Kaiser (my insurance carrier) and the dermatologist immediately got me in for a biopsy. The diagnosis arrived in August.

My condition is mild as I have only been on topical steroid creams. I had read about Dr. Brenner’s research about “foods that eat you” in August, but wasn’t really prepared to go that route. Finally, on December 20, 2005 I decided to bite the bullet and begin eliminating foods that her research concluded could be triggering the disease.

My diet consisted greatly of those foods on her “suspect” list, including onions and garlic, broccoli and cauliflower, tomatoes, potatoes, plenty of fruits. Even chocolate, coffee, and teas of which I consumed plenty daily. I decided to eliminate all categories of offending foods at one time. Here it is, February 6, 2006 and my last blister was December 18, 2005! I had been breaking out in 1-2 blisters every 2-3 weeks, and now it’s 7 weeks blister-free today! I think this is amazing and although it is difficult, especially to eat out at restaurants or at a friends house, it is obviously worth the trouble.

My gum tissue in my mouth is looking healthier than ever and doesn’t peel anymore. In my case I really believe the dietary issue has resolved my pemphigus (or is helping it go into remission), and I think it’s important to spread the word that these food factors may play an important role in a lot of pemphigus patients.
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Philippines - Dr. Benjamin Bince
Jose Reyes Memorial Medical Center,
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Online/Website
www.pemphigus.org/support.html

In the UK, the PV Network is a patient support group providing information and support for people living with pemphigus, their families and caregivers. For information and support call 020-8690-6462 or send a self-addressed, stamped envelope to:
PV Network
Flat C, 26 St. Germans Rd., SE23 1RJ
www.pemphigus.org.uk

RECENT JAMA STUDY SHOWS HOUSE CALLS MAKE COMEBACK
THERE’S A DOCTOR AT MY DOOR!

by Maria Godoy

Dr. Eric De Jonge of the Washington Hospital Center’s House Call Program drops in on an elderly patient at her D.C. home. It seems like an image from a bygone era: A physician steps up to the front door, black bag in hand, to check up on a patient at home. But the number of doctors who offer this type of personalized medical care is actually on the upswing.

At-home visits from the doctor remain rare for most Americans, but the service is becoming increasingly available to the elderly. An analysis published last month in the Journal of the American Medical Association found that house calls to Medicare beneficiaries rose by 40 percent from 1998 to 2004.

Some physicians are affiliated with house calls programs begun in recent years by hospitals such as the Washington Hospital Center, which Joseph Shapiro profiles in a related report. But the practice has also been taken up by one-man practices and physicians groups, the largest of which is the Visiting Physicians Association, which works with more than 25,000 patients in Georgia, Ohio, Wisconsin, Texas and Michigan.

“A lot of people seem to think of house calls as something from a past era in medicine,” says Dr. Steven Landers of Case Western Reserve University, who conducted the analysis. “But there are a lot of forces in the health-care system that seem to be making this service have a bit of a comeback.”

Reviving Past Practice with a 21st-Century Twist

House calls were the norm for physicians until the end of the 19th century, when the rise of hospitals and health insurance and improved transportation led to a shift to the office-based practice. By 1971, only 1 percent of U.S. doctors were making home visits to patients. The travel time involved made them economically impractical, and medical practices became focused on seeing a high-volume of patients daily.

According to Landers, the recent return to house calls in part reflects Medicare’s 1998 decision to boost what the government reimburses physicians for home visits by as much as 50 percent. For doctors, that made house calls less of a money-losing proposition.

And advances in technology have greatly expanded the arsenal of tools in a physician’s black bag. Beyond stethoscopes, visiting physicians now bring along portable X-ray machines, laptop-based lung tests and EKG, and fingertip-based diagnostic devices that can test for a range of measurements, including blood sugar and blood count levels.

“The laptop that I take into patients’ homes can be used as my electronic patient-record system,” notes Landers, who directs the house call program at Case Western Reserve’s department of family medicine.

A Grayer Patient Base

The renewed interest in house calls also reflects America’s aging population. In 2004, some 36 million Americans — 12 percent of the population — were age 65 and over, according the U.S. Census Bureau.

The toll on health care spending is significant. A May 2005 study by the Congressional Budget Office found that the sickest 5 percent of Medicare beneficiaries — the majority of whom have one or more chronic illnesses — account for 43 percent of total spending, or some $142 billion. Continued on page 8…
The frail elderly are less likely to leave home for routine checkups and more likely to seek treatment only once problems have become exacerbated, resulting in more visits to the emergency room and hospitalizations.

“The reason they are in the shape that they’re in is that they are relying so much on emergency room services,” says Constance Row, executive director of the American Academy of Home Care Physicians.

**Improving Health… and the Bottom Line**

According to the Centers for Medicare and Medicaid Services, the average hospital stay for a Medicare beneficiary age 65 and over is nearly six days, at a cost of about $3,500 per day.

Previous smaller-scale studies have suggested that giving these patients better care earlier can reduce costs down the road. For example, a 2004 study of a house call program in Las Vegas found a 62-percent drop in hospital stays among 91 elderly patients, resulting in a net savings of $261,225 per year.

In October, Medicare began a three-year pilot program to test the benefits of house calls on a national scale. The program involves 15,000 Medicare patients in Texas, California and Florida, who will receive free, 24-hour access to in-home care. Medicare officials will compare the medical records of those enrolled in the program to those in a control group to see whether house calls translate into cost savings and improved patient health.

**A Road Less Traveled**
The doctor’s office remains by far the place where most people get their care. (Fewer than 1 percent of Medicare beneficiaries received a house call in 2004.)

Committing to home-based care can be difficult for physicians. Private insurers rarely cover home visits. And while Medicare increased its reimbursements for house calls, these payments don’t cover the overhead costs of an office-based practice. So in order to turn a profit making house calls, doctors often must make them the exclusive focus of their practice and forego an office practice altogether.

“It’s not that physicians in private practice don’t know there’s a need,” Row says. “Everybody knows there’s a need. Its just that they can’t do it.”

Still, house calls have other rewards for physicians. Landers says he felt “overwhelmed” treating chronically ill patients in an office-based practice.

“I went into medicine because I like taking care of sick people and I like the challenge and reward of working with people,” Landers says. “It’s hard to do a good job in a high-volume office,” Landers says. “You see 15 patients or more in any half-day. I was looking for a way to build deeper patient relationships.”

The best part of his job now, he says, is getting to know the friends, family, and neighbors that make up his patients’ support network and community.

*We want to thank NPR for their permission to reprint the article (www.npr.org).*

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**ASA AWARDS $50K TO PEMPHIGUS RESEARCHER**

**CONGRATULATIONS DR. PAYNE**

The IPF would like to congratulate Dr. Aimee S. Payne, M.D., Ph.D., Clinical Instructor and Postdoctoral Fellow, at the University of PA, Philadelphia who has been presented with an award of $50,000 for her current work in pemphigus by the American Skin Association (ASA). ASA is a non-profit organization that provides support for research, education, prevention and treatment of skin disorders and cancers. ASA announced that it has granted Research Scholar Awards for 2006 to four promising investigators conducting research into the causes, prevention and treatment of skin diseases and cancers. Dr. Payne is one of the very deserving recipients.

Dr. Payne works closely with Dr. John Stanley, Chairman of the Dermatology Dept. at UPenn, and a member of the IPF Medical Advisory Board. Dr. Payne is studying the molecular mechanisms and genetics of pemphigus. Her goal is to find novel and potentially safer antibody-targeted therapies. Dr. Payne also participated in the IPF’s International Meeting, “Pemphigus 2005 Progress and Future Directions,” at the NIH in June, 2005.

Dr. Payne has also been rewarded with the Young Investigator Award from the American Academy of Dermatology (AAD) this year in San Francisco at their 64th Annual Meeting.

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Aimee S. Payne, M.D., Ph.D., University of PA, Philadelphia
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pemphigus antibodies to keratinocytes are changes in the cytoskeleton of keratinocytes with retraction of tonofilaments and breaking of the bond between tonofilaments and desmosomes culminating in shrinkage of the basal cells. The detachment of tonofilaments occurs before the desmosomes show any visible alteration or loss in adhesion.

Acantholytic cells are smaller than normal keratinocytes. They have partially collapsed and shrunk in size. That, rather than loss of adhesion, could cause the cells to come apart. The cells shrink more than desmosomes can hold them together. It would explain why cells separate while desmosomes still adhere tightly to each other and why desmosomes are being ripped from the cell surface once the shrinkage reaches a certain level.

THE BASAL CELL SHRINKAGE HYPOTHESIS FOR ACANTHOLYSIS IN PV

Our hypothesis is that the binding of PV antibodies to keratinocytes triggers signaling and intracellular events that collapse the cytoskeletal structure of basal keratinocytes with consequent shrinkage of these cells. Shrinking basal cells pull away from suprabasal cells (resulting in suprabasal acantholysis) and from each other (resulting in the “tombstone” appearance of basal cells). This explanation differs fundamentally from the current explanation for acantholysis, which argues the opposite that acantholysis occurs because desmosomes lose their adhesive properties. This difference is critical to develop better ways of treating pemphigus, as discussed below.

We further propose that acantholysis is limited to basal cells in PV because these cells shrink more than suprabasal keratinocytes when they interact with pemphigus antibodies. This could occur because basal cells are less rigid and shrink more readily than suprabasal keratinocytes when their cytoskeleton is altered, because their cytoskeletal structure is altered to a greater extent by the signaling event, or because different signaling events are triggered in basal cells.

These possibilities are supported by two observations. First, there is a sharp difference in the cytoskeletal composition of basal and suprabasal keratinocytes. Basal cells, but not suprabasal cells, express types 5 and 14 cytokeratins. Conversely, suprabasal keratinocytes express type 1 and 10 cytokeratins, which are absent in basal cells. As cytokeratins are intimately involved in the maintenance of cell size and shape, a differential effect of PV antibodies on the structure and/or rigidity of these two types of cytoskeletons could explain why cell shrinkage is limited to basal cells. Second, there is also a very sharp difference in the cell surface receptors expressed by basal and suprabasal keratinocytes.

For instance, basal cells express the M3 subtype of muscarinic acetylcholine receptors, which is lost when the cells leave that layer, whereas suprabasal muscarinic acetylcholine receptors are expressed by suprabasal keratinocytes. M3 Thus, activation of this or other receptors uniquely expressed on basal cells could account for the signaling events triggered by PV antibodies and for subsequent acantholysis being limited to basal cells.

PREDICTIONS

If correct, this hypothesis leads to predictions that can be tested experimentally to validate the hypothesis, to new
avenues to investigate the pathogenesis of pemphigus, and most importantly to new paradigms to treat the disease.

**Activation of a signaling pathway will be necessary for acantholysis**

The changes in cytoskeletal structure that precede acantholysis require that binding of PV antibodies triggers signaling events that initiate these changes. There is already evidence that such signaling occurs. Binding of pemphigus antibody to keratinocytes stimulates multiple biochemical intracellular events, including the phosphorylation and activation of various molecules, changes in the concentration of Ca2+ and in intracellular cyclic adenosine monophosphate/cyclic guanosine monophosphate ratios; and in the expression of certain receptors and markers of apoptosis and oncosis. Elucidating which of these are primary events in acantholysis should prove a fruitful area of investigation and blocking these events could prevent acantholysis.

**Energy may be required for acantholysis**

The signaling events that trigger changes in cytoskeletal structure may require energy. Hence, acantholysis may be prevented in vitro and in vivo by agents that block energy. Conversely, if acantholysis results simply from blocking Dsg adhesion then it should be an energy-independent process.

**Basal and suprabasal keratinocytes will differ in their property and/or response to pemphigus antibodies, independent of their expression of Dsg 1 or Dsg 3**

The hypothesis predicts that there will be differences between these cells in their rigidity, cytoskeletal structure, surface receptors, and/or in the signaling events, which are triggered by pemphigus antibodies.

**New therapeutic strategies to treat pemphigus**

If acantholysis results from activation of a signaling pathway, then agents that block it could improve the disease. The hypothesis shifts the search for novel approaches to treat pemphigus away from seeking more powerful immunosuppressive agents to agents that interfere with signaling pathways, cytoskeletal reorganization, or energy production. The involvement of these pathways in the pathogenesis of acantholysis may explain why the current immunosuppressive agents used to treat pemphigus, all of which have complex effects on cellular functions, can improve the disease while high circulating levels of pemphigus antibodies are still present, and why topical therapy that has no effect on antibody levels can be effective.

**CONCLUSIONS**

The hypothesis we propose and the ones currently accepted are not mutually exclusive. It may be that each contributes partially to the final pathology of PV. However, our hope is that by challenging current dogma and creating a new paradigm to view the disease, the hypothesis we propose will stimulate novel approaches to fully understand the causes of pemphigus and more importantly to treat the disease.

*Source: J AM ACAD DERMATOL, MARCH 2006, 516 Bystryn and Grando*

**NOTE:** The references were removed from this article to save on space. Full copies are available upon request.
9th ANNUAL PATIENT/DOCTOR MEETING

New York City, New York
September 16-17, 2006

Mark your calendars, pack your bags, and get ready to head for the Big Apple! The IPF is returning to New York City in for our 9th Annual Patient/Doctor Meeting. This year’s event will feature a gala celebration dinner in true New York style at The Water Club on Saturday evening. This spectacular celebration is nestled between two days of exciting and informative information presented by some of the foremost experts in the fields of pemphigus and pemphigoid.

For those arriving Friday night there will be a reception welcoming everyone to the meeting. The meeting itself will be held at the New York University’s College of Dentistry and refreshments will be available during breaks. The meeting will conclude around noon on Sunday allowing attendees plenty of time to return home from a weekend of support, knowledge, and friends. More information will be available at www.pemphigus.org and in future mailings. See you there!