

# the Rheumatologist

An official publication of the ACR and the ARHP serving rheumatologists and rheumatology health professionals

VOLUME 1 NUMBER 7  
JULY 2007



page 18

## DIFFICULT GOUT

Recent research and new management options for tough cases

>> By Robert Terkeltaub, MD

**G**out is arguably the best understood rheumatic disease. The diagnosis of gout is typically straightforward, and effective serum urate-lowering drugs and anti-inflammatory compounds are available to manage the majority of patients with gout. There has been a sense of complacency about gout—until recently. The last two decades have seen a remarkable resurgence of gout in the United States. This comeback has clinicians facing increasingly complex cases in which age, comorbidities, and concomitant medications impose difficult management decisions.

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### CLINICAL CUTTING EDGE

Updates on Sjögren's syndrome, myositis, and vasculitis

>> By Jane Jerrard

Looking for cutting edge clinical information? Here are some treatment advance updates from the ACR State-of-the-Art Clinical Symposium. See the June issue, p. 14 for more symposium summaries.

#### Strides in Diagnosing Treating Sjögren's

"One interesting change is the prevalence of Sjögren's," said Frederick B. Vivino, MD, a rheumatologist at Penn Rheumatology Associates and the Sjögren's Syndrome Center in Philadelphia. "Many experts consider it to be the second most common autoimmune rheumatic disease." In his presentation, "Sjögren's Syndrome: Comprehensive Diagnosis and continued on page 16

## INVESTIGATE THE COMMITTEE ON RESEARCH



page 15

The COR promotes basic and clinical research in rheumatology

>> By Jane Jerrard

*This is the second part in our ACR committee profile series.*

If you're not a researcher, you may not be aware of the work done behind the scenes by ACR volunteers dedicated to promoting new research in rheumatology. This article introduces what those volunteers do and why—and what it means for you and your practice.

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# Make Education A Priority

All rheumatologists need to train and support the specialty's next generation >> By Neal S. Birnbaum, MD

**W**ho will take care of my patients when I retire? As a clinician with an established rheumatology practice, I've found myself asking this question more frequently in recent years, and academic rheumatologists are the key to answering it. To solve some workforce issues—like who will take

over my practice—we need a larger supply of training programs, quality trainees to enter the programs, and academic rheumatologists prepared to teach.

## The Rheumatology Workforce

The ACR's 2006 Rheumatology Workforce Study,

which was completed by The Lewin Group, found that the median age of adult rheumatologists in 2005 was 51. These doctors are in their most productive working years now, but are set to retire within the next 15 to 20 years. Although 94% of these physicians currently treat patients, the size

of the overall patient population has grown dramatically in recent years. In many areas, rheumatologists are already having difficulty keeping up with demand for their services. Demand promises to increase even more as the large baby-boomer generation ages and requires more rheumatology care. While the demand for rheumatologists' services is projected to increase by 46% over the next 20 years, the number of practicing adult rheumatologists is projected to remain relatively flat, increasing by only 1.2% during the same period. Pediatric rheumatology doesn't face quite as steep a challenge in the coming years because a parallel surge in the patient population is not expected, but the trend toward excess demand is still there.

## Training Future Clinicians

One way to mitigate this excess demand is to expand the number of rheumatology training programs and fellowship positions, which would increase the supply of rheumatologists. Some progress is being made in this area. Over the past five years, an average of 150 rheumatology fellows have completed adult training programs each year, compared with an average of 115 fellows completing these programs each year over the previous five-year period.

But to attract and train new clinicians and researchers, training programs require skilled academic rheumatologists who are committed to rheumatology training, patient care, and research. Without this faculty, the recent growth in rheumatology training programs cannot be maintained. In a February 2007 report on the state of the rheumatology training environment, the ACR Committee on Training and Workforce Issues noted: "Academic rheumatology programs must successfully engage in a variety of inter-related but distinct activities to provide a quality, stable, and accredited fellowship program. These activities include clinical care, education, and research. The success of each of these activities is first and foremost dependent upon the presence of qualified academic rheumatology faculty."

## Research and Funding

Currently there are between 700 and 800 academic rheumatologists in the United States.<sup>1</sup> Academicians are generally required to conduct research and compete successfully for outside grant funding to cover at least part of their salaries. The balance must usually be covered by reaching relative value unit targets in the clinical setting, a challenge when balanced with a myriad of

research, teaching, and administrative responsibilities. According to the Lewin study, 73% of academic rheumatologists are required to cover more than half of their salaries through grants, yet many are finding it increasingly difficult to do so. In recent years, funding from the National Institutes of Health has declined substantially. The ACR Research and Education Foundation (REF) and other organizations have strengthened their own grant programs to help fill this gap. The REF "Within Our Reach" program—a major funding source for RA research—is one such example.

Sixty-six percent of academic rheumatologists in the Lewin study reported that it took five to 10 years to achieve independent investigator status. Further, more than 80% of rheumatologists who left academics within the last five years said they did so because of "lack of support" or "difficulty funding research." They were also attracted to non-academic careers by higher pay—the median compensation for private practitioners rose by 28.1% between 1998 and 2002, whereas compensation for academic faculty rose only 11.3% during the same period.<sup>1</sup>

When the Young Investigator Subcommittee of the ACR Committee on Research polled fellows about their career choices in 2006, they ranked salary among their chief concerns. It appeared from this survey that baseline interest in academia was strong but fellows were concerned about both salary and funding difficulties. The supply of new academic rheumatologists will almost certainly become limited if these financial issues are not addressed.

Funding issues must be tackled at both the local and federal levels. Institutions do not always recognize the value of rheumatology divisions or the downstream revenue they generate. As rheumatologists, we must correct these misperceptions when they arise. In addition, we should continue to advocate at a federal level for increased research funding and reimbursement for our services, both of which will contribute to the health of our academic divisions and therefore to the strength of the subspecialty.

In recent years, the ACR has met annually

with Stephen Katz, MD, PhD, director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, to advocate for increased rheumatology grant funding. These interactions complement existing congressional advocacy efforts by ACR members on proposed legislation that would affect research funding or medical education support. Rheumatologists in clinical practice think mainly about advocacy related to access to care and reimbursement issues, but lobbying efforts for research and training are equally important. In fact, in 2005 the ACR developed a rheumatology research agenda to guide our advocacy efforts in this area.

#### Make a Difference in Rheumatology's Future

The best way for you to positively affect the specialty's future is one relationship at a time. According to an unpublished 2006 ACR survey of U.S. adult and pediatric fellows, early exposure to rheumatology can strengthen interest in the field.<sup>2</sup> Nearly half of respondents stated that they first became interested in rheumatology in medical school. By far the most important factors that influenced fellows to choose rheumatology were a clinical mentor and a clinical rotation. Rheumatologists in academia have obvious opportunities to mentor trainees, but there are also opportunities for practitioners who are willing to mentor. The ACR organizes online mentoring networks and annual meeting informal mentoring sessions. Practitioners are always in high demand and short supply for these sessions. In addition, the REF offers preceptorships that require research and clinical mentors.

If we are worried about who will care for our patients when we retire, we should be equally concerned with the current challenges facing rheumatology training programs and those who run them. These programs will nurture the next generation of practitioners, researchers, and teachers who will support our patients at the bedside and develop new therapies that will improve patients' quality of life.

If our patients are to benefit from future therapies and research advances, we must be concerned about the research funding available to develop those therapies. We must advocate for adequate research funding as well as access to care and new therapies that improve patient outcomes.

Academic rheumatology issues are not only the concern of the academic rheumatologists in our midst. It is every rheumatologist's responsibility to ensure continued growth of the subspecialty and, as a result, the future care of their patients. THE RHEUMATOLOGIST

**Dr. Birnbaum is president of ACR. Contact him via e-mail at [birnbaum@rheumatology.org](mailto:birnbaum@rheumatology.org)**

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# the Rheumatologist

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# Another Question, Dear Readers

You wowed me with your gout suggestions—now let's talk quality >> David S. Pisetsky, MD, PhD

**Wow.** That's the first word that came to my mind as I read the responses to my recent "Rheuminations" article about a difficult gout case. The point of my article was that, even with a condition as seemingly simple as gout, complexity intrudes and can wreak havoc with even the established approach to patient care.

I felt a "wow" quality for several reasons. First and foremost, I was excited that readers took the time to write in and share their opinions. Writing is

of Siberia, and a host of companies hawking products to soup up my ELISAs. While there is some comfort in receiving any email—it is a sign that I am alive and someone thinks I am of value—I really want to hear from you, my readers. Did you like what I wrote? Did my words connect? Did I make sense? I am therefore thrilled by the volume of responses.

To the contributors whose replies are printed on page 8, I say a sincere and heartfelt "thank you" for reading and writing.

## "Best" Treatment Choice?

The second reason I felt a "wow" quality is the recognition that there are a slew of ways to treat gout in the patient I described. To eliminate any suspense, my preference would be a brief course of glucocorticoids. My preference here is most certainly not evidence-based, primarily be-

cause there is no evidence. Rather, I like a course of prednisone because it fits my treatment philosophy (not invasive if I don't have to be) and, on the occasions where I have had a similar clinical situation, it has worked very well.

Could I have justified a course of adrenocorticotropic hormone (ACTH)? Absolutely. Intra-articular steroids? Sure. Intravenous colchicine? Maybe or maybe not. On the basis of science, I think colchicine would be a great choice—it stops the inflammasome in its tracks—but the literature describes nastiness with this drug. I do not want to ravage the bone marrow for a joint problem that will likely go away by itself.

Now that I have discovered *compadres* out there who like to think about gout, I promise that soon you will have another case to chew on. I think that the next one will be harder and, frankly, I need advice.

The third reason I had a "wow" feeling concerns the ongoing discussion about quality that bears on the pay-for-performance initiative. From what I have been reading about the looming disaster on healthcare financing, however, we should also have a "pray-for-performance" initiative.

I would like to ask you some questions. Do any of the different approaches to the management of gout I described represent more quality than the others? Is there one approach that would be demonstrably better or more solidly grounded in data? Are they all equal?

My argument is that, within limits, every approach described in

fact represents quality and is based on experience, informed judgment, and a serious and sober assessment of the risks and benefits.

Some physicians may worry more about creating a hemarthrosis than others, but the extent of that worry likely relates to the number of joint taps performed previously with a patient on anticoagulation. If a physician has never had a bad outcome, he or she is likely to feel confident about sticking a needle in a joint when the INR (international normalization ratio) is 3.

On the other hand, if the physician had once caused a bleed, heard a colleague tell of a mishap, or been asked to serve as an expert witness in a lawsuit about such a circumstance, the needle would stay in its protective sheath, safely away from the red, throbbing joint.

In the same way, someone who has seen the blood count plunge after a slug of colchicine would likely never go that route again.

## Side Effects Aside

The issue is not just side effects.

If, on too many outings, prednisone tapers or doses of ACTH failed to calm the gout, trust me, it would soon be needle time. For both the specialty and the individual practitioner, therapy evolves. It is not set in stone. Physicians are not idiots. They do what works and they stay away from what harms.

While I am for quality improvement as much as anyone, I worry that we may be going in the wrong direction. Because the world has computers, there is an illusion that these machines—as slick and as fast as they are—can simplify, quantify, and render judgments on the decision-making in some of the knottiest and most vexing clinical situations that can be imagined. Even with the best algorithms in Google-dom, medicine is a tough nut to crack.

We are embarking on a great experiment in the delivery of healthcare. Like all good experiments, this one has a hypothesis and the hypothesis is that we can improve care by offering providers incentives for quality. That is a very worthy goal, but the big and untested assumptions are that we can measure quality and that the incentives are sufficient to change behavior—to the extent that behavior needs to be changed. Of course, we can change the equation by reducing reimbursement for lack of quality, but let's not go there right now.

At times like this, as I look at the future of my specialty, I feel like the patient who has gout. I am in fear. My anxiety is high and, in anticipation of the next attack (in this case, more regulations and bureaucracy), I worry that a wave of fearsome and flaming pain is rushing toward me.

Am I a realist or a Chicken Little when it comes to the future?

Please write in to [piset001@mc.duke.edu](mailto:piset001@mc.duke.edu). You helped me on my last case. Now help me on this one.

THE RHEUMATOLOGIST

Dr. Pisetsky is physician editor of *The Rheumatologist* and professor of medicine and immunology at Duke University Medical Center in Durham, NC.


## From what I have been reading about the looming disaster on healthcare financing, we should have a "pray-for-performance" initiative.

a lonesome calling and, while I send a blizzard of words into the world on printed pages and the electronic beams of cyberspace, until I get a reply, I live in a vacuum.


Via countless e-mails, I hear regularly from Medscape, lonesome Olga from the frozen steppes

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## LETTERS TO THE EDITOR | FEEDBACK FROM OUR READERS

In May's "Rheuminations" column ("Make Peace with Complexity," p. 6), we asked how you would manage gout in a patient with multiple comorbidities and complications. (See the full description at right.) We received an overwhelming number of letters recommending a range of treatment approaches. We've published a selection of those responses here, and we want to thank everyone who wrote in. Keep those letters coming!

—The Editors

#### Readers' Treatment Strategies

Tylenol #3. Actually, I would consider a steroid taper, also, since the immunosuppression issue is probably overstated.

J. Stephen Thompson, MD, Rheumatologist  
Arthritis Center of the Rockies, Loveland, Colo.

#### SEND US YOUR CLINICAL CASE

Want to hear how your colleagues would treat a challenging case from your practice? Send details to [dantolin@wiley.com](mailto:dantolin@wiley.com). We may publish your case in an upcoming issue of *The Rheumatologist*.

No non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine. Ice works well for pain—so do narcotics, though with his respiratory status, I'm not so keen on them. I favor an intra-arterial steroid. If you're nervous about causing a hemarthrosis, perhaps give it under ultrasound guidance. I've never had a problem with intra-articular bleeding in patients on warfarin with either joint injection or aspiration.

My counter-case to yours was a file I was asked to review as a medicolegal expert: A young man with

congenital heart disease on warfarin went to the emergency room with one swollen, painful joint. Aspiration was not done because he is on warfarin. Instead the doctor stopped the drug, thinking he had a hemarthrosis. While off warfarin, he stroked out from a cardiac embolus. Later he had recurrent acute monoarthritis that turned out to be gout! The emergency room doctors were sued.

My literature review for that indicated that most who considered the matter felt it was safe to aspirate or inject a joint even in an anti-coagulated patient. Some suggested a smaller caliber needle as a precaution and increased pressure on the site after.

Philip Baer, MDCM, Rheumatologist  
Malvern Medical Arts Centre, Toronto, Ontario

What I would do for the patient, in order of preference:

1. Intra-articular steroids (as long as I felt the knee was not infected);
2. Adrenocorticotropic hormone (ACTH); or
3. Systemic corticosteroids if the patient is adequately covered for infection with antibiotics, but I would try a low to moderate dose (20 mg to start with rapid taper). This option is not very good, not only because of infection concerns but also because it could cause fluid retention.

Bonita Libman, MD, Associate Professor of Medicine  
University of Vermont, Burlington

I would have no problem injecting the knee with corticosteroids with an INR (international normalization ratio) around 3. I have injected many joints under these circumstances without any complications (just have an experienced hand perform it). Intravenous (IV) steroids can also be used.

I think that steroid use for brief periods is safe (again, from personal experience). How many chronic obstructive pulmonary disease (COPD) patients with exacerbations from pneumonia are given IV steroids without terrible consequences? I feel that steroids are given a bad rap and in short bursts, as used for treating gout—especially with NSAIDs contraindicated—they are a viable option.

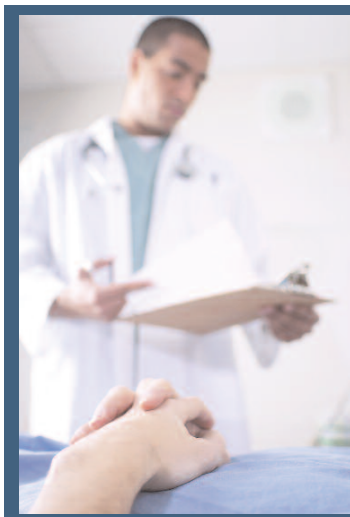
With creatinines of 1.5 to 1.8 in a similar setting, IV colchicine can be tried at 1 mg and possibly repeated in 24 hours. I have used this administrative route many times in the past with good results. The referring attending is always reluctant to use it as well and, unfortunately, formularies are following suit.

Steve Fink, DO, Chief of Rheumatology  
VA Medical Center, Seminole, Fla.

The patient most likely has gout, but he could have a septic knee. I feel you have no choice but to aspirate his knee. I have aspirated and injected hundreds of joints in patients on coumadin. To my knowledge, none has developed a hemarthrosis. Given your patient's circumstances I would have no problem aspirating his knee. If crystals were seen and the gram stain is negative, I would then treat with intra-articular steroids.

IV colchicines are not on formulary in many hospitals and a bad idea with elevated creatinine. ACTH is not much different than exogenous steroids, but would be my second option.

James S. Cohen, MD, Rheumatologist  
Arthritis Care Center, Indianapolis, Ind



### THE PATIENT

- > Seventy-two-year-old man with heart failure;
- > Taking oxygen, furosemide, and coumadin;
- > Ejection fraction of 20, creatinine of 2.5, blood urea nitrogen of 60, INR near 3; and
- > Fever and an infiltrate on chest X-ray that could be pneumonia, atelectasis, or pulmonary congestion.

logic dose of systemic corticosteroid (prednisolone <8mg/d) produces immunosuppression and might be sufficient for the acute attack. If your patient had a bronchospastic component, the pulmonary specialist would likely have recommended >2 mg/kg Q8hr with impunity. I would also give colchicine 0.6 mg BID for prophylaxis.

Matthew O. Swartz, MD, Rheumatologist  
Prince William Hospital, Manassas, Va.

I suggest either a moderated dose of systemic corticosteroids (i.e., prednisone 10 to 15 mg daily with

a tapering regimen over two weeks) with continued close monitoring of fluid status or, if a clinician were feeling cavalier (vs. naive) enough or truly believed in his or her dexterity with a needle, an intra-articular corticosteroid injection to the affected gouty joint.

I recently had a similar situation and was able to maneuver a pleasant elderly woman out of it with the former tactic (though she had several affected gouty joints). Additionally, I have previously provided intra-articular corticosteroid injections to gouty joints in individuals who were anti-coagulated with thankful success. (Whether I possessed the correct thought process in attempting such a procedure under those conditions can be debated.) But I count my lucky stars that those individuals were able to avoid any complications from the procedure.

Lastly, I would also determine which option the treated individual prefers and/or is comfortable with and base my ultimate decision on their preference.

Dennis M. Liu, MD, Rheumatologist  
Tuality Community Hospital, Hillsboro, Ore.

I have treated similar patients by injecting the joint with a 27-gauge, 1.5-inch needle. No problem with hemostasis.

Benjamin Lechner, MD, Rheumatologist  
Hallandale, Fla.

Your patient was characteristic of 95% of those we now see, and meets "Lightfoot's Criteria for Gout Needing a Rheumatologist":

1. Veteran;
2. Heavy smoking history;
3. Bruits in at least six sites, including at least one renal artery;
4. Ejection fraction less than or equal to 25%;
5. Creatinine around 2.5mg/dL on his or her best day;
6. On coumadin for at least two of the following reasons:
  - a. Ventricular dilation with akinetic areas;
  - b. Recurrent thrombophlebitis;
  - c. Recurrent arterial thrombi from their plaques; and
  - d. An artificial heart valve.
7. Enough exposure to alcohol to compromise easy regulation of prothrombin times; and
8. Bronchopneumonia from tobacco-related lung disease.

In that setting, every drug for gout is contraindicated. Therefore, the clinical decision-making is easy. You use the drug that is least worst.

I would use, briefly, steroids systemically. (Many are already on them for COPD.) I would also hold coumadin for a few days to tap the joint, as a septic joint in the face of pneumonia is a real possibility.

Robert Lightfoot, MD, Professor of Medicine, Rheumatology Division  
University of Kentucky College of Medicine, Lexington

THE RHEUMATOLOGIST

I think I'd vote for an intra-articular injection of steroids as long as some antibiotics were already on board, and I'd strongly consider colchicine 0.6 QOD or Q3D to prevent future flares, as the likely trigger of lasix with congestive heart failure is going to continue. Perhaps the risk of an intra-articular bleed with an INR of 3 is less than the likely morbidity of ensuing inflammation in that knee.

Jonathan Samuels, MD, Director, Clinical Immunology Laboratory  
NYU Hospital for Joint Diseases, New York City

I would have given IV colchicine, 1 mg x1, to your elderly man with gout on top of multisystem failure.

Ronem Roubenoff, MD, MHS  
Senior Director, Immunology Medical Research  
Biogen Idec, Inc., Cambridge, Mass.

In the old days, acute attacks were attenuated with ACTH and I have seen this work on several occasions. In your case, this might be like flogging a very tired horse. I doubt anyone could argue that a low, physio-

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The REF offers an extensive awards and grants program with research and education opportunities for clinicians, students, health professionals, researchers and academic institutions. Through these programs, the REF can usher in tomorrow's rheumatologists and rheumatology health professionals while sustaining today's practitioners and researchers.

To learn more about the awards and grants offered, or to apply, please visit [www.refawards.org](http://www.refawards.org). Applications are due August 1, 2007.

>>> All applications must be submitted online.



AMERICAN COLLEGE OF RHEUMATOLOGY  
RESEARCH AND EDUCATION FOUNDATION

# From the COLLEGE

## NEWS FROM THE ACR AND THE ARHP

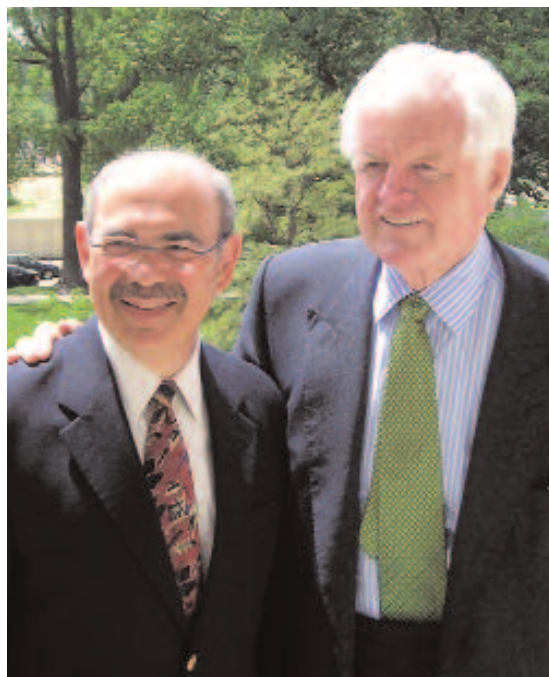
### ADVOCACY IN ACTION

#### ACR Board Lobbies Congress

ACR Board of Directors members recently spent time in Washington, D.C., discussing rheumatology-related issues with members of Congress, including Sen. Edward M. "Ted" Kennedy (D-Mass.). The senior senator from Massachusetts is the chair of the Senate Health, Education, Labor, and Pensions Committee, which oversees health legislation that affects rheumatologists.

Sen. Kennedy was well informed on issues affecting rheumatologists and their patients. As the original sponsor of the Arthritis Prevention, Control, and Cure Act (S.626/H.R.1283), he supports the ACR on one of its most important legislative priorities. Sen. Kennedy understood each concern the board members raised, could relate to the issue personally, and offered his assistance. The board members from Massachusetts and ACR President Neal S. Birnbaum, MD, were fortunate to spend time and initiate a relationship with Senator Kennedy.

Prior to meeting with members of Congress, ACR board members attended a dinner with keynote speaker Rep. Frank Pallone, Jr. (D-N.J.), chairman of the House Energy and Commerce Subcommittee on Health. Rep. Pallone's committee controls the majority of healthcare legislation in the House. He revealed the congressional healthcare priorities in the House for 2007: Reauthorization of the State Children's Health Insurance Program, which



ACR President Neal S. Birnbaum, MD, (left) and Massachusetts Sen. Edward M. Kennedy.

was started in 1997 and is scheduled to end on September 30, 2007; and implementing a temporary fix for the scheduled 10% cut to the Sustainable Growth Rate (SGR).

He also shared with the board that the proposed 10% cut to 2008 Medicare payments likely will not be implemented; Congress will pass a temporary fix, with a goal of more comprehensive reform to the SGR (the system that determines Medicare reimbursements) by the end of 2008.

During the Capitol Hill visits, the board of directors along with ACR senior staff met with more than 60 offices to discuss current ACR legislative pri-



From left to right: Sen. Edward M. Kennedy; Jonathan Kay, MD; Daniel Hal Solomon, MD; Paul Romain, MD; and Neal S. Birnbaum, MD.

orities. Along with urging co-sponsorship of the Arthritis Act and fixing the flawed SGR system, the ACR asked Congress to revoke the Deficit Reduction Act of 2005 that requires cuts for imaging reimbursements (specifically DXA scans) and also to increase funding for National Institutes of Health research programs.

Establishing relationships with members of Congress, like Sen. Kennedy and Rep. Pallone, will continue to increase rheumatology's presence in Washington and allow our voice to be heard.

### PRACTICE UPDATES

#### ACR Unites with AMA to Correct SGR

Fair Medicare reimbursement is of great concern of physicians today. During the past few years, the SGR has called for damaging cuts to physician payments. Each year, however, Congress has placed a temporary fix on the scheduled cuts.

The payment cut for 2008 is scheduled to be 10%. This would be the most devastating cut to date for all practicing physicians. Therefore, the ACR, along with the American Medical Association (AMA) and 85 other physician and health professional organizations, recently signed a letter to Congress that includes these recommendations for 2007 Medicare SGR legislation:

- 1> The SGR should be repealed and replaced with an updated system that reflects increases in physicians' and other health professionals' practice costs.
- 2> Congress should support initiatives by organizations representing physicians and other health professionals to bridge gaps in care and ensure appropriateness of services provided to Medicare beneficiaries.
- 3> If immediate action is not possible, Congress must:
  - > Establish by law a transition plan and completion date for eliminating the SGR;
  - > Provide positive physician/health professional updates by statutes for each year until the repeal takes place;
  - > Stabilize payments for a minimum of two years;
  - > Fully fund the positive updates; and

> Urge the administration to removed physician-administered drugs from the SGR and make other refinements.

4> The transitional 2007 Medicare Physicians Quality Reporting Initiative should be re-examined before being expanded in future years.

Band-aids to SGR are not enough; there must be a legislative fix. Finding a fair solution to the Medicare reimbursement payment issue is a top legislative priority of the ACR, and it will continue working collaboratively with the AMA and other physician and health professional groups and utilizing its grassroots network to ensure fair reimbursements for physicians in the future. Contact your congressional representatives today and voice your support for these recommendations.

### TIPS ON TRIGGER-POINT INJECTION CODES

Confused about how to code trigger-point injections? Here are some hints for correct coding.

There are two CPT4 codes used for this procedure:

- > 20552: Injection(s); single or multiple trigger point(s), one or two muscle(s); and
- > 20553: Single or multiple trigger point(s), three or more muscles.

These CPT4 codes are based on the number of muscles affected, not the number of injections given.

**Example:** Mary, age 51, comes in for a follow-up visit for her diagnosis of rheumatoid arthritis. The physician or practitioner does an examination, including a review of symptoms, takes a history of present illness, and makes a medical decision of moderate complexity. The physician or practitioner performs an appropriate level of an E/M visit. During the visit, the patient complains of stiffness and swelling in the hands, elbows, and neck. Also, an X-ray of the left hand (two views) is taken and read during the visit. Because of the severity of the swelling, the physician or practitioner decides to give the patient six trigger-point injections.

**Correct Coding:** 99213-25, 20553, 73120/LT



**Incorrect Coding:** 99213-25, 20552x6 or 99213-25, 20552, 20553x5, 73120

These are common mistakes when billing for trigger-point injections, but correct coding will help reimbursement.

If you have any questions about this or other coding and reimbursement issues, contact the ACR's certified professional coders Melesia Tillman at [mtillman@rheumatology.org](mailto:mtillman@rheumatology.org) or Resaee Freeman at [rffreeman@rheumatology.org](mailto:rffreeman@rheumatology.org) or by phone at (404) 633-3777.

### Be Aware of New Waived Tests

Keeping current on changes to laboratory certifications for common lab tests can save your practice time—and money. Since the passage of the Clinical Laboratory Improvement Amendments (CLIA) in 1988, all health-assessment laboratory tests are ranked for complexity, and their complexity dictates which labs can process Centers for Medicare and Medicaid Services (CMS)–reimbursed tests. In accordance with CLIA, each laboratory facility must register with CMS to receive a CLIA certification. There are five certifications, each with differing degrees of complexity, listed from least to most complex: Certificate of Waiver, Certificate of Provider-Performed Microscopy Procedures, Certificate of Registration, Certificate of Compliance, and the Certificate of Accreditation.

Of the five, Certificates of Waiver have the most frequent changes to the tests certified labs can perform. This is because physician groups frequently request that CMS review and re-classify tests so that they may be performed by waiver-certified facilities. Once new “waived” tests are approved, CMS should immediately contact its contractors to ensure proper claim processing, but sometimes this communication is delayed.

Physicians who send lab tests out for processing should know which tests require only a waiver-certified laboratory; CMS contractors may not be aware of changes and may initially deny a claim for a recently re-evaluated test sent to such a lab. If a physician is well informed, he or she can appeal such denials and have a better chance of success. Physicians who have in-office “waiver-certified” laboratories should also be aware of new tests and procedures their lab can perform.

Because the list of tests that can be performed at Certificate of Waiver–certified labs changes frequently, physicians should monitor it on a monthly or quarterly basis. Visit [www.cms.hhs.gov/transmittals/downloads/R1195CP.pdf](http://www.cms.hhs.gov/transmittals/downloads/R1195CP.pdf) for more information.

[continued on page 12](#)

## CODING CORNER!

### July's coding challenge:

A 68-year-old female diagnosed with rheumatoid arthritis is scheduled for an arthrocentesis of the shoulder and the elbow. This is the third joint injection in a series of four. At the patient's request, the physician is injecting Enbrel. How would you code this? **See page 17 for the answer.**

## REGISTER ONLINE FOR THE ANNUAL SCIENTIFIC MEETING

Registration is underway for the ACR/ARHP Annual Scientific Meeting in Boston. More than 10,000 rheumatologists and health professionals from around the world will converge in Boston November 6–11 to share best practices and learn about exciting innovations in rheumatology science and education. Log on to [www.rheumatology.org/annual](http://www.rheumatology.org/annual) to access the tentative program, registration information, and much more. Register early to ensure access to sessions with limited seating. We look forward to seeing you in Boston!



### “Meet the Professor” Sessions and Workshops for Trainees

The ACR offers several “Meet the Professor” sessions and workshops where trainees can interact and consult with respected clinical teachers with expertise in a particular area. Fellows and other trainees have registration preference for these sessions. Space is limited, and these sessions require a separate registration fee. Visit [www.rheumatology.org/annual](http://www.rheumatology.org/annual) for more information and to register.

#### THURSDAY, NOVEMBER 8

##### ACR Meet the Professor

- > 024 Emery—Pediatrics: Pediatric Rheumatology for Adult Rheumatologists
- > 025 Greenwald—Osteoporosis: Pitfalls in Bone Density Testing
- > 027 Isenberg—SLE: Novel Treatments
- > 036 Wallace—Antiphospholipid Syndrome

##### ACR Workshop

- > 018 Schumacher, Jr., Chen, and Clayburne—Synovial Fluid Analysis & Crystal Identification

#### FRIDAY, NOVEMBER 9

##### ACR Workshop

- > 092 Bruyn and Schmidt—Musculoskeletal Ultrasonography: Basic

##### ACR Meet the Professor

- > 080 Ardoin—Caring for the Young Adult with Rheumatic Disease
- > 082 Callen—Dermatological Manifestations of Rheumatic Diseases
- > 084 Higgins—Pediatrics: Difficult-to-Treat Juvenile Idiopathic Arthritis
- > 090 Silver—Scleroderma: Systemic Sclerosis

#### SATURDAY, NOVEMBER 10

##### ACR Meet the Professor

- > 136 Bingham, III—RA: Difficult Cases
  - > 137 Carlson—Pain: Soft Tissue Rheumatism
  - > 139 Davey—Immunology: Basic Immunology for Clinical Rheumatology
  - > 142 Langford—Vasculitis: Update
  - > 156 Baraf—Rheumatology Practice 101: Starting Out in Practice for the Graduating Fellow
  - > 162 Levy—Pediatric Systemic Lupus
  - > 167 Von Scheven—Pediatrics: Pediatric Rheumatology for Adult Rheumatologists
- ##### ACR Workshops
- > 129 Deodhar and O'Rourke—Joint Injection Techniques
  - > 151 Deal—Osteoporosis: Focus on DXA Interpretation
  - > 152 Troxell—Renal Histopathology in SLE and Vasculitis
  - > 155 Murphey—Musculoskeletal Imaging



## ARHP Angle Advocacy: An essential component of professional practice

>> By Karen L. Kerr, MSN, NP, CPNP, APRN-BC

In our challenging and cost-conscious healthcare environment, advocacy is an essential skill for all health professionals. As rheumatology health professionals, we advocate for our patients with insurers, institutional administrators, employers, and teachers. To bring about needed healthcare reforms, we must also learn to be effective political advocates.

Political advocacy may seem daunting, but it is a skill that we all can master. The ACR and ARHP have developed tools to help busy health professionals become more effective advocates. Through the Political Advocacy page on the ARHP Web site, ARHP members can learn about important issues affecting rheumatology patients, practice, and research, and access tools for communicating with their legislators about these issues.

The ACR/ARHP Grassroots Action Center offers a variety of ways members can become involved in the College's advocacy efforts. The Legislative Action Center provides tools for identifying your senators and representatives, information about current legislation ACR is

advocating for, and tools to help you compose a letter to fax or e-mail to your legislators. Rheumatology health professionals have a wealth of knowledge and expertise to share with their congressional leaders.

Other ways to be an effective advocate include:

- > Visit your legislator in his or her home district. Face-to-face meetings with members of Congress can be very effective. Many congressional leaders hold town meetings in their home districts, which afford an excellent opportunity for you to let them know how specific issues or policies affect rheumatology patients and practice. To schedule an appointment to meet with your senator or representative, contact your legislator's district office.
- > Participate in the ACR's Advocates for Arthritis program. During this annual spring event in Washington, D.C., ACR and ARHP members and patients meet with legislators or their staff to discuss current issues affecting rheumatology patients and practice. (See “Rheumatology Goes to Washington,” May 2007, p. 14, for highlights from this spring's Advocates for Arthritis program.)

> Display an ACR advocacy recruitment easel in your office's waiting room. These contain pre-addressed postcards that patients can mail to the ACR to become involved with ACR's advocacy efforts.

> Joining the ACR Advocacy List Serve. The Advocacy List Serve is a forum for communicating updates on current legislative and regulatory issues affecting rheumatology practice, research, and patients. Members can subscribe to this list serve to increase their political awareness and keep on top of important issues.

Advocating for our patients and our practice is too important to leave for someone else to do. Advocacy is an essential component of professional practice and the responsibility of every health professional. I invite you to join me and add your voice on Capitol Hill. Together we can make a difference.

**Karen Kerr is president of the ARHP and a pediatric nurse practitioner at Children's Hospital of Michigan in Detroit. Contact her via e-mail at [arhp@rheumatology.org](mailto:arhp@rheumatology.org)**

From the COLLEGE continued from page 11

## PATIENT FACT SHEET

### Antiphospholipid Antibody Syndrome

A recently identified autoimmune disorder, antiphospholipid antibody syndrome (APS) mainly affects young women between age 30 and 40. Those affected by APS may otherwise be healthy or have an underlying disease such as systemic lupus erythematosus (SLE).

APS is "an autoimmune disease associated with frequent clotting in arteries and veins and/or fetal losses," according to fact-sheet author Pier Luigi Meroni, MD, professor of rheumatology at the University of Milan in Italy. "The clotting results from the presence of proteins in the blood called antiphospholipid autoantibodies formed against the person's own tissues. In circulation, these autoantibodies are able to interfere with some mechanisms of coagulation, leading to clot formation or thrombosis."

It is not completely clear why patients develop these autoantibodies. Some evidence suggests that environmental factors—such as infections in the presence of a predisposing genetic background—play a role in triggering autoantibody production.

Dr. Meroni also notes that "the need for a long-term oral anti-coagulant therapy significantly affects the lifestyle of the patients, creating the need for regular controls for the anticoagulation effect and special attention paid to the diet and to situations at risk of bleeding, such as falls." Correcting thrombosis risk factors (diabetes, hypertension, hypercholesterolemia, obesity, smoking, and estrogen therapy for menopause or contraception) is mandatory in APS patients and significantly affects lifestyle.

Preventive treatment for obstetrical manifestations—such as heparin injections and low-dose aspirin—is quite effective. The majority of the women can eventually have healthy babies.

For more details on diagnosing, treating, and living with APS—or for information about other patient-education materials—visit [www.rheumatology.org/public/factsheets](http://www.rheumatology.org/public/factsheets).

## ACR Journal Tables of Contents to be Sent Electronically to Members

Starting next month, ACR and ARHP members will receive e-mail notification when new issues of *Arthritis & Rheumatism* and *Arthritis Care & Research* have been published online. For added convenience, these e-mails will include the complete table of contents for each new issue. Any member who does not wish to receive e-mailed tables of contents may unsubscribe at any time.



Since outreach began in March 2006, more than \$17 million has been raised, including gifts from the ACR, research-minded individuals, and our industry supporters.

For more information about the "Within Our Reach" campaign, including a list of the grant recipients, visit [www.rheumatology.org/ref/withinourreachcampaign.asp](http://www.rheumatology.org/ref/withinourreachcampaign.asp).

treatment, if at all," she says. "I was also informed about potential and possible side effects of the drugs I would be taking, and that was almost as scary as getting my RA diagnosis in the first place."

Enis knows that she's lucky to have responded well to the drug therapy, and she's also optimistic that she hasn't experienced any major side effects from therapy so far. RA isn't as taxing on her body anymore, but the disease still weighs heavily on her mind.

"I will probably be on drug therapy for the rest of my life, and I have accepted that," she says. "But I don't want my daughters or my grandchildren to ever have to deal with this disease or worry about the long-term effects of treatment. I won't accept that for their futures."

She and her husband decided to look for ways to support advances in RA research and treatment. When they learned about the ACR REF's "Within Our Reach" campaign from Enis' rheumatologist, they immediately decided to lend their support.

"I would love to think that there could be a cure for RA available for the next generation of patients," she says. "My rheumatologist saved my life. I am indebted to the rheumatology community, so I am more than glad that Hunter and I are able to support their efforts to fight and defeat this disease."

## REF NEWS

### First Round of "Within Our Reach" Grants

The ACR Research and Education Foundation (REF) "Within Our Reach" campaign awarded approximately \$6 million to 15 recipients this month.

More than 70 applications were received for the first round of research grants funded by the national, multi-year, \$30-million fundraising campaign aimed at accelerating innovative research for RA. The peer-review process lasted two months, with more than 40 reviewers nationwide evaluating the applications.

The first round of grants has three categories:

- **Innovative basic research:** Support for exploratory research on new issues or approaches for which there is currently an insufficient theoretical or empirical basis for a competitive research project application;
- **Translational research:** Support for established independent physician-scientists dedicated to translational research—the two-way transfer between work at the laboratory bench and patient care; and
- **Clinical practice:** Support for issues focused on directly affecting patient access and quality of care in clinical rheumatology practice.

"Within Our Reach," the largest private fundraising campaign in the REF's history, is driven largely by major gifts from a diverse donor base.

### Support for a Future without RA

Shirley Enis of Jacksboro, Texas, has decided to get involved with "Within Our Reach" because the campaign has the capacity to improve RA patients' quality of life, alleviate long-term effects of RA, and ultimately ensure that future generations can enjoy life without RA.

"We always have a big family Thanksgiving, and I look forward to fixing a huge meal for everyone," says Enis. While Thanksgiving is usually a time of joy for the Enis family, a Thanksgiving about five years ago was a time of uncertainty and concern.

"It was getting harder and harder to use my hands, and pain was becoming almost a constant," Enis recalls. "By Thanksgiving of that year, I could barely lift a pot or pan—let alone prepare the feast I wanted to share with my family. I knew something was wrong. I was constantly in pain and starting to lose hope."

After seeing a rheumatologist, Enis was diagnosed with early onset RA and qualified to participate in a research group testing new drug therapies. "Almost immediately I noticed a difference," she says. "My pain began to subside and my strength returned. I started feeling normal again."

For many, this would be the story's happy ending, but not for Shirley and her husband, Hunter. While she is pleased with how the medications have helped her during the last five years, she is the first to acknowledge that she is one of a small number of success stories.

"I was told before entering the clinical research trial that some patients do not respond as well to

### "WITHIN OUR REACH" LEADERSHIP SUPPORTERS

The REF gratefully acknowledges the following companies and individuals who have demonstrated leadership support for the "Within Our Reach" campaign. This information was current as of May 1:

#### Pinnacle (\$5 million+):

- Abbott Immunology
- American College of Rheumatology
- Bristol-Myers Squibb

#### Partner (\$1 million+)

- Genentech, Inc.,

#### Milestone (\$250,000–\$499,999)

- J. Peter Cahill (in memory of Carol K. Cahill)
- Shirley and Hunter Enis
- Betsy and John McLinden

#### Visionary (\$100,000–\$249,000):

- Myles McDonough
- Anonymous, Ft. Worth, Texas

## AWARDS FOR STUDENTS AND EXPERIENCED PHYSICIANS

The REF offers an extensive awards program with research and education opportunities for all facets of the rheumatology profession, including awards specifically for rheumatology students and experienced physicians. Below is a partial list of the programs available.

**ACR REF/Abbott Medical/Graduate Student Achievement Award:** Recognizes medical or graduate students for significant work in the field of rheumatology;

**ACR REF Academic Reentry Award:** Assists fully trained basic and clinical research scientists to resume their research careers after taking at least a one-year hiatus; and

**ACR REF/Amgen Pediatric Rheumatology Visiting Professorship Program:** Places a board-certified professor of pediatric rheumatology with an academic institution where no established pediatric rheumatology expertise exists for a period of one to three days.

Application materials for all awards are available online now and applications are due on August 1, 2007. For more information, visit [www.rheumatology.org/REF](http://www.rheumatology.org/REF).

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## ACR IN DEPTH

# The Quality Movement Explained

**T**o Err is Human," published by the Institute of Medicine in 1999, set off a firestorm of quality initiatives when it announced that at least 44,000 to 98,000 people die in hospitals every year because of medical errors. The first quality initiatives, which were aimed at hospitals, have now trickled down to physician practices. For two years there have been reports of payors moving to a pay-for-performance system or value-based purchasing.

This past December, Congress passed the 2006 Tax Relief and Healthcare Act. One component of the legislation was the Physician Quality Reporting Initiative (PQRI), which will pay physicians a bonus for reporting quality measures along with Medicare claims. The program provides a 1.5% lump-sum payment based on the quality of patient care rather than the quantity or nature of services rendered. (See "Medicare Quality Movement Reaches Clinicians," June 2007, p. 1 for more information on PQRI.) PQRI is one example of actions taken by payors in recent years to hold providers more accountable for the care they give and to tie it directly to compensation. This trend could alter the way Medicare payments are calculated, so physicians should join the quality movement early.

## Quality and Medicare Reimbursement

Congress and the CMS are struggling with the flawed Medicare Physician Fee Schedule and providing appropriate reimbursement to physicians (see "ACR Unites with AMA to Fix SGR," p. 10). The Balanced Budget Act of 1997 enacted the SGR that was originally intended to control the growth in Medicare physician spending. The Medicare Payment Advisory Commission (MedPAC, also established by the Act) advises Congress on the Medicare program and offers testimony about the SGR and the Medicare program. In March 2007, MedPAC reported that, "the SGR is widely considered to be flawed; it neither rewards physicians who restrain volume growth nor punishes those who prescribe unnecessary services."<sup>1</sup> Congress and the CMS now realize that the SGR needs to be fixed. The current fee schedule is based on the quantity of resources consumed rather than quality or value. CMS has asserted that it is on a path to "transform Medicare from being a passive payer to an active purchaser" through value-based purchasing programs like PQRI. According to the CMS, the goal of PQRI is to "encourage higher quality and avoid unnecessary costs to enhance the value of care."

The ACR Government Affairs Department continues to stress that a new formula must be enacted without further short-term fixes. A new formula must be created, but what will it cost? Many suggested alternate formulas have large price tags and pay practitioners regardless of the quality of the service. Medicare spending has increased by 9.3% while the gross domestic product only increased 6.5% between 1980 and 2004. A recent MedPAC report stated that, "despite this rapid growth in spending, a large body of evidence suggests the increased cost of healthcare has not come with a corresponding increase in quality."<sup>2</sup> MedPAC has included recommendations to Congress that relate to quality, efficiency, health information technology, and physician payment reform.

Pressure to move toward value-based purchasing and away from fee-for-service healthcare

has also surfaced from outside CMS in recent years. President George W. Bush has repeatedly spoken in support of the idea. He issued an Executive Order in August 2006 requiring transparency in quality measurement and pricing, national standards for health information technology, and programs that promote quality and efficiency. In addition, he has included allowances for quality-related programs in his past three annual budgets. In the private sector, health plans and employer coalitions like Bridges to Excellence have established pay-for-performance or pay-for-reporting programs. Several payors have established physician ranking systems to allow patients to choose a physician based on their "star ranking."

## ACR Approach to Quality

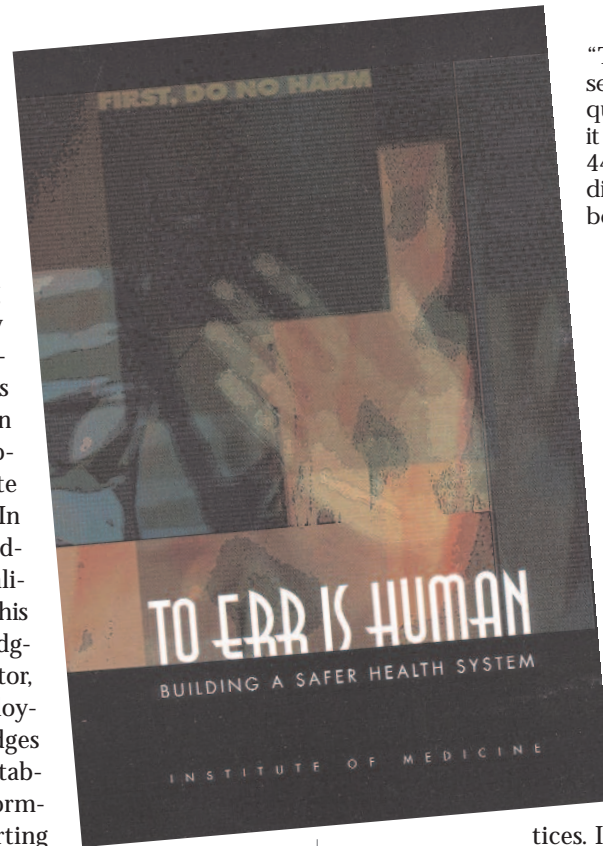
The quality movement is well underway, and PQRI is but one facet of it. In the midst of such a changing environment, what should the ACR do?

Some advocate that, on principle, the ACR and its members should refuse to be involved in any program that measures physician performance. Yet ACR members are ultimately responsible for delivering high-quality patient care. If members indeed provide such care, then there is no reason to object to being held accountable for it. Others suggest that the ACR and its members take no action and wait for the current quality "trend" to pass. Yet evidence suggests that healthcare providers will be required to participate in some form of quality measurement in the near future, if they are not already involved.

Still others recommend that the ACR get involved in the quality process and influence it from within. The ACR has chosen this path. Its goal is to become increasingly involved in the current quality movement so that the ACR and its members have as much input as possible into the systems by which rheumatologists and rheumatology health professionals will be evaluated. The ACR believes that physicians and health professionals should only be evaluated against evidence-based measures developed by rheumatology professionals. Additionally, reporting data for quality measurements should be rewarded with financial incentives meaningful enough to encourage providers to participate. PQRI uses evidence-based measures, some of which were developed in collaboration with the ACR. It also provides financial compensation for participation, albeit minimal; the ACR will continue to advocate for increased payment for those who participate in the program.

## Why Get Involved?

ACR members have much to gain by getting involved in PQRI—especially at this early stage.



"To Err is Human" set off a firestorm of quality initiatives when it announced that at least 44,000 to 98,000 people die in hospitals every year because of medical errors.

First, participants will receive confidential feedback to support quality improvement in their practices. (This information will not be made publicly available.) Second, participants may earn bonus incentive payments for meeting quality-reporting requirements. Finally, participants will be making an investment in the future of their practices. It is expected that higher

bonus incentives will be offered in the future, pay-for-performance programs in the private sector will become more numerous, and public reporting of performance results will become standard practice. ACR members who prepare now will be in a better position later.

## Join the Quality Movement

To get involved with PQRI:

- Visit the ACR Web site ([www.rheumatology.org/practice/qmc/pqri.asp](http://www.rheumatology.org/practice/qmc/pqri.asp)) and the CMS PQRI Web site ([www.cms.hhs.gov/PQRI](http://www.cms.hhs.gov/PQRI)) for additional information on PQRI. Note in particular the Educational Resources page of the CMS PQRI Web site;
- Explain PQRI to your staff and educate them on the importance of reporting the quality measures; and
- Create new superbills that include quality-reporting codes to assist your office staff.

Your office processes and systems must be able to accommodate PQRI to be successful both now and in the future. Establishing a quality structure will make it easier to meet measurement and reporting goals. The July 1 start date has already passed, but practices can still participate in PQRI.

The ACR encourages its members to participate in PQRI this year—and to get started as soon as possible. Every day you wait after July 1 will make it more difficult to meet the minimum requirements for the July 1–December 31, 2007, reporting period. Meanwhile, the ACR will continue to work on behalf of its members to ensure that the measures used by CMS and others are reasonable and that members have the information and tools they need to succeed.

## References:

1. Testimony: Assessing Alternatives to the Sustainable Growth Rate System. March 6, 2007. Available at: [www.medpac.gov/publications/congressional\\_testimony/030607\\_E\\_C\\_testimony\\_SGR.pdf](http://www.medpac.gov/publications/congressional_testimony/030607_E_C_testimony_SGR.pdf). Last accessed May 31, 2007.
2. Testimony: Improving Medicare Efficiency and Value. April 18, 2007. Available at: [www.medpac.gov/publications/](http://www.medpac.gov/publications/)

THE RHEUMATOLOGIST

# Investigate the Committee on Research

The COR works to promote basic and clinical research in rheumatology

>> By Jane Jerrard

**T**his is the second part in our ACR committee profile series.

## Committee Composition

Fifteen volunteers make up the Committee on Research (COR), and they come from diverse backgrounds. "The committee includes representatives from basic research and clinical research, as well as health service researchers, pediatric rheumatologists, and a rheumatology fellow," explains committee chair E. William St. Clair, MD, professor of medicine at Duke University Medical Center in Durham, N.C. "There are members who represent the ARHP, the Arthritis Foundation, and the ACR Research and Education Foundation. We also have a liaison to the [ACR] Government Affairs Committee, and to NIAMS [National Institute of Arthritis and Musculoskeletal and Skin Diseases] and NIAID [National Institute of Allergy and Infectious Diseases]. This diverse membership allows us to address research from multiple points of view."

"Any member can identify their interest in joining the committee through the ACR Web site," stresses Dr. St. Clair. "My impression is that we have a lot of potential volunteers out there. There's a lot of interest in serving on ACR committees."

The entire COR meets on a regular basis, including two face-to-face meetings each year and several conference calls; its subcommittees may hold additional calls.

## At the Helm

Committee Chair Dr. St. Clair volunteered for COR in 2004 and served one year before being appointed its chair. He previously served on ACR's Annual Scientific Meeting Planning Committee and the Education Committee.

"I have a background in both basic and, primarily, clinical research," he says, "but I spend most of my time now at the bedside working on studying new therapies for rheumatoid arthritis and other rheumatic diseases."

During his first year on COR, Dr. St. Clair led an important initiative: "My task during that ... year was to help develop a research agenda [for ACR], which would define our research priorities for upcoming years," he explains. "I convened a working group and we fleshed out a draft of the agenda" in a series of conference calls. After receiving comments from the membership, the ACR board approved the agenda in the fall of 2005 after a public comment phase.

"The fallout is that we're now faced with de-



veloping a strategy for the implementation of that agenda," says Dr. St. Clair. The final research agenda will shape COR's focus and tasks for years to come.

## Ambitious Agenda

The COR agenda lays out research priorities, including etiology of disease, mechanisms of disease, and advances in therapy. It also makes recommendations for future research.

"Our initiative this year has been to implement the agenda," says Dr. St. Clair. "There are three areas, each defined by a subcommittee: funding opportunities, clinical research infrastructure, and awareness. Their efforts will lead to a number of action items that the committee will take before the ACR board of directors over the next year." COR will develop action items from the efforts of those subcommittees.

"One of our first projects was a white paper developed by [Clifton Bingham III, MD, assistant professor of medicine in the rheumatology division at Johns Hopkins University in Baltimore] and his subcommittee, on the appropriate training of clinical investigators," says Dr. St. Clair. "This was brought to the board in early 2007."

## Promoting Research to Members

A major COR initiative is promoting basic and clinical research. "An important way the ACR promotes research is at the Annual Scientific Meeting," says Dr. St. Clair. Specifically, COR is responsible for two pre-meetings offered at the Annual Scientific Meeting: a Basic Research Conference and a Clinical Research Conference.

"The topics and chairs for the Basic Research Conference and Clinical Research Conference are selected by COR," explains Dr. St. Clair. "The topics are chosen because of their importance to the field of rheumatology and scientific interest. Leaders in the field are selected as chairs, who then organize the program and select the speakers."

The Basic Research Conference has been enormously successful, adding considerably to the vitality of the basic science available at the Annual Scientific Meeting. "An important goal of the basic research conference is to provide a venue for established investigators to interact with young investigators, creating opportunities for mentoring and stimulating excitement about research among the trainees," points out Dr. St. Clair. "Also, we invite leaders in the field who are presenting at the Basic Research Conference pre-meeting to speak at the annual meeting, further enriching the portfolio of basic science presentations available to our membership."

The ACR Basic Research Conference is now a permanent fixture of the annual meeting. The focus of the 2007 conference is "Musculoskeletal Engineering and Regeneration," chaired by Rocky S. Tuan, PhD, from NIAMS and Rank Luyten, MD, PhD, from Katholieke Universitet in Belgium.

In comparison, the Clinical Research Conference is relatively new; the 2006 Scientific Meeting was its third year. It has also been very successful, largely due to the efforts of initial conference organizer Edward Yelin, PhD, professor of medicine in the rheumatology division at the University of

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CLINICAL | continued from page 1

# CLINICAL CUTTING

## Updates on Sjogren's syndrome, myositis, and vasculitis

>> By Jane Jerrard

Management," he stressed that, "just like in lupus, you're dealing with an entire spectrum of disease." Dr. Vivino reviewed diagnosis of Sjögren's, including unusual presentations of symptoms like inflammatory myositis, fever of unknown origin, chronic fatigue syndrome, elevated erythrocyte sedimentation rate, and leukocytoclastic vasculitis.

"Sicca symptoms may be minimal or nil," warned Dr. Vivino. There may be a discrepancy between symptoms and results of objective tests of eye and mouth dryness. "The bottom line is that if you have a patient with symptoms that fit, you're obligated to order tests for Sjögren's."

He stressed using the American-European criteria for earlier and better diagnosis of Sjögren's syndrome. "These criteria are in use in nearly every children's center in the world," said Dr. Vivino. "They clearly represent an advance over what we had before."

The criteria call for four of the following six symptoms to be present for diagnosis:

#### Subjective

- > Dry eye symptoms; and
- > Dry mouth symptoms.

#### Objective

- > Abnormal test for dry eyes;
- > Abnormal test for dry mouth;
- > Positive anti-SSA/SSB\*<sup>†</sup>; or
- > Positive lip biopsy.\*

\*Required

"One of the four objective criteria must be proof of the presence of autoantibodies," Dr. Vivino pointed out. "This clearly represents an advance over what we had before."

**The bottom line is that if you have a patient with symptoms that fit, you're obligated to order tests for Sjögren's.**

—Frederick B. Vivino, MD

Errors are often made in reading salivary gland biopsies; a previous study by Dr. Vivino found that 53% of 60 accessions had errors. Other problems include lack of focus score, misinterpretation of focus score, and failure to examine all sections. "It behooves us to talk to our pathologists about accurate test results," he said.

He pointed out that Sjögren's can lead to a lot of disease complications, specifically lymphoma. "Lymphomas are the most important

cause of morbidity and mortality in Sjögren's syndrome patients," said Dr. Vivino. "This is confusing, but the best predictors of lymphomagenesis include persistent parotid enlargement, persistent lymphadenopathy, palpable purpura, mixed monoclonal cryoglobulinemia, and low complement of C4."

As for symptoms, there has been recent progress in treating dry eyes. This symptom has greatest quality-of-life effect. Research has shown that inflammation is tied to dry-eye disease. New evidence points to secretagogues, such as pilocarpine and cevimeline, that can alleviate symptoms. Fatty acids seem to play a role as well.

Dr. Vivino ended by discussing appropriate treatment for Sjögren's, recommending immunosuppressives, such as hydroxychloroquine, or corticosteroids, but warned that these don't have proven benefit for dry mouth or dry eyes.

#### Distinguish Myopathy from Mimics

In "Myositis: From Autoantibodies to Clinical Trial," Chester V. Oddis, MD, professor of medicine at the University of Pittsburgh, provided guidelines for diagnosing and treating myositis syndromes.

Dr. Oddis began by reviewing the diagnostic criteria for idiopathic inflammatory myopathy, which include:

- > Symmetric proximal muscle weakness;
- > Elevation of serum muscle enzymes (creatinine kinase, aldolase, aspartate aminotransferase, alanine aminotransferase, or anti-diuretic hormone);
- > Myopathic electromyographic abnormalities;
- > Characteristic muscle pathology; and
- > Skin rash of dermatomyositis.

He then discussed several mimics of inflammatory myositis, including endocrine myopathies of hyper- and hypothyroid, metabolic myopathies, muscular dystrophies, and (the most common) drug or toxic myopathies caused by alcohol, colchicines, statins, and more.

"We all struggle with statins and statin myopathy," said Dr. Oddis. Factors that increase risk of statin myopathy include increasing age, female gender, renal insufficiency, hepatic dysfunction, hypothyroidism, diet, and polypharmacy.

Dr. Oddis recommended a muscle biopsy to distinguish myopathy from immune-mediated myositis, or polymyositis, that's amenable to treatment with steroids.

"In a patient with refractory polymyositis, consider the mimics of inflammatory myopathy," he advised, "and you also have to consider inclusion body myositis [IBM]." Although it's the most

common myopathy, this is often missed. IBM is more prevalent in elderly males and includes an insidious onset of painless muscle weakness with slow progression. There's a characteristic pattern of muscle atrophy in forearm flexors, quadriceps, and intrinsic muscles of the hands.

Although dermatomyositis (DM) may appear to be polymyositis with a rash, "it's much more complicated than this," explained Dr. Oddis. In polymyositis, the target is myofiber; in dermatomyositis, the target is blood vessels—treatment for the two must be different.

In a classic DM model, the autoimmune disease is mediated by an adaptive immune system and you'll find a locally humorally mediated response with B and T helper cell infiltration. You'll also find perifascicular atrophy of muscle fibers caused by ischemia. But investigations over the last few years have found specific gene transcriptional patterns in DM muscle tissues, including genes identified as type 1 interferon-induced. This is similar to a genetic signature found in lupus.

Dr. Oddis reviewed the two classifications of idiopathic inflammatory myopathy: clinical groups, including adult and juvenile, and serologic groups, or those with autoantibodies. The second group includes myositis-specific autoantibodies. Categories of myositis-specific autoantibodies include anti-synthetases, which present with acute and aggressive onset with pulmonary symptoms such as interstitial lung disease. Other symptoms include high fever, inflammatory arthritis, and sometimes deforming arthritis of the hands. These patients are often thought to have pneumonia and/or rheumatoid arthritis, said Dr. Oddis. The pulmonary involvement can be life threatening.

There is very little evidence-based treatment for pharmacologic therapy of idiopathic inflammatory myopathy, according to Dr. Oddis. Current treatment may include corticosteroids, immunosuppressive agents, combination regimens, intravenous immunoglobulin, and biologic agents such as anti-TNF agents, monoclonal anti-B cell agents, and monoclonal anti-complement agents.

A current NIH trial is assessing the efficacy of rituximab in polymyositis and DM, said Dr. Oddis.

#### Childhood Vasculitis Update

Rayfel Schneider, MD, associate professor of pediatrics at the University of Toronto in Ontario and head of rheumatology at the Hospital for Sick Children there, presented "Pediatric Vasculitis," a review of the current classification of childhood vasculitis, diagnostic pitfalls, and new treatment developments.

Beginning with the 2005 practical classifica-

tion for childhood vasculitis—which Dr. Schneider calls “a work in progress”—he reviewed large-vessel, medium size-vessel, and small-vessel vasculitides. He then focused on Wegener’s granulomatosis (WG)—a small-vessel vasculitis—and primary angiitis of the central nervous system (PACNS) in children, because, he says, “we’re seeing an increasing number of patients with isolated vasculitis of the CNS and we’ve done some work in that area.”

Dr. Schneider outlined recent research on Wegener’s granulomatosis in children, pointing out common symptoms including fever, arthralgia, and weight loss; glomerulonephritis; upper airway disease; and pulmonary disease. Less common symptoms include eye involvement, skin vasculitis, arthritis, and venous thrombosis.

“Wegener’s in children is more common in females,” Dr. Schneider says. “Think about Wegener’s in children with ‘atypical’ [Henoch-Schoenlein purpura]. Constitutional symptoms and upper airway, pulmonary, and renal involvement are all very common at presentation, and some patients may present with [deep venous thrombosis].”

**TABLE 1:**  
**PACNS: Proposed Treatment Approach**

	Acetylsalicylic Acid +/- Anticoagulation	Steroids	Cyclophosphamide
<b>Non-progressive</b> Stroke with proximal vessel stenosis	+	No ? short course	No
<b>Progressive</b> High risk* or actual progression	+	+	+
<b>Small vessel vasculitis</b> (biopsy)	+	+	+

\*cognitive dysfunction + multifocal MRI lesions + distal or bilateral vessel stenoses

Dr. Schneider then reviewed the proposed diagnostic criteria for PACNS, which include newly acquired neurological deficit, angiographic and/or histological features of CNS vasculitis, and no evidence of a systemic condition associated with these findings. Mimics must also be excluded.

He stressed that PACNS is a heterogeneous disease. It can present with acute stroke or diffuse neurological deficits—or with both. Permanent neurological deficits are frequent.

All diagnostic modalities have limitations, Dr. Schneider pointed out. “Lab and CSF tests aren’t

sensitive or specific—the same is true of MRIs—and angiography is frequently positive and lacks sensitivity for small vessel disease.” *The solution:* Brain and leptomeningeal biopsies should be used in cases of children with suspected PACNS who have negative angiography. Additionally, identifying patients at high risk of progression may help determine whether they’ll require immunosuppressive therapy.

At the Hospital for Sick Children, four patients with biopsy-proven small vessel vasculitis were treated as follows. All four were given prednisone, two were given cyclophosphamide, and one was given azathioprine. Three of the four recovered with no neurological deficit, and there was a relapse in one patient recently, six years after treatment.

Dr. Schneider’s research shows that the patients with angiographic PACNS most likely to get progressive disease had three indications: neurocognitive dysfunction; multifocal, bilateral MR lesions; and distal stenoses on angiogram. This led him to think that the classification for vasculitis should be re-examined and should include the following categories: progressive, non-progressive, and small vessel (biopsy), each with a separate treatment. (See Table 1, above.) | THE RHEUMATOLOGIST |

Jane Jernard is a journalist based in Chicago.

**HEAR THE SESSIONS**

These and other sessions from the ACR State-of-the-Art Clinical Symposium are available as audio CDs, MP3s, and podcasts. Visit [www.ACRMeetings.com](http://www.ACRMeetings.com) to view the sessions currently available from the meeting.

**INVESTIGATE THE COMMITTEE ON RESEARCH** | continued from page 15

California, San Francisco, says Dr. St. Clair.

The Clinical Research Conference, which is now a permanent fixture of the ACR annual meeting, has goals similar to the Basic Research Conference. The 2007 conference will focus on drug safety, and is chaired by Daniel H. Solomon, MD, MPH, assistant professor of Medicine in the division of rheumatology, immunology, and allergy at Brigham & Womens Hospital in Boston. “The chair, who is an expert in the field, organizes the program, and selects the speakers,” explains Dr. St. Clair.

**Additional Goals**

In addition to implementing the research agenda and providing two pre-meetings on research each year, COR continues to focus on several ongoing goals. One is to preserve and grow the rheumatology research infrastructure. “We’ve moved forward on that initiative with the white paper,” says Dr. St. Clair.

The committee also focuses on providing leadership and guidance for new researchers through its young investigators subcommittee. The subcommittee was formed two years ago and has eight ACR members who are not members of COR. “We were charged with helping the young investigator constituency,” says young investigator representative Christy C. Park, MD, assistant professor of rheumatology at Northwestern University Feinberg School of Medicine in Chicago. “We started from scratch; we thought we should gauge the interest in a career in research among younger members, starting with fellows.” The subcommittee has conducted two surveys of rheumatology fellows and is analyzing the results thoroughly. “We asked what factors made them choose academic research,” explains Dr. Park, “and we asked a lot of open-ended questions, too. A one-to-five rating doesn’t really give all the answers.”

Dr. St. Clair explains, “We’re studying career outcomes of physician investigators, identifying young investigators in the ACR, and examining what factors lead to their success as academic in-

vestigators. The answers will help us develop strategies to help them succeed.”

The subcommittee also presented a special session for fellows on academic research for the second time at the scientific meeting in November. “This was very well attended last year,” says Dr. Park. “We hope that this brings some visibility to our group, so that [the fellows] can voice their concerns to us.”

Another initiative of the young investigators is recognizing mentorship. “We recommended to the REF a new award recognizing mentorship,” says Dr. Park. “We want to highlight the importance of mentoring with the Investigative Mentorship Award [given for the first time in November 2006].”

**Impact of the Committee**

The work that the entire COR does has a direct influence on rheumatology research and, by extension, on ACR members and other practicing rheumatologists. “By its nature, the main impact of the commit-

tee is on the research community, although ultimately, research activities [affect practicing rheumatologists] by helping develop novel therapeutics,” says former committee member Gary Firestein, MD, professor of medicine and chief of rheumatology at the University of California, San Diego. “The committee helps to identify new areas of research, new collaborations with other organizations, unmet medical needs where our organization can begin to focus attention, and funding opportunities in an area where research funding is badly needed.”

Dr. St. Clair adds, “By supporting basic and clinical research, our efforts can directly lead to improvements in care of patients and advances in the diseases we see every day. We’re also very supportive of the training of academic rheumatologists; the committee tends to support that subgroup and thus improve quality of care.” | THE RHEUMATOLOGIST |

Jane Jernard is writing the series on ACR committees.

**CODING CORNER!**

**Question on p. 11**

**July’s coding answer:** The proper way to code this visit is as 20610, 20610-59, 90772-GA. You could not code an E/M visit because there is no documentation of an examination being done. Because the shoulder and the elbow are both large joints, you would use a -59 modifier on the second code to notify the carrier that the injection was for a different area of the body. The Enbrel injection is not covered by Medicare, so you would need to have the patient sign an Advance Beneficiary Notice (ABN) before the service was performed. Without a signed ABN, the patient would not be liable for the charge. The GA modifier notifies Medicare that an ABN is on file.

"Grandpapa's Torments" was the Rodnan Commemorative Gout Print featured at the 2005 ACR/ARHP Annual Scientific Meeting.

# DIFFICULT GOUT



Recent research and new management options for tough cases

>> By Robert Terkeltaub, MD

Further, physicians are increasingly limited by the lack of new Food and Drug Administration (FDA)-approved therapeutic options for gouty inflammation and hyperuricemia management for patients who present with the key elements of difficult gout. (See Table 1, p. 21.)

#### Increased Prevalence and Clinical Complexity

Over the last two decades in the United States, the prevalence of gout has approximately doubled. A perfect storm of factors has driven increases in gout prevalence and clinical complexity.<sup>1</sup> The graying of the population as a whole is a central factor because the greatest rise in gout prevalence by far has been

among the aged. This situation is clinically problematic because polypharmacy, significant comorbidities, and altered drug disposition and toxicity profiles are common problems in the elderly. The wide use of diuretics in association with underlying chronic renal insufficiency and/or congestive heart failure has rendered difficult gout partly an iatrogenic problem in many patients. The clinical character of tophaceous gout is changing, such that the elderly female with chronic polyarticular gout presents a common problem in the clinic and for consultative practice of inpatient rheumatology. (See Figure 1, p. 19.)

Factors confluent with aging that are changing the prevalence and character of gout include the marked increased prevalence of hypertension (with associated thiazide diuretic use); altered dietary trends; and the rising prevalence of obesity, metabolic syndrome, and end-stage renal disease over the last few decades.<sup>1</sup> Improved survival in coronary artery disease, congestive heart failure, and diabetes mellitus, and broad use of loop diuretics (and possibly low-dose acetylsalicylic acid as well) also appear to

#### OWN THIS PRINT

This and other Rodnan Gout prints are available at [www.rheumatology.org/ref](http://www.rheumatology.org/ref). All proceeds support the ACR Research and Education Foundation's grant and award programs.

contribute to the expanded pool of subjects with chronic, severe hyperuricemia. Finally, the limitations of allopurinol therapy render gout management difficult

in a sizeable fraction of patients, particularly those with significant renal insufficiency or uric acid overproduction where uricosuric therapy is not a viable alternative to allopurinol. (See Table 2, p. 21.)

#### Limitations of Allopurinol

Allopurinol is primarily a pro-drug that must be intestinally absorbed and then converted in the liver to the active metabolite oxypurinol. The half-life of oxypurinol is largely determined by renal elimination and is normally 24 hours. Oxypurinol accumulates in association with diminished glomerular filtration rate. Notably, severe hypersensitivity to allopurinol appears partially dose-dependent. Major allopurinol hypersensitivity syndrome associated with multi-organ system damage has a mortality rate of approximately 20%. Fortunately this problem has been uncommon (i.e., no more than 100 reported cases). Nevertheless, a drug rash—typically preceded

by pruritus—occurs in about 2% of allopurinol-treated patients. Only a half of these subjects (at most) successfully resumes maintenance allopurinol after oral desensitization.

Pharmacogenomics of severe cutaneous adverse reactions to allopurinol in Han Chinese are such that the odds ratio is 580:1 in HLA-B\*5801-positive subjects.<sup>2</sup> However, it is not known if this finding holds for other populations. Stepwise upward adjustment of starting allopurinol doses based on creatinine clearance is common and acceptable medical practice to dampen the risk of severe allopurinol hypersensitivity. Yet there is no precise method to predict or prevent allopurinol hypersensitivity in the population at large. Moreover, optimal dosing of allopurinol remains controversial—particularly in patients with chronic renal insufficiency.

Concern about precipitating major allopurinol hypersensitivity syndrome often drives practitioners to use allopurinol maintenance doses that are too low for many patients (specifically, doses less than or equal to 300 mg/day in patients with preserved renal function and 100–200 mg/day in patients with creatinine clearance less than 60 mL/min), which probably enlarges the pool of refractory gout. The reported patient compliance with maintenance allopurinol is around 50%, indicating a systematic failure of gout patient education by practitioners.

Precipitation of acute gout flares is a common form of allopurinol intolerance, but can be satisfactorily addressed in most patients by prophylactic colchicine with evidence-basis, or by prophylactic non-steroidal anti-inflammatory drugs (NSAIDs) without evidence-basis at this time. However, allopurinol intolerance—manifesting, for example, as minor gastrointestinal and central nervous system toxicity—occurs in up to 10% of patients. Allopurinol hepatotoxicity typically presents as elevation in transaminases, a manifestation that can be difficult to precisely attribute to allopurinol. Unfortunately, more severe hepatotoxicity can develop, often cryptically. The nonselectivity of allopurinol effects in both purine and pyrimidine metabolism potentially factors into gastrointestinal, central nervous system, and hematologic toxicities.

### Advances: URAT1 and Uricosurics

Hyperuricemia in most patients with both primary and secondary gout is driven by renal underexcretion of uric acid. Stunning advances have occurred in the understanding of uric acid handling in the nephron. Urate anion exchange with organic anions at the apical side of renal proximal tubule epithelial cell by URAT1 (SLC22A12)—a member of the organic anion transporter (OAT) family—is the linchpin for renal reabsorption of urate anion from the tubular lumen.

The work of Hitoshi Endou, MD, PhD, and colleagues has also revealed that the particularly potent and effective uricosuric benzbromarone, as well as several less potent uricosurics (probenecid, losartan, sulfipyrazone, and high doses of salicylates), exert uricosuric activity via inhibition of URAT1.<sup>3</sup> Further, testosterone increases and estrogen decreases URAT1 expression. Certain URAT1 single nucleotide polymorphisms (SNPs) have been linked to altered susceptibility to gout in different cohorts. Indeed, the ability to pharmacogenomically assess for potential responsiveness to specific uricosurics is close at hand.

The identification of URAT1 functions, including URAT1 association in macromolecular complexes that jointly influence sodium and urate reabsorption, provides a platform to rationally design a new generation of more selective, and potentially more effective, uricosurics. However, attendant risks of urolithiasis and renal toxicity limit the potential of more potent, rationally designed uricosurics to be clinically safe agents in managing the most needy subjects with difficult gout. Many patients with dif-

ficult gout are intolerant of allopurinol but cannot receive uricosurics as an alternative due to renal insufficiency or uric acid overproduction.

### Novel Xanthine Oxidase Inhibitors

Xanthine oxidase is reversibly interconvertible between reduced and oxidized forms (xanthine dehydrogenase and xanthine oxidase, respectively)—both of which catalyze the formation of uric acid as the end product of purine nucleotide catabolism.<sup>4</sup> (See Figure 2, below.) However, oxypurinol dissociates from—and does not effectively inhibit—uric acid formation by the oxidized form of the enzyme. Though oxypurinol is tolerated in some allopurinol-hypersensitive patients, oxypurinol carries many of the limitations of allopurinol, is variably absorbed in the gut, and has not yet performed as a satisfactorily effective antihyperuricemic agent in adequately powered clinical trials. One wonders if xanthine oxidase may exist predominantly in the oxidized form in some patients where robust doses of allopurinol fail to satisfactorily lower serum uric acid. In my clinical practice, I order serum oxypurinol levels for patients in whom there are questions about either compliance with allopurinol or unidentified pharmacogenomic limitations to allopurinol treatment.

Given the aforementioned limitations of allopurinol, there is interest in selective xanthine oxidase inhibition for hyperuricemia using drugs without a purine-like backbone. One such drug, febuxostat, selectively occupies the substrate access channel to the catalytic site of xanthine oxidase. Significantly, febuxostat inhibits both the reduced and oxidized forms of xanthine oxidase and does not affect interconversion of the enzyme from one form to the other. In a large, randomized, phase III study of gout patients by Michael Becker, MD, and colleagues, febuxostat at doses of 80 and 120 mg daily was more effective than standard dosing (300 mg daily) of allopurinol in reducing serum urate to a target level of less than 6 mg/dL over one year of treatment.<sup>5</sup> Febuxostat remains under FDA review, and detailed assessment of febuxostat in patients with renal insufficiency is expected.

A serum urate level of less than 6 mg/dL is widely advocated as an ideal therapeutic target because it is well below the theoretic limit of urate solubility in human tissues of between 6.7 and 7.0 mg/dL, the benchmark provided by in vitro studies in physiologic buffers and plasma. In response to 80 mg and 120 mg of febuxostat daily, the mean drop in serum urate from baseline to the final visit was 44.7% and 51.5%, respectively.<sup>5</sup> The majority of allopurinol-treated patients (approximately two-thirds) did not attain sustainable serum urate lowering to less than 6 mg/dL at the final visit.

An important finding in the febuxostat phase III trial was that 300 mg allopurinol daily lowered mean serum urate by a mean of approximately 33%.<sup>5</sup> Hence, the average patient with a serum urate of less than or equal to 9 mg/dL should achieve ideal serum-urate lowering with the typical daily dosage of allopurinol. In my experience, higher doses of allopurinol can safely achieve optimal serum-urate lowering in many additional patients. An additional finding in the febuxostat study was that the frequency of gout flares at the end of the study period was comparable in febuxostat- and allopurinol-treated patients, despite the more potent serum-urate lowering by febuxostat. Indeed, serum-urate lowering to less than the “ideal” target level of less than 6.0 mg/dL (but to levels between 6.0 and 6.7 mg/dL) may be sufficient to improve



FIGURE 1: The changing face of gout. This 84-year-old female presented with draining toe tophi (see left foot) and polyarticular, chronically painful, progressive chronic tophaceous gouty arthritis of five years. Comorbidities included congestive heart failure on 120 mg furosemide daily and renal insufficiency with a creatinine clearance of 25 mL/min.

the course of gout in many patients.

Febuxostat-induced serum-urate lowering, like that due to allopurinol, was associated with a surge in flares of gouty arthritis when prophylactic colchicine was withdrawn only eight weeks into the therapy after the washout period.<sup>5</sup> I advocate starting low-dose prophylactic colchicine two weeks before initiation of urate-lowering therapy. I also advocate maintaining the colchicine regimen for six months in the average patient, and longer in patients with persistent tophi. More intensive serum urate-lowering therapy has the potential to induce more active tophus remodeling, a state that is likely pro-inflammatory at tophaceous deposits.

### Uses for Uricase

Uricase is one of several enzymes of the final purine degradation pathway in nonprimate mam-

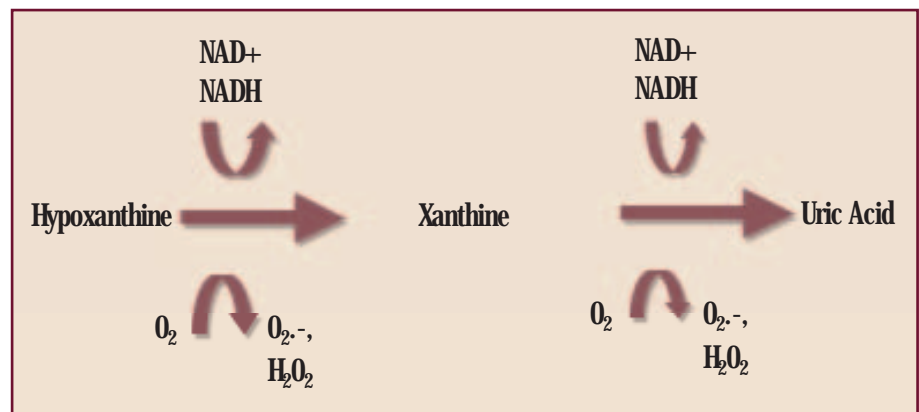
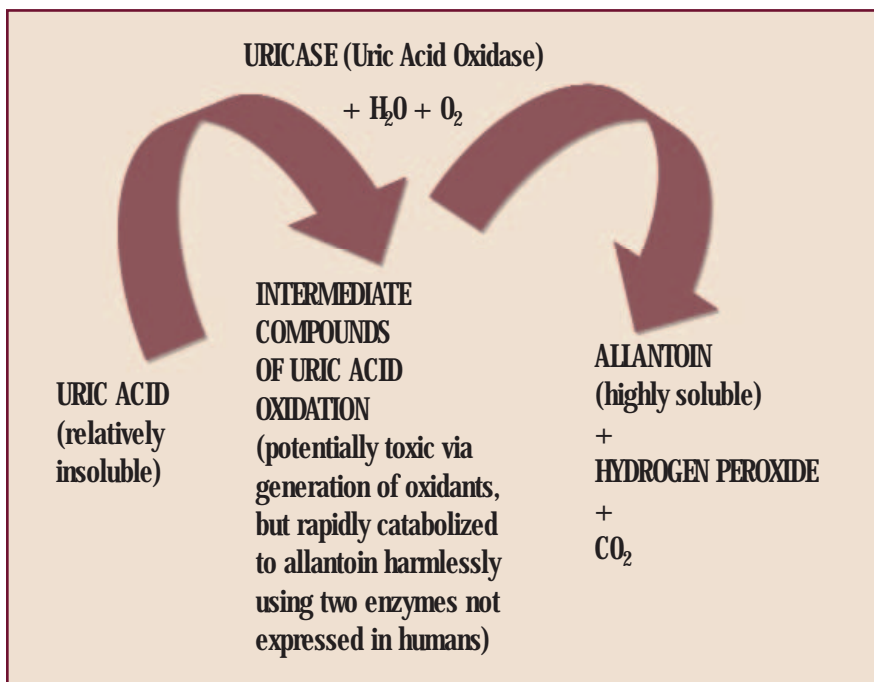


FIGURE 2: Xanthine oxidase is interconvertible between a reduced form (xanthine dehydrogenase) as depicted above and an oxidized form (xanthine oxidase) as depicted below. Allopurinol and oxypurinol do not effectively inhibit the oxidized form of xanthine oxidase.

mals and lower primates that catalyzes the conversion of relatively insoluble uric acid to highly soluble allantoin. (See Figure 3, p. 20.) Uricase gene silencing in evolution has rendered the human urate balance delicate. Normal rodents, for example, have a serum urate level of about 1 mg/dL, which is approximately sixfold less than that of normal humans. Humans' lack of uricase expression may protect them from oxidative stress such as neuronal toxicity of nitric oxide-derived oxidants. Uric acid is the major circulating antioxidant. It was recently demonstrated that the oxidation of uric acid by uricase produces reactive and

continued on page 20



**FIGURE 3:** Enzymatic activity of uricase (uric acid oxidase). Uricase oxidizes sparingly soluble uric acid to highly soluble allantoin, generating both intermediate forms of uric acid subject to further metabolism and, as a byproduct, the oxidant hydrogen peroxide. Expression of uricase, and the enzymes that rapidly degrade intermediate forms of uric acid generated by uric acid oxidation, were lost in humans during evolution. This circumstance may have arisen because uric acid is the most abundant circulating antioxidant in humans and uricase activity generates oxidative stress.

potentially toxic intermediates in lower mammals that are rapidly degraded by two enzymes that humans also fail to express. Further, the slow, spontaneous conversion of uric acid to allantoin yields the oxidant hydrogen peroxide as a byproduct.

Currently, the recombinant fungal uricase rasburicase is FDA approved for abbreviated, single-course use to prevent tumor lysis syndrome in subjects with hematologic malignancy. This recombinant uricase is neither humanized nor modified by PEGylation. Thereby it is particularly immunogenic and limited by a relatively short half-life. Side effects, including anaphylactic reactions, have been limiting. Robust amounts of neutralizing antibodies to uricase can also develop. PEGylation of uricase promotes less immunogenicity and a longer half-life, and appears better suited for urate-lowering therapy in refractory gout. Indeed, PEGylated uricase preparations have induced profound serum urate-lowering in clinical trials. The shift from subcutaneous to intravenous administration of PEGylated porcine recombinant uricase (Puricase) reduced hypersensitivity reactions.<sup>6</sup> However, immunogenicity could still constrain safety and longer-term efficacy of current PEGylated uricase preparations in clinical development.

Oxidative stress via uricase-induced hydrogen peroxide generation is another potential concern with enzyme therapy use. Erythrocyte-borne catalase should theoretically be sufficient to degrade circulating hydrogen peroxide generated via typical doses of uricase. Nevertheless, latent vulnerability to oxidative stress with uricase administration is indicated by hemolysis and methemoglobinemia as classic uricase side effects in patients with G6PD deficiency. In my opinion, the primary therapeutic niche for uricase in gout will be limited duration treatment (months) as induction therapy to debulk macroscopic tophi in carefully selected patients with extensive disease refractory to other treatments.

**Inflammation in Difficult Gout**

Difficult gout includes patients who are intolerant of, or refractory to, standard therapeutic approaches to gouty inflammation: NSAIDs (or alternatively COX-2 selective inhibitors), systemic or intra-articular glucocorticosteroids, adrenocorticotrophic hormone (ACTH), or colchicine.<sup>7</sup> Clinicians can carefully adjust colchicine doses in line with renal function and employ combinations of low-dose

colchicine with other anti-inflammatories to manage some of these subjects with renal or hepatic dysfunction, gastrointestinal comorbidity, poorly controlled diabetes mellitus, age, and post-operative state.<sup>7</sup> However, polyarticular gout flares refractory to therapy do occur. A striking example is seen in major organ-transplant recipients receiving cyclosporine who develop severe gouty arthritis despite maintenance low-dose prednisone. Some patients have major gout flares when starting or adjusting uric acid-lowering therapies, including the intensive serum urate-lowering regimens currently under clinical development.

The primary pathologic hallmark of acute gout is neutrophil influx into the joint fluid, consistent with interleukin 1 (IL-1)-induced and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )-induced activation of endothelium and with tissue generation of neutrophil chemoattractants that drive and sustain the inflammation. Certain molecular mechanisms of action of anti-inflammatory agents used in gout could be exploited for difficult gout. For example, the rapid onset

recognition molecules outside cells, as well as on the cell surface and in the cytoplasm. Innate immune responses to urate crystals that drive gouty inflammation include extracellular crystal-induced complement membrane attack complex assembly, which promotes the CXC chemokine receptor 2 (CXCR2)-binding chemokine expression essential for the neutrophil influx that drives gouty inflammation.<sup>9,11,12</sup> (See Figure 4, below.)

Experimental gouty inflammation is triggered by IL-1 receptor signaling by resident cells at the site of urate crystal injection.<sup>13</sup> Macrophage recognition and uptake of urate crystals by the cell surface Toll-like receptors (TLRs) 2 and 4 and by signaling of the shared intracellular TLR adaptor protein MyD88 drives both pro- and anti-inflammatory cytokine expression.<sup>14</sup> Depending on the locus of experimental urate crystal injection, TLR2 and TLR4 expression determines dominant anti-inflammatory effects (such as induction of transforming growth factor  $\beta$ ) or pro-inflammatory effects in vivo. However, MyD88, which also is a critical adaptor protein for the IL-1 receptor, is central to both urate crystal uptake by cultured macrophages and urate crystal-induced inflammation in vivo.<sup>13,14</sup>

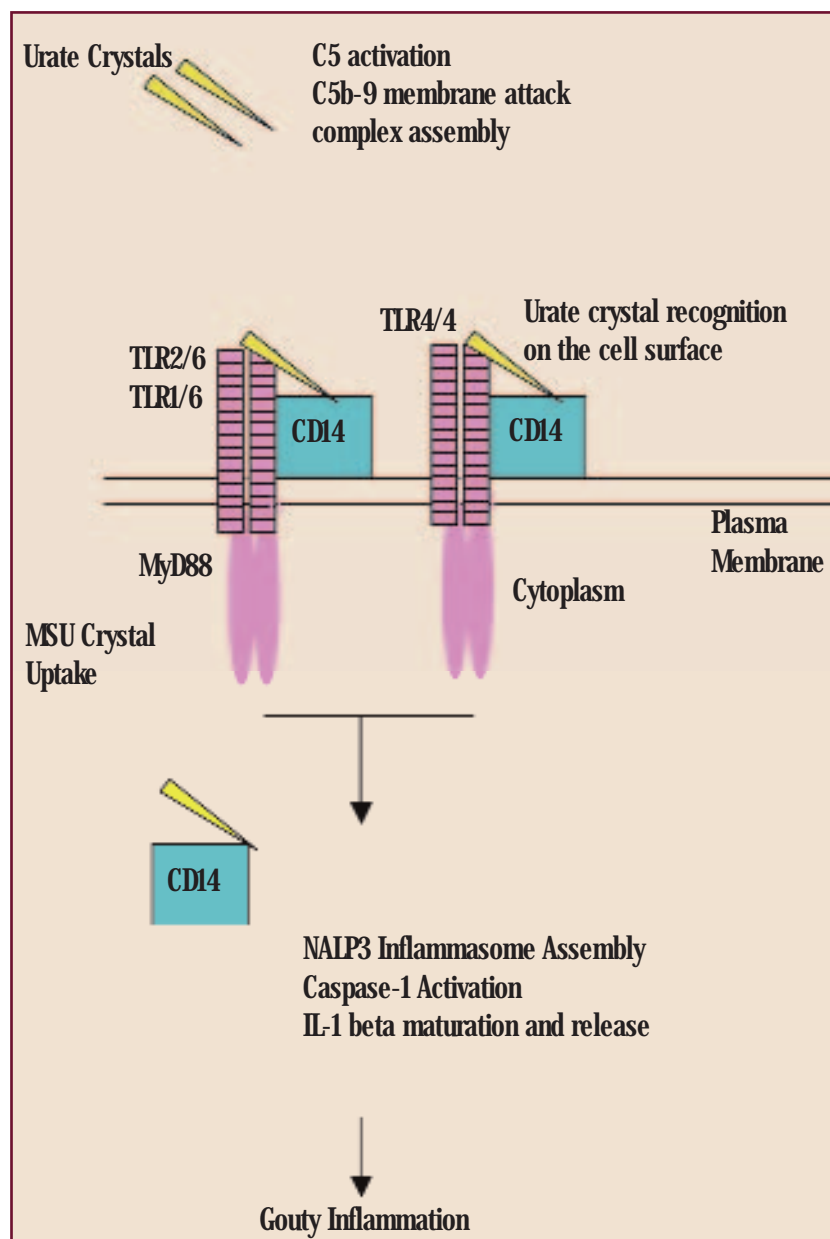
In the cytoplasm, urate crystals also employ the cytoplasmic pattern recognition receptor NALP3 (cryopyrin) to drive inflammation.<sup>11,12</sup> Upon ligand recognition, NALP3, like other mem-

of the therapeutic action of ACTH in gout appears mediated by binding to the melanocortin receptor 3 (MR3) on phagocytes in the periphery. Stimulation of MR3 by itself can suppress experimental gouty inflammation.<sup>8</sup> We also know that low-dose prophylactic colchicine prevents gouty inflammation in part by inhibiting redistribution the neutrophil adhesion molecule E-selectin in vascular endothelium.

**Primitive Innate Immune Response**

Acute gout is a prototype of the primitive innate immune “early induced” response, with the characteristic recurrent, paroxysmal nature of gouty arthritis representing failure of monosodium urate crystals to directly induce durable protective immunity.<sup>9</sup> Uptake of both apoptotic neutrophils and urate crystals by resident and recruited “professional phagocytes” mobilizes a rapid effort to quell the inflammation.<sup>9,10</sup> The recent elucidation of new molecular biologic mechanisms of gouty inflammation may light the way to novel therapeutics.

Innate immunity against invading pathogens involves the distribution of pattern recognition receptors and



**FIGURE 4:** Major extracellular and intracellular innate immune recognition mechanisms for monosodium urate crystals. The schematic depicts extracellular urate crystal surface-induced C5 cleavage, as well as urate crystal recognition at the macrophage surface by TLR2 heterodimers with TLR1 or TLR6 and by TLR4 homodimers and their shared surface adaptor protein CD14. The illustration also depicts urate crystal phagocytosis mediated by TLR2 and TLR4 and particularly by the shared TLR intracellular adaptor protein MyD88, and consequent intracellular urate crystal recognition by the NALP3 inflammasome, a process bridged by crystal-associated CD14 from the cell exterior. Consequent caspase-1 activation and IL-1 $\beta$  maturation and secretion drive gouty inflammation. The clinical-translational significance of the NALP3 inflammasome engagement is discussed in detail in the text.

bers of the nucleotide-binding oligomerization domain (NOD)-like receptor family, assemble with other proteins in large complexes termed inflammasomes. When NALP3 complexes with caspase-recruiting domain (CARD)-carrying adaptor proteins, activation of the latent inflammatory mediator caspase-1 is stimulated. The activated NALP3 inflammasome complex thereby induces proteolysis of pro-IL-1 $\beta$  and subsequent maturation and release of IL-1 $\beta$ .<sup>11</sup>

Like TLRs, NALP3 contains leucine-rich repeats.<sup>15</sup> Leucine-rich repeat domains of TLRs recognize various pathogen-associated molecular patterns. Therefore, the leucine-rich repeat domain of NALP3 is believed to directly sense components of microbial and other pathogens, stress signals (e.g., high amounts of adenosine triphosphate [ATP] released from dying cells), and urate crystals. Extracellular urate crystal binding of the CD14, an adaptor protein shared by TLR2 and TLR4, does not alter phagocytosis of urate crystals by macrophages, but CD14 switches macrophage encounters with urate crystals that are non-inflammatory into pro-inflammatory events.<sup>16</sup> CD14 does so by allowing urate crystals to fully engage the NALP3 inflammasome to activate caspase-1 and induce release of mature IL-1 $\beta$ .<sup>16</sup>

#### Autoinflammatory Cryopyrinopathies Identify Potential Therapeutic Targets

Over the last few years, mutations in NALP3 have been linked to certain autosomal dominant inherited auto-inflammatory syndromes of differing severity. These syndromes include familial cold-induced auto-inflammatory syndrome, Muckle-Wells syndrome, and neonatal onset multisystem inflammatory disease/chronic infantile neurological cutaneous and articular syndrome.<sup>15</sup> The self-resolution of periodic flares of systemic inflammation in these auto-inflammatory cryopyrinopathies is remarkably similar to the typical course of gouty arthritis, which reflects the shared central role of NALP3.<sup>11</sup> Recent research on auto-inflammatory syndromes has brought to light new mechanisms of action of the venerable gout anti-inflammatory therapeutic colchicine. Specifically, urate crystal-induced NALP3 inflammasome protein complex assembly is suppressed by high concentrations of colchicine, likely by interfering with

TABLE 1: Key Features of Difficult Gout

- > Destructive tophi;
- > Polyarticular gout or frequent flares of monarticular or oligoarticular gout;
- > Allopurinol hypersensitivity or intolerance;
- > Renal insufficiency with creatinine clearance more than 60;
- > History of urolithiasis or documented uric acid overproduction;
- > Cardiovascular, diabetic, hepatic, or upper gastrointestinal tract comorbidities;
- > Intolerance or refractory state to NSAIDs, colchicine, ACTH, and/or glucocorticosteroids;
- > Major organ transplantation or cyclosporine use;
- > Polypharmacy and drug interactions (e.g., statins, macrolide antibiotics, or anticoagulants);
- > Age 70 or older; and
- > Failure to satisfactorily lower serum urate.

internalization of urate crystals and thereby inhibiting crystal delivery to the inflammasome.<sup>11</sup>

Therapeutic studies of autoinflammatory cryopyrinopathies have already provided information of substantial potential value for developing novel and more selective molecular therapeutics for difficult gout inflammation. The responsiveness of familial cold-induced autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal onset multisystem inflam-

matory disease/chronic infantile neurological cutaneous and articular syndrome to IL-1 receptor antagonism is particularly noteworthy because a preliminary, uncontrolled study of

10 gout patients suggested therapeutic benefit of anakinra. Significantly, experimental gouty inflammation in rodents appears more IL-1 $\beta$  driven than TNF- $\alpha$  driven.<sup>12</sup> Further investigation for gouty arthritis is warranted for not only IL-1 inhibitors but also the caspase-1 inhibitors currently under clinical development for osteoarthritis treatment. The ATP-binding function of NALP3 is critical for inflammatory signaling, as is NALP3 leucine-rich repeat domain interaction with the heat shock protein HSP90.<sup>17,19</sup>

Hence, inflammation in difficult gout could be prime applications of novel therapeutics that selectively target the NALP3 ATP-binding domain or HSP90.<sup>17,18</sup>

#### Conclusion

Gout is increasingly common and has become more clinically complex in recent years, particularly in older patients. Clinical development continues for novel, effective hypouricemic agents to counter the limitations of the current generation of universally available primary uric acid-lowering agents for gout (allopurinol and probenecid) in difficult gout. The linkage of gouty inflammation to innate immunity transduced by the NALP3 inflammasome, and the definition of gouty inflammation to be caspase-1 and IL-1 $\beta$  driven (as in familial autoinflammatory cryopyrinopathy syndromes) augur well for novel treatment strategies for gouty inflammation in refractory patients. THE RHEUMATOLOGIST

Dr. Terkeltaub is San Diego VA rheumatology section chief and professor of medicine and rheumatology training program director at the University of California, San Diego. He thanks his lab and clinical colleagues and patients and staff at these institutions.

He is supported by research awards from the VA Research Service and National Institutes of Health and also receives research grant support from TAP Pharmaceuticals. In the last year, Dr. Terkeltaub served as a paid consultant to TAP, AR Scientific, Abbott, Regeneron, and Novartis.

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The last two decades have seen a remarkable resurgence of gout in the United States. This comeback has clinicians facing increasingly complex cases in which age, comorbidities, and concomitant medications impose difficult management decisions.

TABLE 2: Pharmacology of Allopurinol in the Clinic

- > Allopurinol is a pro-drug for oxypurinol;
- > Oxypurinol does not effectively inhibit the oxidized form of xanthine oxidase;
- > Renal elimination of oxypurinol complicates dosing with renal insufficiency;
- > Allopurinol nonselectively affects purine and pyrimidine metabolism;
- > Drug interactions may occur (e.g., with azathioprine or ampicillins);
- > Hepatotoxicity and minor gastrointestinal and central nervous system side effects may occur;
- > Rash occurs in about 2% of treated patients;
- > Major allopurinol hypersensitivity syndrome is rare but has a mortality rate of approximately 20%;
- > Oxypurinol cross-reactivity with allopurinol limits oxypurinol as an alternative to allopurinol in hypersensitive patients;
- > Many patients do not achieve serum urate level less than 6 mg/dL on standard doses, and optimal dosing is controversial, particularly with renal insufficiency;
- > Tophus reduction is typically slow; and
- > Patient compliance is only about 50%, indicating a need for improved patient education.

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# Reading RHEUM

## HANDPICKED REVIEWS OF CONTEMPORARY LITERATURE

### KNEE PAIN

#### Acupuncture Seems Effective in Treating Chronic Knee Pain

>> By Gail C. Davis, RN, EdD

White A, Foster NE, Cummings M, Barlas P. *Acupuncture treatment for chronic knee pain: a systematic review*. *Rheum*. 2007;46:384-390.

#### Abstract

**Objectives:** To evaluate the effects of acupuncture on pain and function in patients with chronic knee pain.

**Methods:** Systematic review and meta-analysis of randomized controlled trials (RCTs) of adequate acupuncture. Computerized databases and reference lists of articles were searched in June 2006. Studies were selected in which adults with chronic knee pain or osteoarthritis of the knee were randomized to receive either acupuncture treatment or a control consisting of sham (placebo) acupuncture, other sham treatments, no additional intervention (usual care),

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or an active intervention. The main outcome measures were short-term pain and function, and study validity was assessed using a modification of a previously published instrument.

**Results:** Thirteen RCTs were included, of which eight used adequate acupuncture and provided Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) outcomes, so were combined in meta-analyses. Six of these had validity scores of more than 50%. Combining five studies in 1,334 patients, acupuncture was superior to sham acupuncture for both pain (weighted mean differ-

ence in WOMAC pain subscale score=2.0, 95% confidence interval [CI] of 0.57-3.40) and for WOMAC function subscale (4.32, 0.60-8.05). The differences were still significant at long-term follow up. Acupuncture was also significantly superior to no additional intervention. There were insufficient studies to compare acupuncture with other sham or active interventions.

**Conclusions:** Acupuncture that meets criteria for adequate treatment is significantly superior to sham acupuncture and to no additional intervention in improving pain and function in patients with chronic knee pain. Due to the heterogeneity in the results, however, further research is required to confirm these findings and provide more information on long-term effects.

#### Commentary

Knee pain (accompanied by interference with function) is a common problem in the general population, and its prevalence increases with age. Acupuncture as a form of sensory stimulation has become increasingly popular as a form of treatment, especially for individuals who experience drug-related problems. In this study, White et al. conducted a systematic review and meta-analysis to evaluate the effects of acupuncture on pain and function in patients with chronic knee pain. Acupuncture was defined as "adequate" for this study if it "consisted of at least six treatments, at least one per week, with at least four points needed for each painful knee for at least 20 min, and either needle sensation (de qi) achieved in manual acupuncture, or electrical stimulation of sufficient intensity to produce more than minimal sensation."

A computerized search of databases (excluding Asian databases) of RCTs identified 157 that were potentially eligible for review. This number was reduced to 13, representing 2,362 patients. Studies were not limited to specific settings, and were conducted in North America (3), the Far East (2), and Europe (8).

The data were extracted from the selected studies independently by two of the authors. Quality, or internal validity, of each RCT was assessed. The review compared studies according to their short-term (25 weeks from randomization with the selected measurement being that nearest 12 weeks) and long-term (last measurement between 26 and 52 weeks) effects. Acupuncture was significantly superior to the comparison groups for short-term pain reduction and improvement of function. Assessment identified that one study contributed to high heterogeneity; when it was removed, results remained the same. Significant long-term effects of acupuncture were also found for both pain and function based on the analysis of three high-quality studies. The size of the effect on pain was 0.4 (small to moderate), and the 95% CIs were wide (0.1, 0.6).

While further evidence is needed before any clear claims regarding acupuncture's use in treating chronic knee pain can be made, the findings suggest that it can be helpful. Its effect is noted as being comparable with taking NSAIDs. Because taking medicine is often associated with side effects, acupuncture may provide a good alternative treatment. Large, high-quality RCTs are needed to provide further evidence.

Until such studies are available to further guide the treatment of knee pain, I believe that the current

evidence supports serious consideration for the use of acupuncture. The decision to use it should be made jointly by the patient and healthcare provider with consideration given to such factors as the patient's desire to try an alternative treatment method, whether the patient is taking an anticoagulant or certain herbs, the availability of a well-qualified acupuncture practitioner, time commitment, and cost.

### ANTI-TNF AGENTS

#### Infliximab in Giant Cell Arteritis and Polymyalgia Rheumatica

>> By Eric S. Schned, MD

Hoffman GS, Cid MC, Rendt-Zagar KE, et al. *Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis*. *Ann Intern Med*. 2007;146:621-630.

#### Abstract 1

**Background:** Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is present in arteries in giant cell arteritis (GCA).

**Objective:** To evaluate the efficacy of infliximab, an anti-TNF- $\alpha$  agent, in GCA.

**Design:** Randomized, controlled trial.

**Setting:** Twenty-two sites in the United States, United Kingdom, Belgium, Italy, and Spain.

**Patients:** Forty-four patients with newly diagnosed GCA that was in glucocorticosteroid (GCC)-induced remission.

**Intervention:** Participants were randomly assigned in a two-to-one ratio to receive infliximab (5 mg/kg of body weight) or placebo. Sixteen patients were assigned to GCC plus placebo, and 28 patients to GCC plus infliximab.

**Measurements:** End points were measured through Week 22, when an interim analysis resulted in early stopping of the planned 54-week trial. Primary end points were the number of patients who remained free of relapse through Week 22 and adverse events. Secondary end points were time to first relapse, biomarkers, cumulative GCC dose, and the number of patients who remained relapse free while the GCC dosage was tapered to 10 mg/d.

**Results:** Infliximab therapy did not increase the proportion of patients without relapse at Week 22 compared with placebo (43% versus 50%, respectively; difference, -7 percentage points [95% CI, -38 to 23 percentage points];  $p=0.65$ ), nor did it increase the proportion of patients whose GCC dosages were tapered to 10 mg/d without relapse (61% versus 75%, respectively; difference, -14 percentage points [CI, -42 to 14 percentage points];  $p=0.31$ ). The incidence of infection was 71% with infliximab and 56% with placebo (difference, 15 percentage points [CI, -14 to 45 percentage points]).

**Limitations:** The sample was too small to rule out modest effects of infliximab and included only patients with a new diagnosis. Only one dose of infliximab was evaluated, and the study was terminated early.

**Conclusions:** This trial is too small to draw definitive conclusions, but it provides evidence that using infliximab as maintenance therapy in patients in GCC-induced remission of newly diagnosed GCA is of no benefit and may be harmful. If infliximab has benefit, it is unlikely to be great.

Salvarani C, Macchioni P, Manzini C, et al. Infliximab plus prednisone or placebo plus prednisone for the initial treatment of polymyalgia rheumatica. *Ann Intern Med.* 2007; 146: 631-639.

### Abstract 2

**Background:** A reliable alternative to steroids for treating polymyalgia rheumatica (PMR) has not yet been identified. Although infliximab has been used occasionally in steroid-resistant cases, its efficacy has not been demonstrated in a controlled study.

**Objective:** To compare the efficacy of prednisone plus infliximab with that of prednisone plus placebo in patients with newly diagnosed PMR.

**Design:** Randomized, placebo-controlled trial.

**Setting:** Seven rheumatology clinics in Italy.

**Patients:** Fifty-one patients with newly diagnosed PMR. Patients with associated GCA and those who had been previously treated with steroids or biological or immunosuppressive agents were excluded.

**Intervention:** Initial therapy with oral prednisone tapered from 15 mg/d to 0 mg/d over 16 weeks according to a standard protocol, plus infusions of placebo or infliximab, 3 mg/kg of body weight, at Weeks 0, 2, 6, 14, and 22.

**Measurements:** The primary efficacy end point was the proportion of patients without relapse or recurrence through Week 52. Secondary outcomes were the proportion of patients no longer taking prednisone, the number of relapses and recurrences, the duration of prednisone therapy, and the cumulative prednisone dose.

**Results:** Four patients (three in the infliximab group and one in the placebo group) did not complete the trial. The proportion of patients who were free of relapse and recurrence at 52 weeks did not differ between groups (six of 20 patients [30%] in the infliximab group versus 10 of 27 patients [37%] in the placebo group; adjusted risk difference, -3 percentage points [95% CI, -31 to 24 percentage points];  $p=0.80$ ). In a sensitivity analysis that included dropouts, the best-case scenario yielded a difference of 5 percentage points (CI, -21 to 31 percentage points) between the groups. The secondary outcomes at Weeks 22 and 52 did not differ between the groups.

**Limitations:** The study had a small sample and a short follow-up. A low dosage of infliximab was used, and the prednisone dosage was rapidly tapered.

**Conclusions:** Although too small to be definitive, the trial provides evidence that adding infliximab to prednisone for treating newly diagnosed PMR is of no benefit and may be harmful. If there is benefit, it is unlikely to be large.

### Commentary

The need for meaningful alternatives to GCCs in treating GCA and PMR is painfully obvious to rheumatologists. Eighty percent of patients with GCA will experience at least one adverse event due to GCCs and overall morbidity of this therapy is high, especially in an older population. Unfortunately, studies to find safer treatments, such as methotrexate, to reduce the dose or duration of GCC therapy and lead to prolonged remissions have been disappointing to date.<sup>1,2</sup>

Growing knowledge of the role cytokine mediators in the vessels affected by GCA, including TNF, raises the possibility that the TNF- $\alpha$  inhibitors might be effective steroid-sparing agents. Several case reports suggested that infliximab could produce remissions in patients with GCA and PMR.<sup>3,4</sup> Case studies are often encouraging—although sometimes misleading because of the bias in publishing positive results. Randomized trials are always important in determining the true value of a therapy, often dashing the hopes provided by the preliminary reports.

Two randomized, placebo-controlled trials with similar designs have recently been published, ex-

ploring the role of infliximab in treating patients with early GCA and PMR respectively. Disappointingly, both studies came to the same conclusion: Infliximab is of no benefit in either disease.

In the first of these studies, Hoffman and a group of international collaborators investigated the effects of infliximab in patients with GCA. These investigators randomized 44 patients with newly diagnosed GCA (less than four weeks' duration) in a 2:1 ratio to receive infliximab, 5 mg/kg, or placebo at Weeks 0, 2, and 6, and every eight weeks thereafter. Patients had already achieved remission with GCCs. GCCs were then tapered in a carefully prescribed fashion so that, in the absence of a relapse, GCC dosage of 10 mg/day would be achieved at four months and would be discontinued by six months.

Importantly, as the data in this study indicate, the proportion of patients who were relapse-free through Week 22 (a primary study end point) was similar between infliximab and placebo patients (43% versus 50%;  $p=0.65$ ).

Further, secondary study end points were also not different between infliximab and placebo groups: cumulative dose of GCCs at Week 22 (3,154 mg versus 3,049 mg;  $p=0.95$ ); the proportion of patients who remained relapse-free during taper of GCCs to 10 mg/day (61% versus 75%;  $p=0.31$ ); mean GCC dose at relapse (13.4 mg/day versus 11.8 mg/day;  $p=0.59$ ); and biochemical markers of inflammation (C-reactive protein, erythrocyte sedimentation rate, and interleukin-6 levels).

There was no difference in the proportion of patients who achieved complete remissions, defined as no sign of active GCA for at least 12 weeks after cessation of GCCs: 39% versus 44% ( $p=1.00$ ). Of the patients who achieved complete remission, 73% of the infliximab group and 86% of the placebo group later had a relapse. Of note, there was no difference in the frequency of adverse events or serious adverse events between the two groups. Thus, while the addition of infliximab was safe, it did not add benefit.

In view of the putative role of cytokines in the pathogenesis of GCA, these results may appear surprising. There are several explanations for the failure of infliximab to show activity. The authors acknowledge that a higher dose of infliximab might have been efficacious. Also, methotrexate was not administered concomitantly with infliximab and this might have altered efficacy. However, only about one-quarter of patients developed anti-infliximab antibodies 20 weeks after the last dose was administered, so that lack of efficacy could not be attributed to anti-drug antibodies.

In a related study, Salvarani and Italian colleagues investigated the effects of TNF blockade on patients with PMR. These investigators randomized 51 patients with newly diagnosed PMR (mean duration of symptoms before therapy of 10 to 11 weeks) in a 1:1 ratio to receive infliximab, 3 mg/kg, or placebo infusions at Weeks 0, 2, 6, 14, and 22. All patients received prednisone 15 mg for the first four weeks, which was then tapered at four-week intervals to 15 mg, 10 mg, 5 mg, and 2.5 mg daily dosages. Patients with clinical or histological evidence of GCA were excluded.

The proportion of patients free of relapse at 52 weeks—the primary end point—was not different between infliximab and placebo groups, and the groups also did not differ in all secondary end points, including the proportion of patients without relapse at Week 22 (55% versus 54%;  $p=1.00$ ); the propor-

tion of patients no longer taking GCCs at Week 22 (55% versus 64%;  $p=0.56$ ) or Week 52 (50% versus 54%;  $p=1.00$ ); median relapses in all patients (one versus one;  $p=0.69$ ); median cumulative dose of prednisone at 52 weeks (17.1 gm versus 12.2 gm;  $p=0.31$ ). There was no difference in adverse drug events (eight in each group).

The authors acknowledge several limitations of the study. Patients all had newly diagnosed PMR. Pathophysiological studies show an association between high TNF- $\alpha$  production and steroid-resistant disease. Could infliximab have a beneficial role in more chronic PMR? Also, the dose of infliximab was low—3 mg/kg—and prednisone was tapered quickly over 16 weeks, which could have contributed to the high frequency of flare-ups.

## I do not routinely add second-line agents in my new patients with giant cell arteritis and polymyalgia rheumatica, but I am aggressive in trying to minimize adverse effects of glucocorticosteroids.

These two studies will probably put an end to investigations on the use of infliximab as a steroid-sparing agent for GCA and PMR. The studies are small and the confidence intervals were wide for most outcomes in both studies. While it is possible that a small beneficial effect could exist for infliximab in these diseases, the expense of this agent probably would preclude its cost-effectiveness for relatively small potential benefits.

The search for good alternatives to GCCs will undoubtedly continue—and it should because the side effects of this therapy are high in older patients. Because of evidence that other cytokines—notably interleukin-1, interleukin-6, and interferon-gamma—contribute to vascular inflammation in GCA, it is likely that these cytokines will be targeted in future trials.

So what does one do while waiting for more definitive solutions? I do not routinely add second-line agents in my new patients with GCA and PMR, but I am aggressive in trying to minimize adverse effects of GCCs. I add prophylactic bisphosphonates, follow bone-density scans, vaccinate, and treat hyperlipidemia, hypertension, and hyperglycemia.

Despite conflicting evidence on efficacy, I have occasionally added methotrexate in some of my patients on long-term steroids who have intolerable adverse effects from GCCs. I've sometimes been successful in subsequently tapering GCCs.

Lastly, I vigorously pursue other possible—and common—causes of confounding musculoskeletal pain that patients may find responsive to GCCs, but can be treated safely in other ways, such as rotator cuff inflammation or tears, cervical disc disease, and myofascial pain—what I call pseudo-polymyalgia. Treating these might allow steroid tapering in otherwise resistant disease.

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## METRICS IN RHEUMATOLOGY

# THE PERIPATETIC THEODORE PINCUS, MD

Tireless champion  
for patient  
self-report

>>By Gretchen Henkel

**B**egin a conversation with Theodore Pincus, MD, about his scientific career, and you'll soon be discussing a range of topics, from the history of rheumatology to Edward Gibbon's *The Decline and Fall of the Roman Empire*. "The thing about Ted is that he is an effervescent person," says Halsted R. Holman, MD, who was chair of medicine at Stanford University's School of Medicine when Dr. Pincus became an internal medicine resident in the early 1970s and is now the emeritus Guggenheimer Professor of Medicine there. "He has great enthusiasm about whatever he's into."

Dr. Pincus' far-reaching intellectual curiosity has taken him down many paths in his 40-plus years in medical science. He is currently a professor of both medicine and microbiology at Vanderbilt University in Nashville, Tenn., reflecting his decades-long interests in both basic science and clinical medicine. He is well known among his rheumatology colleagues for his discovery of the association of education with outcomes in RA, and known worldwide for his tireless advocacy for the



Dr. Pincus with his family in Boulder, Colo.

## From Surgery to Immunology

From his days as an undergraduate at Columbia University in New York City, Dr. Pincus had been interested in analyzing the nature of antibodies involved in immune complex disease. One mentor, Charles Christian, MD, then the head of rheumatology at Columbia, had employed him in his laboratory while he was an undergraduate student.

After receiving his medical degree in 1966 from Harvard Medical School, Dr. Pincus began a surgical residency. But history intervened: It

was the time of the Vietnam War, and he joined the Public Health Service to work at the National Institutes of Health (NIH) in lieu of active military duty. While at the NIH, he conducted immunology research under the directorship of Norman Talal, MD, and devised a simpler version of an earlier DNA antibody test that could be used in the clinic to diagnose lupus. "And it worked!" says Dr. Pincus. "That study was published in *The New England Journal of Medicine* in 1969 and actually, in a sense, set the stage for the rest of my career."

## Stanford and Beyond

After his four years of public health service at the NIH, he applied for an internal medicine residency at Stanford. He recalls that Dr. Holman was very gracious about his application and did not require any "remedial" training (as other programs had suggested) after his hiatus from a surgical residency. "That was no problem," says Dr. Holman. "We didn't believe in

disciplinary lines or required training programs or the like. It was no problem for us to take a smart, engaging surgeon and say, 'OK, you want to be a doctor in medicine? That's fine with us.' "

In the early 1970s, rheumatology was just emerging as a distinct discipline. "We were interested in people who brought skills and potentially different valuable ideas," says Dr. Holman, "and [Dr. Pincus] fit right into that category." After Stanford, Dr. Pincus returned to Cornell for his second year of residency to be near Dr. Christian, who had moved from Columbia to the Hospital for Special Surgery. When he applied for a rheumatology fellowship, he was told that Robert Good, MD, PhD, at Memorial Sloan-Kettering was offering a position as assistant professor in molecular virology research, which paid \$15,000 more than a fellowship. With a new baby to provide for, Dr. Pincus opted for the assistant professorship.

He continued his work on deciphering genetic control of viruses at the cellular level at the University of Pennsylvania's Wistar Institute in Philadelphia as a professor in molecular virology, where was gradually introduced to the joys of clinical work.

## Treasure in a Jim Beam Carton

In 1980, Dr. Pincus accepted an invitation to develop a rheumatology program at Vanderbilt University in Nashville, and began commuting from Philadelphia to Nashville every Wednesday. Coincidentally, in April of that year, James F. Fries, MD, professor of medicine at Stanford University School of Medicine (Calif.), first publication of the HAQ appeared in *Arthritis & Rheumatism*. In fact, Dr. Pincus recalls reading the article on the plane to

[Dr. Pincus] has certainly been the most important proponent for the use of self-report questionnaires in clinical practice.

—Frederick Wolfe, MD

value of a patient self-report questionnaire such as the Health Assessment Questionnaire (HAQ) in assessing and documenting patient status, course, and outcomes.

"If you look at the movement to evaluate outcomes of management in chronic disease, Ted was in on the beginning of it," says Dr. Holman. "And, if he wasn't the first one, he was clearly the most effective in showing the relationship of patients' education to outcome."

Frederick Wolfe, MD, director of the National Data Bank for Rheumatic Diseases in Wichita, Kan., and a long-time collaborator with Dr. Pincus, agrees. "He has certainly been the most important proponent for the use of self-report questionnaires in clinical practice."

How did Dr. Pincus become, as he calls it, "a disciple of the HAQ"? The story does not unfold in a straight trajectory. But then, neither did his career path.

### CAREER TIMELINE

1967—Serves as staff associate at the U.S. Public Health Service of the National Institutes of Health.

1973—Completes a one-year internal medicine residency at Cornell-New York Hospital.

1966—Graduates from Harvard Medical School in Boston. Completes a one-year surgery internship at Massachusetts General Hospital, Boston.

1972—Completes a one-year internal medicine residency at Stanford University.

1974—Completes a one-year internal medicine fellowship at Memorial Sloan-Kettering Cancer Center in New York.



Dr. Pincus with a statue of Puccini outside the composer's villa at Torre Del Lago, Italy. It was taken during a visit to Pisa, the home of *Clinical and Experimental Rheumatology*, for which Dr. Pincus has edited an annual supplement concerning contemporary topics in rheumatology since 1999.

Nashville: "I regarded this as a clinical tool that might improve clinical medicine."

He immediately began using the questionnaire in his clinics. "I've always been interested in measurement in clinical care," he says. "That's what my DNA test was about: measurement. So I've always been sort of a 'quant.'"

In 1982, Dr. Pincus inherited a box of records from William Sale, MD, an orthopedic surgery resident who was leaving the university for private practice. Filed inside a carton bearing a Jim Beam whiskey label were records from 75 patients with RA whom Dr. Sale had studied and assessed in 1973.

"That was very far-sighted," says Dr. Pincus. "I had nothing to do with the assessment, but it included a whole list of questions about daily living as well as joint exams—basically what we do today, but with a less developed methodology."

The patients had received injections of thiopeta, an antineoplastic alkylating agent. Dr. Pincus was curious how these patients had fared in the nine intervening years because of concern that there might be an increased risk of cancer associated with alkylating agents. He enlisted the help of a medical student, who contacted the patients whose records were in the box. A physical therapist gave Dr. Pincus lessons on performing function measures (grip strength, walking time, and button test), and he began the follow-up with these patients on Saturdays.

Interestingly, Dr. Pincus was able to account for all 75 of the original study patients. "In a way, we were lucky," he says, "because this part of Tennessee had less population mobility than, say, California and New York." But even more startling were the results from their efforts. Of the original 75 people, 20 had died—a statistically-significantly higher number than what would have been expected. He also noted severe declines in functional status for almost all the remaining patients. These two findings contradicted the conventional wisdom of the time (based on population studies) that RA was not a severe disease. He

also found that premature death in RA could be predicted by two unexpected variables: functional status, as documented on Dr. Sale's precursor HAQ, and education level.

This was the eureka moment for Dr. Pincus: Outcomes for people with RA could be better predicted by questionnaires than by X-rays or lab tests. His first paper about his findings was initially rejected by many journals; it was then that he realized that promoting the questionnaires as both clinical and research tools would be a struggle.

"I really thought that as soon as I told the world about this thing with the questionnaires that everybody would start using them," he recalls. "In a sense, the questionnaire was a marker like blood pressure or cholesterol: It could predict premature death."

He took a three-month sabbatical from his lab to rewrite the paper and refine its methods. The three months turned into 26 years. "I never thought I'd be sitting here, still struggling to convince people to use this," he says. "I thought I would be honored—well, I am honored by this telephone call. I really couldn't believe that people didn't use this questionnaire, and I became a proselytizer for its use."

#### A Bad Rap for Questionnaires?

Dr. Pincus modified the original HAQ to make it shorter and easier to use in clinical practice. In 1985, he used modern measures to do a repeat of the 1973 Sale study and found that the questionnaire was the best predictor of death in patients with RA at five years post-assessment. In subsequent decades, he has repeatedly proven that the multidimensional HAQ (MDHAQ) is as robust in predicting patient outcomes as the longer version.

The issue of doing outcome measurement for chronic diseases within the context of the individual practice has not been settled to this day, notes Dr. Holman. "When Ted began to deal with the HAQ in the 1980s, doctors—myself included—were very reluctant to add this into our practices. It added a dimension of work that you weren't reimbursed for, and most people didn't know how to use it."

Dr. Holman believes a large part of the resistance stems from medical education's cleaving to the acute disease rather than the chronic disease model. This transformation in medical education is still in its infancy, he says.

Yusuf Yazici, MD, assistant professor of medicine at New York University Hospital for Joint Diseases, first met Dr. Pincus after a talk he gave at the World Trade Center in 2000, and was convinced to incorporate questionnaires into his practice. "I was just finishing training and starting out, so it was easier to do than to change to another system [of patient evaluation]," says Dr. Yazici.

He believes physicians and patients may have a negative association with questionnaires because of the exhaustive instruments employed in clinical trials. "For them, 'questionnaire' means two hours of sitting down with someone to fill it out," he says. "In the questionnaire that Dr. Pincus has devised, the shorter, simplified version is as robust as the full-length clinical trial questionnaire. And it's much simpler and more straightforward to use."

Drs. Pincus, Yazici, and Martin Bergman, MD, a

rheumatologist at Arthritis and Rheumatology in Ridley Park, Pa., presented a study at an ACR meeting documenting their comparison of the standard versus the MDHAQ. Each physician scored a HAQ, which took about 42 seconds. Then he or she scored the MDHAQ, which took 7.5 seconds. Dr. Pincus voiced frustration that despite results such as these, the HAQ or MDHAQ is not used more often as a clinical management tool. "It is curious that many rheumatologists say that they 'don't have time' to use a questionnaire in patient care," Dr. Pincus says. "I don't have time *not* to use the questionnaire. ... Our questionnaire saves me at least three minutes per patient—sometimes more."

Undaunted, he continues to travel internationally, speaking and collaborating with researchers. With his indefatigable drive to advance the cause of patient self-report, Dr. Pincus keeps a full calendar of teaching, research, and travel. He has friends and colleagues all over the world, and he enjoys hiking in the woods near Nashville to relax. He often travels to Denver to spend time with his daughter and grandchildren. He's also a lover of the opera (his current favorite is Johann



Dr. Pincus with a patient whose active rheumatoid arthritis has been controlled with a TNF agent.

Strauss' "Die Fleidermaus") and of the *New York Times* crossword puzzles.

With a reputation for straightforwardness, Dr. Pincus often cuts a colorful figure at meetings. Dr. Yazici finds this refreshing, and is impressed with Dr. Pincus' strong opinions balanced by his approachability. "He won't beat around the bush, so you know what he is thinking at all times," Dr. Yazici. "But I think that's a much better way to do business."

Dr. Wolfe, also an avid advocate for and practitioner of patient self-report (he has used questionnaires for every patient he's seen since 1974), has forged a strong personal and professional bond with Dr. Pincus. "Everywhere you go, you see Dr. Pincus telling people how important it is to use self-report questionnaires in clinical practice."

If he is a restless spirit in his quest, Dr. Pincus is also a generous one. "Each year he edits supplements to medical journals summarizing the rheumatology literature," says Dr. Wolfe. "He is selfless in doing all these things. He's a very generous spirit, and he would go out of his way to help people. I think he's a very good man. I'm glad that I'm friends with him and that he's willing to have me as a friend."

THE RHEUMATOLOGIST |

Gretchen Henkel is a medical journalist based in Los Osos, Calif.

1980—Accepts position as professor of medicine and microbiology and chief of rheumatology and immunology at Vanderbilt University School of Medicine in Nashville, Tenn.

1992—Steps down as chief of rheumatology and immunology at Vanderbilt.

1976—Accepts position as adjunct associate professor of medicine (rheumatology) at the University of Pennsylvania School of Medicine in Philadelphia.