

the Rheumatologist

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page 14

Rheumatology with Rhythm

The circadian rhythm offers insight into treating rheumatic diseases

>> By Rainer H. Straub, MD,
and Maurizio Cutolo, MD

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Why do patients hurt more in the morning than in the evening? Why do rheumatologists ask about morning stiffness and not evening stiffness? Why is it important in clinical trials to assess the effects of therapy at the same time point during the day?

The answers to all of these questions relate to the *circadian rhythm*. The term circadian rhythm refers to the 24-hour cycles in the physiological processes of living organisms that include, among others, the cycle of hormone levels or nerve activity. While circadian rhythms are a fundamental feature of the biology of animals, they are usually not considered as important determinants of disease, although their influence is profound.

continued on page 14

Th17 CELLS EXPLAINED

The new kids on the block have rheumatologic ramifications

>> By Virginia Hughes

Boston—In the early 1990s, immunologists thought there were just two types of helper T cells—Th1 and Th2—which, while not by themselves damaging, could activate other effector cells to promote disease. However, discoveries in last few years have proven that the T-cell world is actually much more diverse.

By 2000, researchers had discovered a third class of helper T cells that called into question everything known about Th1 and Th2. Surprisingly, these new cells—named Th17 because they secrete a cytokine called interleukin 17 (IL-17)—have some cytotoxic properties. Most interesting for rheumatologists, Th17 cells can display specificity for

continued on page 21

Take the Measure of Osteoarthritis

The WOMAC index standardized OA status measurement, as described by its creator

>> By Nicholas Bellamy,
MBChB, MD, MSc, MBA, DSc

The quantification of health-related quality of life (HRQoL) in osteoarthritis (OA) plays a key role in determining the severity and outcome of OA. This issue is of key importance to rheumatologists as the population ages and the number of patients with OA dramatically increases. In both research and practice, the evaluation of the therapeutic benefit of interventions—used either alone or in combination—is critical. Reliability, validity, and responsiveness are essential attributes of health status measurement tools, while brevity, simplicity, and ease of scoring are regarded with high importance, particularly in clinical practice applications.¹

Prior to 1981, measurement procedures for quantifying pain, stiffness, and physical disability in hip and knee OA studies lacked standardization. In 1982, with the encouragement of the late

continued on page 18

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page 18

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The Symptoms or the Disease

Where should we focus?

>> By David A. Fox, MD



Through the late fall of 2007, we yet again experienced governmental dysfunction on display in Washington, D.C., regarding important healthcare issues. As Congress and the president bickered over whether to extend and expand federal funding of health insurance for children (the program known as State Children's Health Insurance Program or SCHIP), the prospect of a 10% cut in Medicare reimbursement for physicians' services, effective January 1, 2008, loomed as an ever-more-likely scenario with each passing day. This cut ensued from a budgeting mechanism used by the federal government known as the Sustainable Growth Rate (SGR), a truly Orwellian term for a mechanism that provides neither growth nor sustainability of healthcare services provided to patients by physicians.

Practicing rheumatologists, already struggling to cope with several years of no increase in the Medicare fee schedule—effectively a significant decrease—reached their boiling point. The ACR's advocacy list serve reflected a palpable mix of frustration and anger. At times I thought my computer screen was becoming hot to the touch! At the last minute, a budget compromise averted—or at least delayed—the 10% cut and replaced it with a whopping 0.5% increase, but only until July 1, 2008. What happens after that is anyone's guess.

We Can't Ignore the Underlying Disease

Rheumatologists know that when a patient is sick, it's a mistake to simply treat the symptoms without determining the basic nature of the patient's illness. When faced with an elderly patient who has fever, proximal stiffness, headache, and visual loss—potentially a case of giant cell arteritis—a rheumatologist would never be content with prescribing analgesics and the use of magnifying lenses. Instead he or she would obtain a detailed history, perform a thorough physical examination, order appropriate laboratory tests and diagnostic procedures, and even begin definitive treatment while collecting all necessary data.

One could make the case that, in trying to cope with the issues of the moment—such as threatened cuts in physician reimbursement triggered by the SGR—we have become preoccupied with the symptoms and are in danger of neglecting the disease. It's not that difficult to see that the allocation of resources within the healthcare system of the United States is gripped by a multi-system disease. This disease may not yet have a catchy eponym, but it is defined by several serious and uniquely paradoxical features, including the following:

1 Our country spends more on healthcare, per capita, than any other country, and a greater proportion of our gross national product on healthcare than any other country, yet our life expectancy, infant mortality rate, and other meaningful measures of health lag behind many other nations;

2 Healthcare costs are rising faster than the general rate of inflation, yet the number of uninsured Americans keeps growing;

3 Enormous waste of healthcare resources on expensive tests and procedures of dubious or marginal value is well documented, yet inexpensive interventions of proven benefit are not consistently used;

4 As physicians, we have far better tools to diagnose and treat disease than in the past, but struggle constantly to surmount hurdles to the use of these tools for the benefit of our patients; and

5 Although the prevention and management of chronic disease are clearly the dominant healthcare needs of the population of the United States, the current reimbursement structure fails to provide adequate resources to support the professionals who could meet these needs: primary care physicians, "cognitive" specialists such as rheumatologists, and other healthcare professionals who are essential for the care of such patients.

All of these points have been exhaustively documented, so why belabor the obvious? Because until these problems are fixed, we need to keep attention on the untreated, pervasive, and deeply rooted disease that is undermining the viability of our healthcare system. To not do so would be to neglect part of our responsibility to our patients.

How to Cure Our Healthcare Ills?

The 2008 presidential election process, which is highlighting healthcare reform as one of the top issues for public debate, may provide an opportunity for more substantial examination of potential treatments for our healthcare system disease—let's call it HCSD for short. A variety of therapeutic strategies have been proposed, and several clinical trials are underway at the state level. The exchanges on the ACR's advocacy list serve during the past few months demonstrate the diversity of opinions among ACR members regarding the right treatment or cure for HCSD, ranging from transition to a single-payer system to more modest adjustments of the current healthcare reimbursement structures. This range of viewpoints highlights one of the problems in defining a clear therapeutic plan: the inability of the medical profession to achieve internal consensus about what should be done.

The ACR has not proposed a unique and comprehensive plan for reform, but it has crafted a series of position statements that emphasize the importance of patient access to appropriate care. Arguably we should be doing more to provide a prescription that would effectively treat HCSD, and this is an ongoing challenge for several of the College's standing committees, the ACR board, and the officers. In attempting to tackle HCSD, we need to focus on changes that produce increased value from healthcare expenditures. To do this we need to be willing to take on the issue of how much of the healthcare dollar is consumed by administrative costs and the costs of competitive behavior of health systems—both those that are openly "for profit" and those that are supposedly nonprofit but that behave otherwise.

And what about pharmaceutical prices, and the degree to which these prices are driven up by marketing costs—and not just marketing to consumers but also to physicians?

Any reforms that we advocate, especially those that could benefit our specialty and our members, must also be in the best interest of our patients. This has always been the policy of the ACR and must continue as a guiding principle that underlies all of our positions. And we need to be realistic about the role of a relatively small subspecialty society in tackling the "macro" issues inherent in HCSD. At times our interests and those of our patients are best served by our participation in collaborative advocacy within larger professional organizations such as the AMA, which is clearly on record concerning the need to abolish the SGR. However, often we do need to act on our own.

The past few years have seen a significant aug-

As physician-citizens, make thoughtful choices in November as well as in the remaining primaries and caucuses, with the need to cure healthcare system disease as one of your high-priority issues.

mentation of the ACR's advocacy activities: repeated visits to Capitol Hill by ACR officers, board and committee members, and other ACR members with an interest in advocacy; greatly increased allocations for professional lobbying and advocacy counsel; and the formation of RHEUMPAC. Concurrently, the ACR has worked hard to develop our relationships with federal agencies such as the Food and Drug Administration, the National Institutes of Health, and the Center for Medicare & Medicaid Services. We speak clearly, consistently, and coherently on the range of issues that are important to our members, including our clinical practitioners and our academic researchers. And we communicate much more with each other, whether on the advocacy list serve or in the pages of *The Rheumatologist*.

There are other things that each ACR member can do: participate in our visits to Capitol Hill, call or write your elected representatives in the House and Senate, and contribute to RHEUMPAC. Also, as physician-citizens, make thoughtful choices in November as well as in the remaining primaries and caucuses, with the need to cure HCSD as one of your high-priority issues. | THE RHEUMATOLOGIST |

Dr. Fox is president of the ACR. Contact him via e-mail at fox@rheumatology.org.

GET INVOLVED

To learn more about the ACR's advocacy activities and find out how you can get involved, visit the political advocacy section of the ACR Web site, www.rheumatology.org.



Does Secondary Gain Exist?

How I learned to balance the complex equation of loss and gain from disease >> By David S. Pisetsky, MD, PhD

In this and two subsequent columns, I will discuss the concept of secondary gain as it applies to disability. My goal is to revise a view I long embraced and, indeed, promulgated enthusiastically to students, house officers, and fellows. On many occasions in my teaching clinic, I stated that the concept of secondary gain in disability is misleading if not erroneous because what can be labeled as gain in reality represents loss. Sometimes I was even more dogmatic and said that secondary gain does not exist.

I have been off target in my views, misguided by an effort to develop a more fair-minded and compassionate approach to disability. In what I think will be a constructive effort at revisionism, I will advance another concept of secondary gain that, while nuanced, is hopefully more illuminating. I did not get the inspiration for another look at secondary gain from reading an article in a high-impact journal or hearing a lecture from a touted thought leader. Rather, I rethought my views during a piano concert by Leon Fleisher, a virtuoso with a troubled right hand.

Subjective Pain and Secondary Gain

Like virtually every rheumatologist I know, I have

evaluated patients who seek disability despite minimal signs of arthritis or musculoskeletal disease. Some of these patients lack any objective findings by physical exam, X-ray, or laboratory tests. Nevertheless, they believe that their symptoms preclude employment. The origin of these ailments is mysterious. Patients with fibromyalgia, chronic fatigue syndrome, and whiplash injury are among this group, and deciding whether these patients should be considered for disability is both controversial and vexing. Lacking better explanation for the desire of these patients not to work, the term "secondary gain" is often used.

What is secondary gain? In common parlance, it refers to the benefits or advantages that can accrue from not working. These may include money, freedom from a demanding or boring job, and leisure time for enjoyable activities. All of these benefits are supposedly made better by knowing that a generous check will arrive in the mail every month to pay the bills.

For some patients, the situation is more complicated because secondary gain may represent a desire for control and leverage to pressure family for attention and care. This dynamic can even extend to the physician as pressure to recommend disability.

Suffice it to say, physicians do not like this. Applying the term "secondary gain" to a patient can convey a negative sentiment, often accompanied by annoyance and condescension from the provider. It can also lead to a blame game, in which patients are blamed for their symptoms and desire for disability.

Not Everyone Gains

Clearly, there are patients with arthritis who want to work but have trouble on the job. Even if the jobs are tough and pay little, these people want to keep at it. There is little secondary gain in disability for these people. I can remember a man with a back stiffened with ankylosing spondylitis whose work involved climbing a ladder to stock merchandise in a hardware store. My patient loved his job and took pride in knowing the locations of wire brads and cotter pins on high-up shelves.

Although my patient had safely performed this job for more than twenty years, a new supervisor, afraid of the liability potential if my patient should fall from a ladder and shatter his spine, fired him. Given his physical condition, my patient could not find another job and reluctantly we put him on disability. My patient was bereft. He wanted to stock hardware, not fish for bass, and there was no gain for him.

There are also patients in terrible jobs who would rather sacrifice the usual benefits of work to avoid the stress, misery, or danger of their current job. For these patients, the "gains" reflect resignation and capit-

ulation as much as anything else.

I had an uncertain approach to disability until I attended a lecture by a psychiatrist who researched chronic pain. I have listened to thousands of lectures in my career and dutifully record the CME hours for licensing and credentialing purposes. The evaluation forms for CME programs include questions inquiring whether the lecture was relevant to your practice and would influence the way you treat patients. To be nice to the lecturers and purveyors of CME, I usually put down a "3" or "4" out of "5" on the question about the influence on my treatment. In reality, it is unusual that I learn anything that will really alter what I do. The treatment of many conditions is relatively set and there are an increasing number of guidelines to provide a schema for care. Hearing a really new way of thinking about care is unusual.

The lecture by the psychiatrist was different. His ideas really changed my view because he questioned the concept of secondary gain, advocating a different language or idiom for the people seeking disability. To this scholar, some of the people seeking disability for "secondary gain" were actually experiencing a secondary loss. The sources of the loss were many: loss of pride and self-esteem, loss of human contact and engagement, and loss of tangible accomplishment and achievement. As the psychiatrist said, even with a regular check from the government, sitting at home can be an isolating and boring existence.

In this view, some patients who seek disability in the absence of physical limitation may have emotional limitation, with the request not to work emblematic of underlying psychological or characterologic disturbance. To the psychiatrist, the request for disability could be a symptom, a signal for help. While the idea of secondary gain can call forth resentment and derision, the idea of secondary loss calls forth sympathy and understanding.

And Not Everyone Loses

Having assimilated this viewpoint, I began to shift not only my practice but also my teaching. When one of the fellows evaluating a patient for disability would glibly say that the goal was secondary gain, I would challenge him, "Where is the gain?" The fellow would usually say, "The patient doesn't have to work," to which I would reply, "Would you exchange your job for a life on disability?" So far, no one has said "yes."

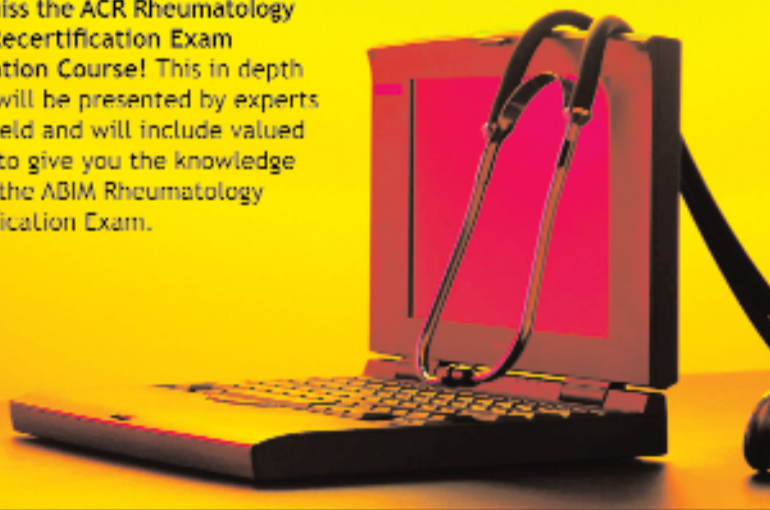
In trying to shift the language of disability, I overcompensated and missed an important aspect of secondary gain. I accepted the negative connotation of secondary gain and wanted to eliminate it rather than understand it. As I have come to realize, secondary gain is a spectrum and comes in positive and negative forms. Rather than trying to nullify the concept, I should have expanded it to comprehend how patients and providers respond to losses that come with illness.

As I will discuss in a future column, providers can measure loss far better than gain and easily miss the success of those individuals with illness who transform their physical disability into a life of achievement and satisfaction and, yes, a very positive type of secondary gain. | THE RHEUMATOLOGIST |

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

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Pain Management Meditations

Thoughts from a career spent understanding—and alleviating—pain >> By Gail C. Davis, RN, EdD

What do we know about arthritis-related pain and its management? I have been studying the pain experienced by persons with rheumatic diseases for 20 years, and the more I learn, the more I realize

that I don't know. I would guess most rheumatologists and rheumatology health professionals feel the same. Understanding and managing pain remains a challenge for many reasons. Just a few of these include:

- > Individual interpretation of pain intensity;
- > Individual perception of living with pain;
- > The relationship between pain and factors such as functional ability and affect (e.g., de-

pression and anxiety); and

- > The selection of pharmacological and non-pharmacological management strategies to “fit” the individual.

What I’ve Learned About Pain

I began my study of pain by developing a measure of the pain experience that has been very helpful in understanding the components of the pain experience as interpreted by the individual patient. Testing of the Chronic Pain Experience Instrument (CPEI) resulted in the identification of three dimensions: function, affect, and helplessness.¹ Probably most of us do not find these results surprising as we think about the experiences faced by people with arthritis. Revisiting the challenges listed above, we know that pain can affect function. Pain may, for example, affect how well one is able to walk, participate in activities that are personally enjoyable, pick up an object or a child, or perform work-related requirements.

When we think of affect, the often-asked question emerges: Does pain cause depression or anxiety, or do high levels of depression and/or anxiety cause pain? The probable answer is that there is a cyclical relationship between pain and affect. This relationship needs to be recognized in planning for pain management. Patients who feel helpless in the face of pain present a real challenge. Not only do they need to learn to use pain management strategies, but they must also believe that this will improve their outcomes. That patients can actually help manage their own pain through appropriate strategies is a belief essential to dealing with feelings of helplessness.

In clinical encounters, it is important to *hear* what persons with arthritis are saying when they talk about how they manage their pain and how they view the success of these efforts. Trying to make sense of these issues led me to do a concept analysis of pain management. The results have been very helpful; I now listen to personal descriptions and

work with patients to plan useful strategies. The concept analysis resulted in three emergent dimensions: pain relief, pain modulation, and pain management self-efficacy.² I have found that discussing pain management within the context of these dimensions has been invaluable.

Definitions to Consider

Pain relief refers to easing or alleviating the pain, primarily by pharmacological management. When thinking about relief, patients can expect the lowering of pain intensity within a certain period of time or they can expect a tolerable maintenance of pain intensity level by an ongoing pharmacological protocol. Pain modulation refers to adjusting to or softening the effects of the pain using a variety of non-pharmacological management strategies. Methods such as distraction, relaxation techniques, or pacing activities to avoid overexertion represent ways that persons can modulate their pain over time.

Learning to use the methods that are appropriate to one’s lifestyle, functional ability, setting, and value structure is important; not every strategy is appropriate for every person. Over time and with practice, individuals can learn helpful strategies to soften the effects of pain or make their experience of living with it more positive. Pain management self-efficacy refers to persons’ beliefs that they can perform selected strategies that will modulate or relieve their pain. Increasing self-efficacy reduces the feelings of helplessness. A collaborative patient-provider approach is necessary to help patients learn to use pain management methods appropriately.

The overall definition of pain management gained from this concept analysis is “success in taking care of or handling the pain by using certain actions and by directing and controlling one’s own use of these actions.” This concept implies personal involvement and self-management.

Patient-Provider Partnership Key

One thing that we do know about arthritis-related pain and its management is that successful management requires the involvement of the individual. Success requires a partnership between the patient and the healthcare providers (e.g., physicians, nurse practitioners, physical therapists, and occupational therapists) involved in care. It seems safe to say that man-

—continued on page 8—▶

ing pain and the pain experience depend to a great extent on the person's self-management, with the healthcare professional playing the supportive role.

There is growing awareness that individual behaviors can influence the symptoms of chronic disease, such as pain and activity limitations. The provider can prescribe medication, teach exercises and ways to perform activities of daily living, and teach management strategies (e.g., relaxation techniques, using activities for diversion, and using positive self-talk), but the individual patient decides whether or not to carry them out. Dialogue between the patient and professional is needed to determine the effectiveness of the techniques and the need for modification or changes.

We have great models of self-management, such as the self-management program begun at the Stanford Arthritis Center by Lorig and Fries.³ Individuals can now also access various Web sites that provide information about their conditions and approaches to managing them. These include the sites of the ACR (www.rheumatology.org/public/factsheets/index.asp), Arthritis Foundation (www.arthritis.org), Medline (www.nlm.nih.gov/medlineplus/arthritis.html), and the Centers for Disease Control (www.cdc.gov/arthritis). While many of the available written materials provide instructions for practice, whether these are accurately implemented by patients may be open to question. The involvement of the practitioner is, therefore, key to implementation through demonstration, guided practice, and evaluation.

Assessing the patient's pain intensity, pain experience, and use of management methods is an im-

portant part of the professional's supportive role when planning and evaluating treatment with the patient. There are numerous instruments available for the assessment of pain intensity, mostly one-item rating scales measuring pain from 0 (no pain) to 10 (pain as bad as it could be).

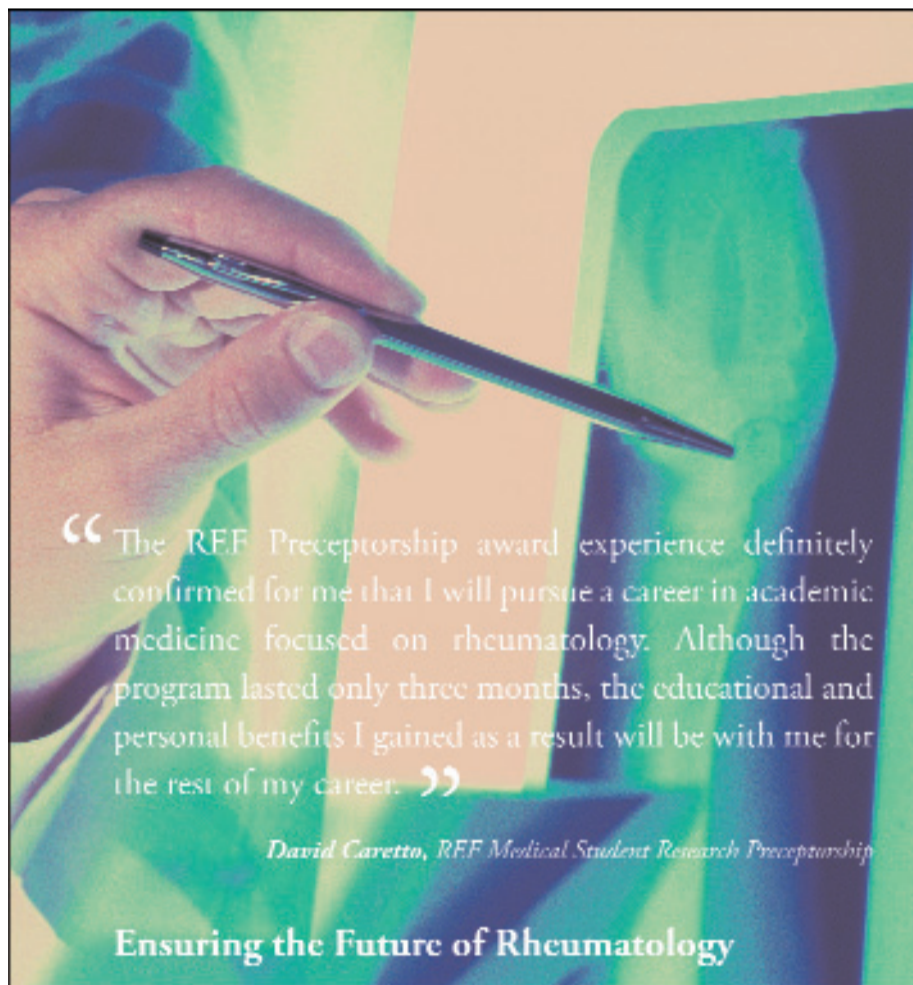
I have made two tools that I've developed available to you for use in your practice. One of these, the CPEI, measures the pain experience. The other—the Pain Management Inventory (PMI)—indexes what management methods the person is using and rates how often these are used and how helpful they are.⁴ These, along with instructions for scoring, may be downloaded from my Web site (<http://myweb.twu.edu/~gdavis>).

I know that all providers want to help their patients with their pain. I hope that my musings are helpful as you strive to meet this important goal in the treatment of patients with arthritis. | THE RHEUMATOLOGIST |

Dr. Davis is professor of nursing at Texas Women's University in Denton and a member of the *TR* editorial board.

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From the COLLEGE

NEWS FROM THE ACR AND THE ARHP

PRACTICE UPDATES

Mind Your Accounts Receivable

Over time, one would expect financial management of a medical practice to become more streamlined and simple. With the abundance of electronic tools, software programs, and the Internet, you can find assistance and problem-solving strategies for economic efficiency. In the rush to take advantage of these support tools, basic facets of financial management, such as billing and col-

- > 4. A/R by suspended, pended, or unbilled accounts (this report ensures no accounts remain hidden during the reporting process); and
- > 5. Accounts written off to collections (typically those more than 120 days past due, unless the claims fall under untimely filing of claims, etc.).

For more information about accounts-receivable and practice-management issues, contact Antanya Chung, director of practice management, at (404) 633-3777 ext. 818 or achung@rheumatology.org.

How Medically Unlikely Edits Affect a Practice

Medically unlikely edits (MUEs), formally known as medically unbelievable edits, took effect with the Centers for Medicare & Medicaid Services (CMS) on January 2, 2007. The function of MUEs is to detect and deny unlikely CMS claims on a pre-payment basis with the intention of improving Medicare's payment process.

MUEs are unit of service edits that are based on anatomic descriptions, CPT code descriptions, CPT coding instructions, and medical reasonableness. These edits will test claims on the same beneficiary, Healthcare Common Procedure Code System, date of service, and provider against a standard

number of units of service. Examples of some edits are:

- > The injection(s), single or multiple trigger point(s), three or more muscle(s) would be set at one;
- > The first hour of an infusion would be set at one; and
- > Medical reasonableness would be set to the maximum number of a service that could be performed on a patient in a day.

MUEs were developed to help curb the costs from fee-for-service claims paid in error. The difference between National Correct Coding Initiative edits and MUEs is that the latter cannot be overridden by a modifier. An example of the reasoning behind MUEs is that there would never be an instance where the provider would have to aspirate three knees. The physician may not bill the patient or have the patient sign an advance beneficiary notice for the service.

Both CMS carriers and practices can be affected by the high cost of incorrect billing. CMS has paid out millions of payments for incorrect services. A practice can be affected by having to resubmit a claim or return an overpayment. It can cost \$10 per claim to submit it correctly the first time, but having to submit a corrected bill increase the cost to \$15 or \$20 a claim. Imagine that a practice incorrectly bills 500 claims a year—the practice could lose \$2,500 to \$5,000 annually on paperwork alone.

Having your coding and billing staff review all claims before submission could greatly decrease some of your office expenses.

More information concerning MUEs is available at www.cms.hhs.gov/MLNMArticles.

If you have any questions about MUEs, contact Melesia Tillman, CPC, CCP, at (404) 633-3777.

CLINICAL GUIDELINES

Marc C. Hochberg, MD, MPH, Named PI for Upcoming OA Guidelines

The ACR has named Marc C. Hochberg, MD, MPH, as the principal investigator (PI) for the upcoming, "Guidelines for the Management of Osteoarthritis [OA] of the Hip, Knee, and Hand." Dr. Hochberg is professor of medicine and epidemiology and preventive medicine and head of the division of rheumatology and clinical immunology at the University of Maryland School of Medicine in Baltimore.

Dr. Hochberg's previous research and leadership in this area qualify him to lead this effort. He was in charge of developing the original 1995 ACR recommendations for hip and knee OA, an effort funded by contracts from the ACR and Arthritis Foundation. He also chaired the Subcommittee on OA Guidelines (1998–2000) that revised the 1995 guidelines. Currently, Dr. Hochberg is a member of the OARSI Guidelines Committee and the ACR Practice Guidelines Subcommittee of the Quality Measures Committee.

The ACR last published hip and knee OA in September 2000; these recommendations are available at www.rheumatology.org and include a February 2005 addendum regarding the risk for cardiovascular thrombotic adverse events from COX-2 selective inhibitors. The ACR has not previously published recommendations for managing hand OA.

Dr. Hochberg plans to start the 12-month development process for the upcoming guidelines in January 2008, and the ACR anticipates publishing the final version in the summer of 2009.

REF NEWS

2008 REF Gout Print To Be Chosen by Ignacio Garcia-De La Torre, MD

While attending the ACR Annual Scientific Meeting in Boston, ACR member Ignacio Garcia-De La Torre, MD, visited the ACR Research and Education booth to purchase the latest Rodnan commemorative gout print, *A Fisher-King*.



Dr. Ignacio Garcia-De La Torre

By making his purchase on site, Dr. Garcia-De La Torre was entered into—and won—a drawing to be the individual who will select the Rodnan print that will be released by the REF in honor of the 2008 annual meeting.

Dr. Garcia-De La Torre, a rheumatologist with the University of Guadalajara in Mexico, was pleased to have the opportunity to select the next print. "I consider them a 'classic' reproduction of the disease in a time when things were so different," he says, noting that he displays his prints in his office. *A Fisher-King* is the third Rodnan print he has purchased.

Each year the REF releases a new print in honor of the ACR/ARHP Annual Scientific Meeting. Proceeds from the sale of each print help fund REF training, education, and research programs. For more information about this and other Rodnan Commemorative Gout Prints, visit the REF Web site at www.rheumatology.org.



ISTOCK.COM

lection, have fallen by the wayside.

Re-evaluating the basics of billing and collections is a good first step for rheumatology practices that want to get their finances in order. Rheumatologists should reacquaint themselves with financial methods to see how their practices are performing. An analysis of accounts receivable (A/R) begins with these three financial elements of each patient/payer transaction:

- > **Charges:** Full fee amounts for the services provided;
- > **Adjustments:** Amounts deducted per contractual obligations—usually with HMOs, PPOs, and other payer-plan participatory obligations; and
- > **Payments:** Amounts paid to the practice by patients and payers (receipts).

Every practice should have financial transparency. Detailed reports should be generated on a timely basis each month, as well as at the end of the year, via the practice's billing system. The report module of the billing system should allow for flexibility in report generation so that both high-level reports and detailed listings, down to patient account levels, can be created. The reports should analyze a variety of data in different ways, but physicians should target one or two specific reports on which to focus when collecting outstanding balances. The most common reports to begin the collection process are:

- > 1. A/R reports of high-level accounts;
- > 2. A/R reports with categories for accounts current, 30 days, 60 days, 90 days, and 120 days or more past due, with billing staff notes detailing account work;
- > 3. A/R by insurance type (i.e., by payer, including self-pay patients);

CODING CORNER!

February's coding challenge:

A 46-year-old male with osteoarthritis of his right knee came in for a routine follow-up visit. The patient had intra-articular corticosteroid injection of his right knee six weeks ago, with reported improvement in knee pain and stiffness. The patient reports stiffness in the knee that lasts five to 10 minutes after long car rides and in the morning. This stiffness occurs once or twice a week. He also reports mild knee pain when climbing stairs. The patient has no other complaints or comorbidities. He is currently on etodolac and ranitidine as needed.

On examination, the patient had normal vital signs; height 5'10", weight 190 pounds, body mass index 27.3. His lungs were clear. The heart's regular rate and rhythm had no murmurs or friction rubs. The abdomen was soft, not tender, with no mass or hepatosplenomegaly. The right knee was crepitus and had mild knee tender-

ness on extreme of flexion, but no warmth or effusion. The left knee was unremarkable with full range of motion and no tenderness.

The diagnosis is clinically stable osteoarthritis of the right knee.

As treatment, the patient was given prescriptions to continue etodolac and ranitidine. He was counseled regarding benefits of daily exercise and weight loss in management of the osteoarthritis. Ways to incorporate daily physical activity into his schedule and recommendations on how to reduce fat and caloric intake were also discussed. The patient was asked to return in four months for a follow-up appointment, sooner if problems arise.

What level of service is this patient encounter?

How would you code this? See page 13 for the answer.

Rheumatology the Winner of 2007 REF 5K Run

On November 9, during the 2007 ACR/ARHP Annual Scientific Meeting in Boston, more than 200 attendees and community friends took steps to ensuring the future of rheumatology by competing in the annual REF 5K Run/Walk. Through the generous donations of those who participated and corporate support from UCB, Inc., the event raised over \$67,500 for REF award and grant programs.

Congratulations to Top Finishers



Best Overall Female: Naomi Sullivan from Bellingham, Wash.

Best Overall Male: Phil Gross from Franklin, Tenn.

For a complete list of 1st, 2nd, and 3rd place finishers in all age categories, visit www.rheumatology.org/ref.

ADVOCATING FOR YOU

Aloha from the 2007 AMA House of Delegates Interim Meeting

The 2007 AMA House of Delegates interim meeting was held November 10–13 in Honolulu. The ACR was represented by its delegate, Melvin Britton, MD, and alternate delegate, Gary Bryant, MD.

Advocacy was the main focus of this year's meeting. Delegates spoke on behalf of doctors who are concerned about the current healthcare legislation in Washington, D.C., and want a change.

Because advocacy is not something that can be done by one person, the AMA approaches it is a group effort that involves the AMA, delegates, specialty societies like the ACR, and states, to name a few. For example, the AMA had phones available in the registration area to encourage delegates to call their representatives and express their concerns on issues such as State Children's Health Insurance Program (SCHIP), Medicare balanced billing, and the 10.1% Medicare physician fee cut.

Although it is a priority of the AMA, the SCHIP resolution was rejected in the AMA House of Delegates. The resolution asked that SCHIP be reauthorized for all children at or below 200% of the Federal Poverty Level. This resolution also includes a transition to insurance coverage for the children who are enrolled in SCHIP by 2010. The AMA believes the House of Delegates should continue to support alternatives that will expand coverage as long as they adhere to AMA policy.

Also discussed at the meeting was Medicare Balanced Billing, a way for physicians to offset the 10.1% physician fee cut. Balanced billing would allow physicians to bill patients for the difference in reimbursement rates and what it costs to treat them. The AMA aims to provide the necessary political and monetary resources to bring this concept to fruition.

A similar plan has also been developed to revise the current Medicare physician fee structure through legislation.

The younger members of the AMA also had a large presence at the meeting. The Medical Student Section sent volunteers to a high school football game in Honolulu to speak with spectators regarding the uninsured in the United States, and to ask that they remember these uninsured when they vote in the presidential election. For more information on the AMA's "Voice for the Uninsured Campaign," visit www.ama-assn.org

Finally, this meeting was one of transition for the ACR, as Dr. Britton retired as the ACR AMA delegate at the conclusion of the meeting. As the ACR's delegate, Dr. Britton has demonstrated a sincere dedication to ACR advocacy efforts, to rheumatology as a specialty, and physicians as a profession, and his hard work is appreciated.

This past summer, ACR members were encouraged to join the AMA to allow the College to keep its delegate and continue to have a seat at the table. Your delegate continues to represent you and your patients at AMA meetings, and the AMA is working on the issues that affect rheumatology.

If you have any questions or concerns pertaining to the AMA or any advocacy issue, contact Kristin Wormley at kwormley@rheumatology.org or Aiken Hackett at ahackett@rheumatology.org. Both can be reached at (404) 633-3777.

EDUCATION

State-of-the-Art Clinical Symposium

The 2008 ACR State-of-the-Art Clinical Symposium will present current, cutting-edge information on a broad array of topics in rheumatology.

This year's conference will offer four "Year in Review" lectures, including topics on RA, lupus, vasculitis, and spondyloarthropathies. Also, 10 workshops in two time slots will be offered to provide attendees an opportunity to interact with topic experts in a small group setting.

The 2008 State-of-the-Art Clinical Symposium will be held Saturday, April 12–Sunday, April 13 in Chicago. A preconference practice management course on "Evaluating and Managing a Successful Practice," will be given Friday, April 11.

Register before March 7 to take advantage of reduced registration fees. For more information or

to register, visit www.rheumatology.org/meetings or contact the ACR office at (404) 633-3777.

ARHP NEWS

2008 ARHP Graduate Student Award

If you work in the field of rheumatology, you know the importance of mentoring students who show interest in the field. With the many specialty options presented to healthcare students, it is of vital importance to open the door to rheumatology.

ARHP Graduate Student Awards open this door by encouraging the interest of non-physician graduate students in the field of rheumatology, giving these students a glimpse into the practice of a rheumatology health professional.



Terri White

continued on page 12

2008 ARHP Member-Get-A-Member Campaign

February 1 – August 25, 2008

AWARDS – EDUCATION – GRANTS – RESEARCH – NETWORKING

TOP THREE REASONS TO RECRUIT NEW MEMBERS:

1. Growth of Your Professional Association

ARHP is a diverse and professional association. New members stimulate new ideas while encouraging and revitalizing current members.

2. Networking Opportunities – A variety of ways to gain insight through professional interaction with others in various practice situations across the country and globe.

3. Rewards and Recognition – The top recruiter will win a \$500 gift certificate to the airline of their choice and will be recognized at the 2008 ACR/ARHP Annual Scientific Meeting in San Francisco, CA and in upcoming publications.

All applications must be postmarked by August 25, 2008 to be considered. To receive credit for your recruited members, your name and signature must appear as the sponsoring ARHP member.

>>> For additional information, visit www.rheumatology.org/arhp or contact Ramona Hilliard at (404) 633-3777 or rhilliard@rheumatology.org.



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"I was so excited and proud when I found out I was selected as one of the 2007 ARHP Graduate Student award recipients," says Terri White, RN, MS, FNP-C. "After hearing this wonderful news, my first thoughts were of gratitude to my mentor, Gail Davis."

As a mentor, Gail C. Davis, RN, EdD, has been the guiding force of White's doctoral studies and dissertation research. "When I first began the PhD program, Dr. Davis encouraged me to join the ARHP as a student," explains White. "During my PhD studies, I have been privileged to be on one of her two nursing research teams—studying osteoporosis and chronic pain related to arthritis in older adults. The research skills I have learned from Dr. Davis are invaluable and a major reason for my success in the doctoral program."

In 2004, Dr. Davis started taking White to the ACR/ARHP Annual Scientific Meetings. At these meetings, White's mentor introduced her to many health professionals and included her in presentations—all of which guided White in her studies.

"Terri is a most deserving student for the ARHP Graduate Student Award," says Dr. Davis, a professor of nursing at Texas Women's University in Denton and a member of the TR editorial board. "Her scholarly performance throughout her doctoral program has been outstanding, and her dissertation work with osteoporosis and rural-dwelling older adults represents such a nice contribution to the field of rheumatology and to the lives of older individuals."

For her dissertation, White decided to explore different methods of teaching bone health and en-

couraging healthy bone behaviors in rural-dwelling older adults. Her research was completed in late October last year and she is hopeful that she will be able to present her findings at the 2008 ACR/ARHP Annual Scientific Meeting in San Francisco.

"When working as a family nurse practitioner in a rural health clinic, I became acutely aware of the disparity of knowledge about osteoporosis and healthy bone behaviors in rural dwelling older adults. My dissertation research is based upon Dr. Davis' previous studies concerning osteoporosis and goal at-

tainment scaling," says White.

White received more than just an award as an ARHP Graduate Student Award recipient; she also received a mentor who helped open the door to a fulfilling career as a rheumatology health professional. In return, Dr. Davis was able to ensure the future of rheumatology by sharing her knowledge and passion for healthcare with a bright and talented student.

"It has been my pleasure to work with Terri, and to provide some guidance as her teacher and



OSTEONECROSIS

Osteonecrosis, also called avascular necrosis or aseptic necrosis, is a condition in which the death of bone cells (due to decreased blood flow) can lead to pain and collapse of areas of bone. This collapse of bone, in turn, can lead to degenerative arthritis of nearby joints, most commonly the hips and knees. Less frequently affected are the shoulders, hands, and feet. In rare instances, osteonecrosis can occur in the jaw—resulting in pain and mouth ulceration. Osteonecrosis is not fatal, but can lead to pain, arthritis, problems with physical activity, and even the need for joint replacement. Most of the 10,000 to 20,000 Americans developing osteonecrosis annually are between age 20 and 50. These individuals usually have a history of serious trauma, corticosteroid use, excess alcohol intake, or other conditions including systemic lupus erythematosus, dysbarism ("the bends" that occur with scuba diving), blood disorders, HIV infection, and radiation therapy.

Physicians suspect osteonecrosis when a person with risk factors for the condition experiences localized bone-type pain. A diagnostic X-ray of the area in question is done and, because these X-rays may appear normal in the early stages of disease, other imaging studies—such as bone scans or MRIs—may be scheduled. Unfortunately, there is no clear evidence indicating the best way to treat osteonecrosis. Treatment often starts with pain medications and limiting weight bearing on affected areas. This type of conservative therapy may work well for patients with early osteonecrosis in small areas of bone. However, it does not work for those with hip or knee osteonecrosis who are facing progressive bone collapse. Instead, surgical procedures may be recommended to relieve pain and, hopefully, prevent bone collapse.

According to patient fact-sheet writer Kevin McKown, MD, "The most important ways to prevent osteonecrosis are to avoid excessive alcohol intake and work with your physician to limit corticosteroid use." Tobacco use also should be avoided, as it has been implicated as a possible risk factor for osteonecrosis.

Download the complete osteonecrosis fact sheet and other patient-education materials at www.rheumatology.org by following the links to patient education from the Practice Support menu.

ARHP Graduate Student Award Deadline

Proposals for the 2008 ARHP Graduate Student Awards are due June 2, and recipients will be announced by the end of July.

Proposals may be submitted by e-mail, fax, or mail. The two top-rated proposals—based on scientific merit, rigor, and potential significance to the field—will be eligible for:

- > A \$500 award;
- > Free registration to the 2008 Annual Scientific

Meeting in San Francisco; and

- > Free ARHP membership for the year of the award or, if the recipient is already a member, free membership for the following year.

ARHP Graduate Student Awards are non-renewable and intended for nonphysician health professionals who have not yet achieved a terminal degree. The award's purpose is to increase the ranks of rheumatology health professionals by en-

couraging and rewarding their research and clinical practice projects in the rheumatology field. To be considered, applicants must submit a project proposal (1,000 words or less), the application form, and a letter of support from their mentor (250 words or less).

For additional information or to download an application, visit www.rheumatology.org/arhp and click on the awards and grants link.

CALENDAR

2007-2008

FEBRUARY 15

- > **Deadline:** ACR Keystone Pediatric Rheumatology Symposium Registration
- > **Deadline:** Winter ACR/ARHP Membership Applications

FEBRUARY 22

- > **Deadline:** Rheumatology Board Recertification Exam Preparation Course Registration

FEBRUARY 25-26

- > **Advocacy Event:** Advocates For Arthritis, Washington, D.C.

FEBRUARY 27

- > **Webcast/Audioconference:** The Stark and Anti-Kickback Law: What does it mean to you?

MARCH 1-5

- > **Meeting:** ACR Keystone Pediatric Rheumatology Symposium

MARCH 3-21

- > **AIM:** AIM RA and AIM Gout Abstraction Site Open

MARCH 7

- > **Deadline:** ACR State-of-the-Art Symposium Advanced Registration and Housing

MARCH 7-9

- > **Course:** Rheumatology Board Recertification Exam Preparation

MARCH 18

- > **Audioconference:** Hypermobility Syndromes: The

True Collagen Disorders

MARCH 26

- > **Audioconference:** Coding for Quality: Fact of Fiction?

MARCH 28

- > **Deadline:** ACR State-of-the-Art Symposium Registration

APRIL 11

- > **Deadline:** ARHP Merit Awards and Committee Volunteer Forms
- > **Course:** Practice Management, Chicago

APRIL 12-13

- > **Symposium:** ACR State-of-the-Art, Chicago

For more information about these or any other ACR, ARHP, or REF activities, visit www.rheumatology.org.

mentor," says Dr. Davis. "One of the nicest rewards of being a mentor is to see students succeed and flourish. She has certainly done this, and I'm certain that she will continue to make a meaningful difference through her research combined with clinical practice."

Through the ARHP Graduate Student Award, health professionals are able to guide and help bright and talented students discover rheumatology. Award recipients, like White, stand to gain a thorough introduction to rheumatology while working alongside some of the best in the field, making this award an opportunity for everyone involved.

MEMBER NEWS

ACR Master Wins 2007 Leadership in Personalized Medicine Award



Dr. Snyderman

ACR Master Ralph Snyderman, MD, chancellor emeritus for health affairs at Duke University in Durham, N.C., and founder and chairman of Proventys Inc., recently received the 2007 Leadership in Personalized Medicine

Award. The award, given by the Personalized Medicine Coalition (PMC), honors Dr. Snyderman's efforts to advance predictive and targeted therapies on a national scale.

The annual PMC award recognizes the contributions of a visionary individual whose actions in science, business, or policy have advanced the frontier of personalized medicine. Snyderman accepted the award at the Harvard Medical School-Partners HealthCare Center for Genetics and Genomics and Harvard Business School conference, "Personalized Medicine: A Call for Action."

"The PMC Leadership in Personalized Medicine Award publicly recognizes those individuals who support and contribute to the innovative and deeply collaborative nature of personalized medicine," said Mara G. Aspinall, president of Genzyme Genetics and chair of the committee that selected Snyderman. "Dr. Snyderman has helped advance the frontier of personalized medicine across a broad front, including clinical care, business, and as an outspoken supporter of the new paradigm."

Personalized medicine is the use of molecular analysis to better manage a patient's disease or predisposition to disease to achieve optimal clinical outcomes by helping physicians and patients choose the approaches best suited to the patient's genetic and environmental profile.

As the Chancellor of Health Affairs at Duke from 1989 to 2004, Dr. Snyderman drew on his experience in biotechnology and healthcare delivery to conceive, pioneer, and implement a comprehensive healthcare approach based on the concept of "prospective health care."

The foundation of this healthcare approach is strategic, personalized, and predictive health planning, rather than reactive treatment. Part of the Duke Health System for the past six years, Duke Prospective Health uses technology to provide individualized and integrated healthcare for patients. This approach, led by Dr. Snyderman, has made the Duke Health System one of the leading academic health systems in the United States and has firmly placed it at the lead-

CODING CORNER!

Coding Corner answer (question on p. 11):

February's coding answer: 99212. Diagnosis 715.96.

This is an established patient outpatient/office visit and should be coded as 99212. The diagnosis would be 715.96.

The chief complaint was osteoarthritis. The history is problem focused, and the history of present illness has four elements—duration, location, modifying factors, and timing. The review of systems is pertinent to the problem (i.e., right knee), while the past family social history was not addressed. The examination is expanded and problem focused, with five systems being examined (constitutional, cardiovascular, respiratory, gastrointestinal, and musculoskeletal).

ing edge of personalized medicine.

In addition to his pioneering work at Duke, Dr. Snyderman has worked continually to put personalized medicine on the national agenda by developing concepts for its implementation and by convening key leaders of the major stakeholders in healthcare—payers, legislators, patients, physicians, and econo-

mists—and engaging them in a dialogue about this new trend in medicine. Dr. Snyderman also made individualized healthcare a focus of his tenure as both the chairman of the Association of American Medical Colleges' (AAMC) Council of Deans (1999–2000) and chair of the AAMC (2000–2001).

THE RHEUMATOLOGIST

Rheumatology

with Rhythm

The circadian rhythm offers insight into treating rheumatic diseases

>> By Rainer H. Straub, MD, and Maurizio Cutolo, MD

In this article, we will address two issues: Why is the circadian rhythm relevant for the clinical practice in rheumatology? and How can the circadian rhythm influence the symptoms of my patient?

In considering symptoms of RA, it is remarkable that the improvement of morning stiffness induced by prednisolone after six months is similar in magnitude to the improvement of morning stiffness during a single day (see Figure 1, p. 15). Under both conditions—the clinical trial and the course of one day—an improvement of 40% to 50% can occur. Imagine, therefore, a situation in which an investigator in a clinical trial did not pay attention to the time point of examination and recorded improvement that reflected the diurnal variation as much as a sustained treatment effect.

Because patient symptoms can vary during the course of a day in clinical trials, assessment of symptoms can also vary depending on the time point of the visit. Patients often feel better later in the day. Should one therefore recommend an afternoon visit for the patient because the symptoms are less severe then? Indeed, many patients would prefer an afternoon visit because it is much easier for them to get up and around and travel to the clinic. Because symptomatology can have a pronounced diurnal cycle with a maximum in the morning, the underlying causal mechanisms are relevant for pathophysiology of rheumatic diseases, for clinical patient care, and for optimizing treatment strategies.

The Discovery of Circadian Rhythms

In the early 1970s, studies using brain-lesion techniques as well as metabolic and electrophysiological experiments indicated that, in mammals, there is a key structure in the brain which governs biological rhythms.¹ As these studies showed, this central circadian oscillator is located in the hypothalamic suprachiasmatic nucleus (SCN) (see Figure 2, p. 16). The oscillator induces 24-hour cyclic changes of membrane potentials of neurons of the SCN.

In the following years, links between the SCN and many centers in brain were discovered. Among others, the endocrine and sympathetic nervous centers are controlled by the SCN. Because the circadian rhythm is generated in the SCN of the hypothalamus, observations can provide new clues to understand neuroendocrine immune pathways relevant to rheumatic diseases. Because these aspects have been best elaborated in RA, the findings in this

disease are discussed here. The mechanisms responsible for oscillation in suprachiasmatic neurons will not be considered but are reviewed elsewhere.²

Circadian Rhythms of Serum Cytokine and Hormone Production

Because of the favorable effects of anti-tumor necrosis factor (TNF)- α and anti-interleukin (IL)-6 therapy in large clinical trials, rheumatologists recognized the central role of these proinflammatory cytokines in rheumatic diseases. These cytokines are also important in symptoms such as stiffness, joint swelling, pain, and mood (see Table 1, p. 15). An important question, therefore, is whether cytokines demonstrate a circadian oscillation. Indeed, both IL-6 and TNF- α display a circadian rhythm, with maximum levels in the early morning hours (see Figure 3, p. 16).² In healthy subjects, the peak value of IL-6 is found at about 6 a.m. In patients with RA, the peak value of IL-6 appears at 7 a.m. Thus, a morning time shift of the peak value occurs with inflammatory disease. In healthy subjects, IL-6 serum levels are approximately 2–4 pg/ml whereas in patients with RA these levels are 20–40 pg/ml.

From these data, it is evident that the amplitude of the curve of cytokine production is higher and the curve is broadened in RA as compared to controls. In healthy subjects, serum levels of IL-6 usually de-

crease by 9 a.m. whereas, in RA patients, these levels can remain elevated until 11 a.m. The increased amplitude and the broadened curve in the morning hours are important for the morning symptoms. Interestingly, a circadian rhythm exists for the production of immunoglobulins in RA, as has been demonstrated for IgA-rheumatoid factor (peak at 8 a.m.).³ Furthermore, circulating immune complexes demonstrate a circadian rhythmicity in RA with a peak between 6 and 9 a.m.⁴ These findings demonstrate that two other important disease-relevant parameters display an elevation in the early morning hours in patients with RA.

In view of these observations, the key question is, What is driving the circadian oscillation of serum levels of cytokines?

Circadian Rhythm of Cortisol

The adrenal hormone cortisol is an endogenous steroid with anti-inflammatory actions. In the 1950s and 1960s, shortly after the discovery of cortisol, the circadian rhythm of this hormone was described. The cycle of the hypothalamic-pituitary-adrenal (HPA) axis has a maximum in the early morning hours at 8 a.m. and a nadir at midnight (see Figure 3, p. 16). Detailed analyses of the circadian curves of cytokines and cortisol have revealed a lag time between the cortisol rise in comparison to the increase of cytokine

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of approximately 60–120 min.⁵ From this study and a recent analysis of several independent investigations, it appears that morning cytokines can drive the increase of cortisol.²

Interestingly, the cortisol rhythm in healthy subjects does not differ from that of patients with RA when disease activity is relatively low to moderate. This similarity pertains to the period, the amplitude, and the time point of the minimum and peak of the cycle. Studies have shown, however, that this rhythm can be disturbed in patients with RA when disease activity is high, leading to a flattening of the hormone curve. Nevertheless, the serum levels of cortisol are similar in healthy subjects compared to patients with RA.

Although levels of cytokine ten times higher than normal should drive a stronger cortisol response, it is notable that the serum levels of cortisol are similar in healthy controls and patients with RA. This phenomenon is called inadequate secretion of cortisol in relation to inflammation. The reasons for this inadequacy relate in part to an inhibition of the HPA axis by chronically elevated cytokines. In other words, secreted cortisol is unable to dampen the proinflammatory response. As such, cytokine levels stay high.

What, then, is the factor that drives the nightly cytokine surge? At present, it is thought that the cor-

TABLE 1:

How Cytokines Modulate Disease Manifestations and Mood

Symptom	Mechanism
Stiffness	Morning stiffness results from plasma extravasation into the interstitial space of muscles and connective tissue. Plasma extravasation is a consequence of vasodilatation and vessel leaking which are stimulated by proinflammatory cytokines, prostaglandins, bradykinin, and other mediators.
Swelling of joints	Similar to morning stiffness, morning swelling of joints is the consequence of fluid transfer from intravascular to intra-articular space. It is a consequence of vasodilatation and vessel leaking, which are stimulated by proinflammatory factors.
Pain	Proinflammatory cytokines, bradykinin, prostaglandins, and other mediators bind to nerve terminals of afferent pain fibers in the inflamed tissue. Receptors for these factors have been discovered on the membrane of nociceptive neurons. Upon binding of these factors to the nerve terminal, an action potential is generated which informs pain centers in the central nervous system of local activation of pain fibers.
Bad mood	Cytokines can induce sickness behavior and depression-like symptoms. Interferon-alpha administration in patients with hepatitis C elicits depression scores similar to depressed patients. Anti-TNF therapy in patients with RA can decrease depression-like symptoms.

tisol nadir at midnight and the parallel increase of proinflammatory hormones such as prolactin and melatonin drive the increase of nightly TNF- α and IL-6. These two cytokines drive cortisol, which finally dampens the cytokine surge, and so forth. The influence of one system on the other can be viewed as an infinite loop. Because the circadian rhythm is

generated in the higher brain centers of the endocrine and nervous system (in the hypothalamus), the circadian rhythms of cytokines mirror the activity of neuroendocrine centers in the brain.

These findings are intriguing and provide a strong indication that neuroendocrine pathways influence disease-related pathophysiology. They also suggest new therapeutic options.

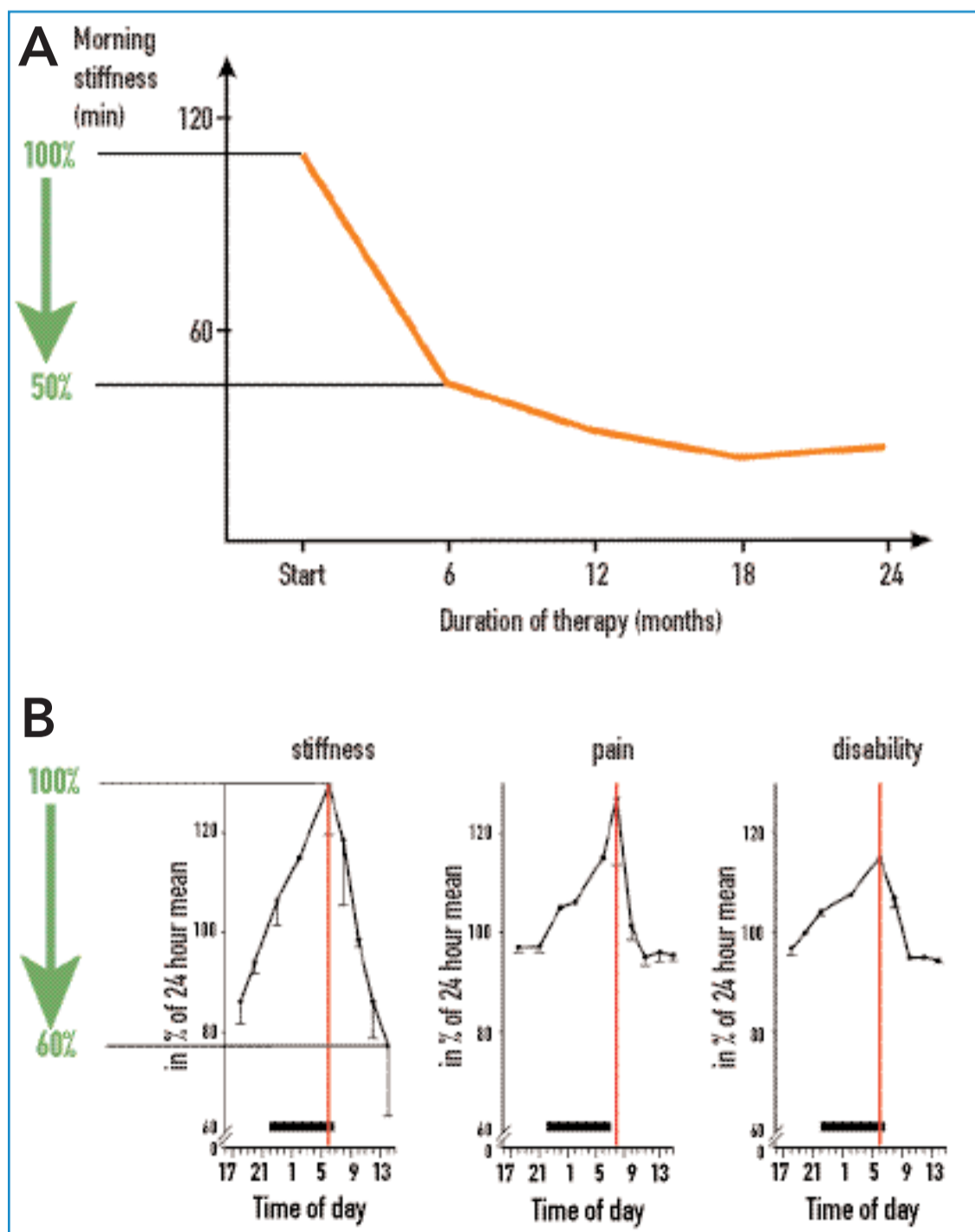


FIGURE 1: Effect size of prednisolone therapy and circadian changes of symptoms. **A:** Influence of prednisolone therapy on morning stiffness is demonstrated in patients with RA.¹⁰ The effect size is approximately 50%. **B:** Diurnal variation of typical symptoms in patients with RA.² The effect size is approximately 40%. The peak is indicated by a red vertical line.

New Clues to Therapeutic Intervention

One would think that a therapeutic increase of circulating glucocorticoids should alleviate symptoms in patients with RA, and this has been demonstrated in Figure 1, Part A (left). These glucocorticoids are usually given after the patient awakes in the morning. One pioneering study demonstrated that administration of the same dose of prednisolone at 2 a.m. was significantly better than that dose given at 7:30 a.m. because it decreased morning stiffness, morning pain, disease activity assessed by the Lansbury index, and serum IL-6 after only five days of glucocorticoid treatment.⁶ These authors included two similar groups of patients with RA, who received 5.0–7.5 mg prednisolone either at 2 a.m. (therapeutic group I, n=13) or at 7:30 a.m. (therapeutic group II, n=13). Baseline values of the two therapeutic groups were very similar. No placebo group or a cross-over design was included, but the results are quite remarkable.⁶

Although this study did not attract widespread interest or make the daily press, it stimulated pharmaceutical companies to develop time-release prednisone tablets. Recent data of a double-blind, placebo-controlled, randomized study in hundreds of patients with RA demonstrated a marked effect on morning stiffness and serum IL-6.⁷ The question appears to be why immunosuppressive treatment with glucocorticoids can inhibit pro-inflammatory sequelae better when given at an early time point, 2 a.m. (on the increasing flank of TNF- α release), than a later one, 7:30 a.m. (on the falling flank of TNF- α release) (see Figure 4, p. 16).

These observations are very important in understanding anti-inflammatory counter-regulation of immune responses. It has been demonstrated that glucocorticoids induce the transcription of the I κ B α gene, which results in an increased rate of I κ B α protein synthesis and inhibition of proinflammatory NF- κ B effects.⁸ Other studies have shown that glucocorticoids can interfere with the transcriptional activation potential of DNA-bound NF- κ B complexes leading to anti-inflammatory effects.⁹ These effects appear very early in the turning-on phase of a proinflammatory response (see Figure 4, p. 16). We hypothesize that the turning-on phase of a proin-

continued on page 16

inflammatory reaction is much more vulnerable to immunosuppressants than the turning-off phase. This suggests that regulation of an important proinflammatory factor such as TNF- α must occur very early; otherwise an overwhelming secretion of this harmful cytokine will occur.

In view of the circadian rhythm and the impact of the timing of immunosuppressive administration

on efficacy, it would be of great interest to explore timed-release forms of cytokine neutralizers (on the basis of small molecules) or hormonal antagonists of melatonin, for example, as therapeutic modalities. Reformulating old drugs in new drug delivery forms could lead to optimized drug release patterns with improved immunosuppressant activities. Stronger inhibition of nighttime proinflammatory cytokines

such as TNF- α and IL-6 could reduce RA-related symptoms in the early morning—and possibly, over a long time, to less RA-related co-morbidities such as joint disease, cardiovascular disease, osteoporosis, depression, and sleep disturbances. | THE RHEUMATOLOGIST |

Dr. Straub is professor of experimental rheumatology and neuroendocrinology in the department of internal medicine I at the University Hospital in Regensburg, Germany. Dr. Cutolo is professor in the research laboratory and academic unit of clinical rheumatology in the department of internal medicine at the University of Genoa in Italy.

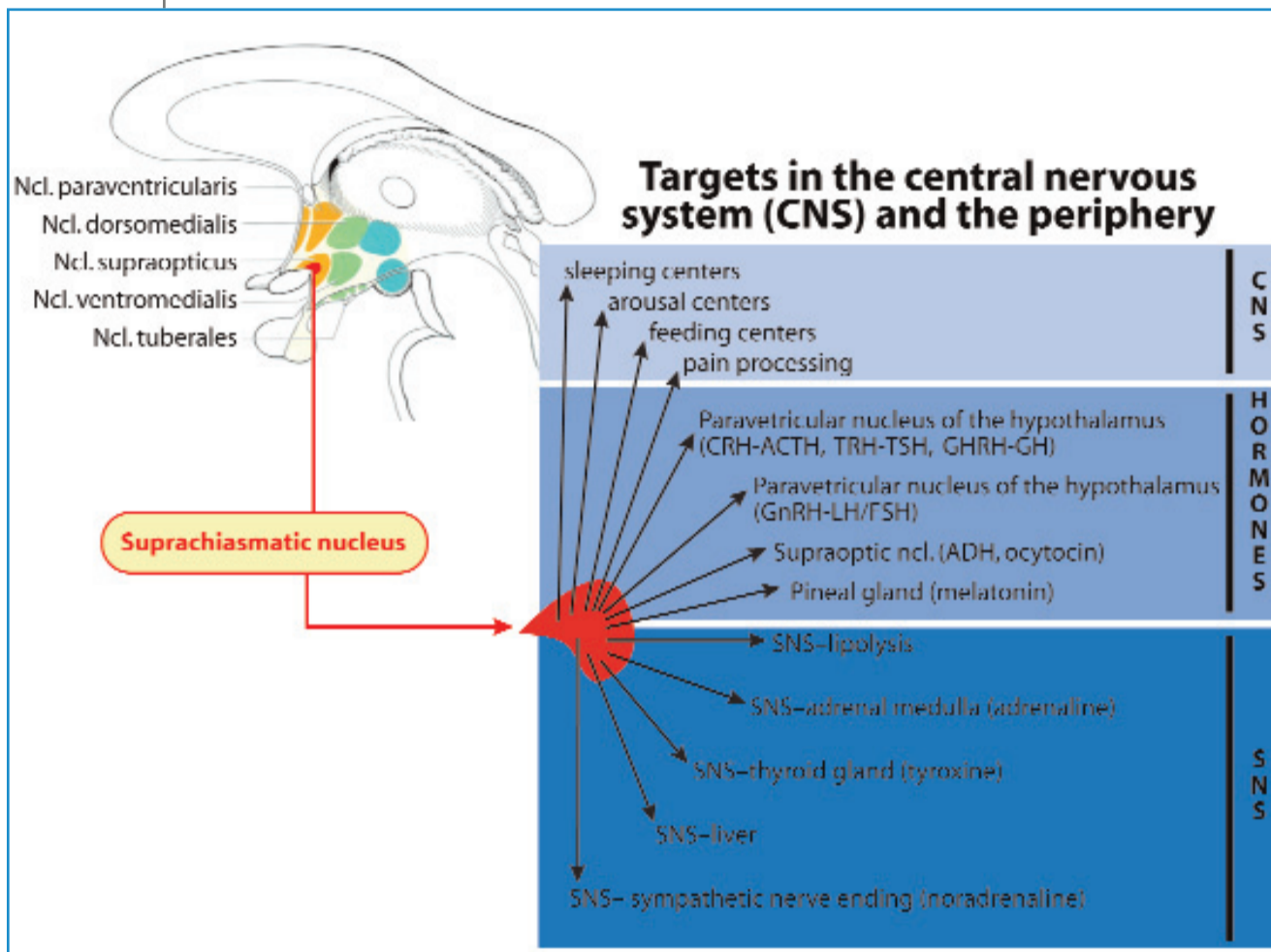


FIGURE 2: Targets of the SCN are depicted. The targets include sleeping, arousal, and feeding centers; other nuclei in the hypothalamus and the pineal gland; and higher centers of the sympathetic nervous system (SNS). The interaction of the SCN neurons with these areas leads to the known circadian rhythmicity of many different neuroendocrine systems that transmit their signals by hormones and neurotransmitters to the periphery. Abbreviations: ACTH, adrenocorticotropic hormone; ADH, anti-diuretic hormone; CRH, corticotrophin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, GH-releasing hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; TRH, thyrotropin releasing hormone; TSH, thyrotropin.

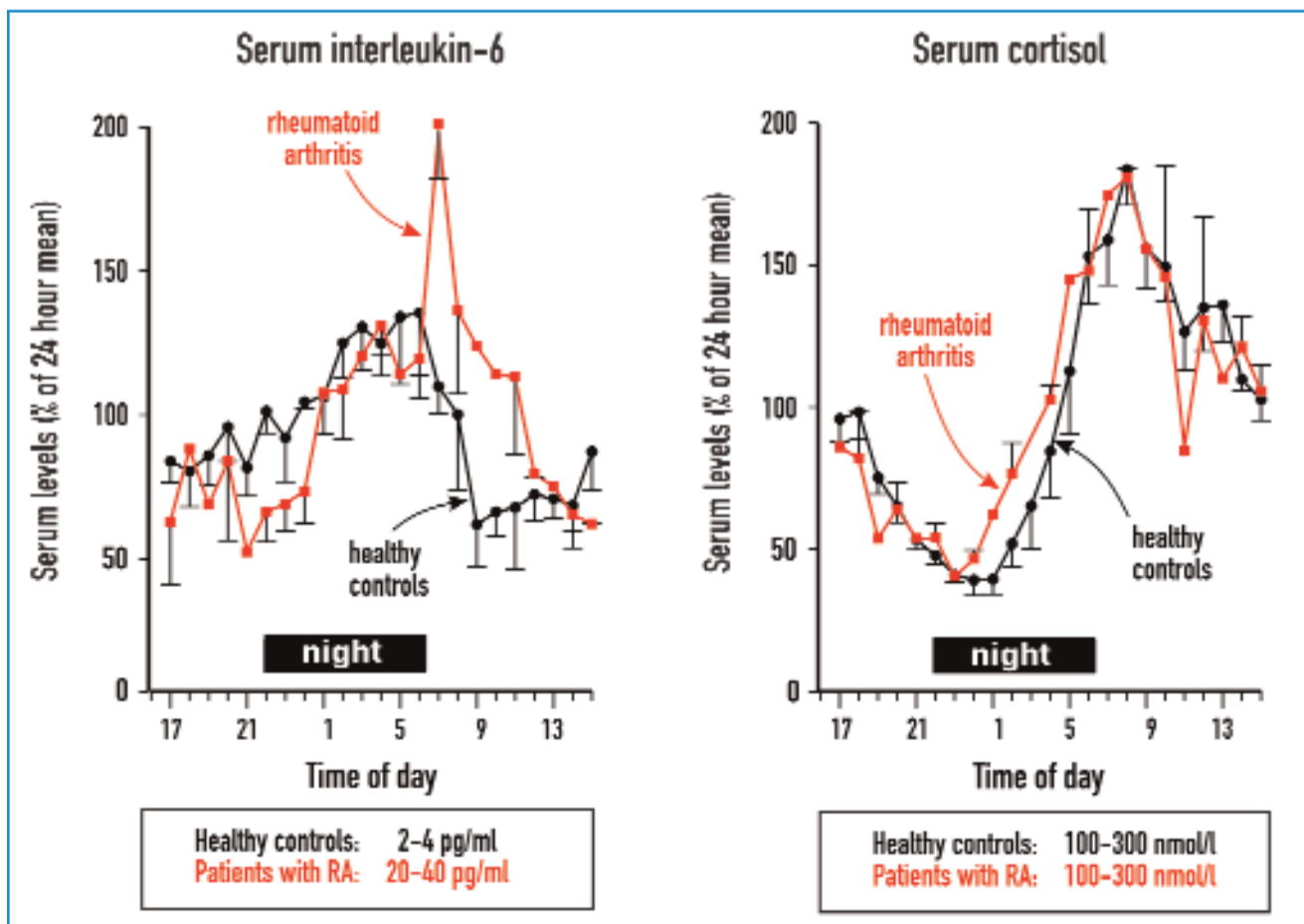


FIGURE 3: Circadian rhythm of IL-6 and cortisol in healthy subjects (black line) and in patients with RA (red line).² The values in the bottom boxes give the absolute serum levels of the respective factors in healthy subjects (black) and in patients with RA (red).

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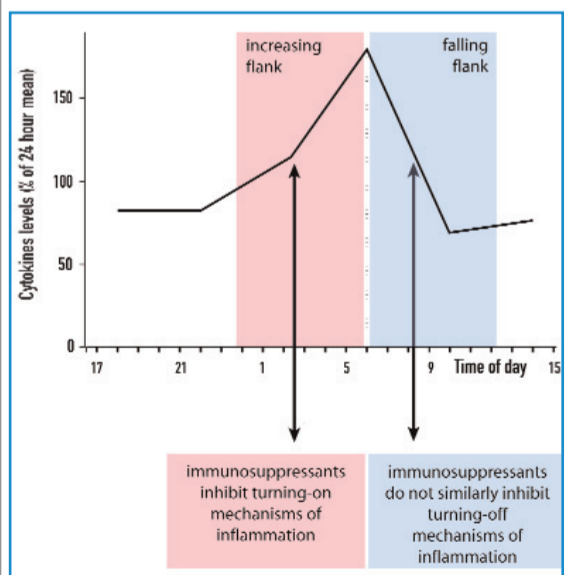


FIGURE 4: The role of administration of immunosuppressants during the increasing and falling flank of TNF secretion. This information is derived from a perfusion study of the rat spleen, which demonstrates a very similar time course of TNF increase and decrease.¹¹ The turning-on phase of a proinflammatory response seems more vulnerable to immunosuppressants such as glucocorticoids than the turning-off phase, so administering immunosuppressants during the turning-on phase may have a stronger capacity to inhibit proinflammatory sequelae.

Take the Measure of Osteoarthritis

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The WOMAC index standardized OA measurement, as described by its creator

>> By Nicholas Bellamy, MBChB, MD, MSc, MBA, DSc

Watson Buchanan, MD, who was clinical professor of rheumatology at the University of McMaster in Hamilton, Canada, I described the development of a health status questionnaire termed the Western Ontario and McMaster Osteoarthritis Index (WOMAC) in the course of completing an MSc thesis in clinical epidemiology and biostatistics.² The WOMAC was conceptualized and an item inventory was proposed between 1981 and 1982; the index was validated and implemented between 1982 and 1999.^{3,4} The original index has undergone significant refinement and there is now a broad range of WOMAC tools to meet different measurement needs.

In comparative analysis against performance-based measurement techniques, the WOMAC has frequently been superior in performance.

A Version for Every Need

The WOMAC contains five pain, two stiffness, and 17 physical function items, and is available in five-point Likert (LK), 100-mm visual analogue (VA), and 11-point numerical rating (NR) scaling formats.⁵ The majority of the validation work has been conducted with the LK and VA formats, although the NRS version has also been studied. There are approximately 1,500 citations (full manuscripts, ab-

stracts, reviews) in the literature to use of the WOMAC. The WOMAC LK3.1 and WOMAC VA3.1 versions, in particular, have been extensively used, especially for assessing efficacy in clinical research environments and, increasingly, in clinical practice. (See Table 1, p. 19, for more on versions of the WOMAC.)

These are some of the features that have made the WOMAC a widely used tool:

- > Extensive patient involvement in the item inventory development, which reduced the potential influence of paternalism and anchored it to aspects of the disease experience that are relevant to OA patients;
- > Numerous studies that have evaluated clinimetric properties of the index (e.g., validity, reliability, and responsiveness) and issues such as LK versus VA scaling and blind versus informed presentation;^{3,5}
- > Development and validation of more than 70 alternate-language forms of WOMAC VA3.1 and WOMAC LK3.1;
- > Continual research and development into content and administration issues, including the application of WOMAC in telephone interviews and electronic data capture formats;⁵
- > Recognition by the Outcome Measures in Rheumatoid Arthritis Clinical Trials group (OMERACT), Osteoarthritis Research Society International (OARSI), and the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials group, and regulatory agencies such as the Food and Drug Administration and European Medicines

Agency, among others;^{6,7}

- > Provision of the WOMAC, in the required scaling format, alternate language form, and administration format, for academic, industrial, clinical, and educational applications, including pivotal projects and programs such as the National Institutes of Health (NIH) Osteoarthritis Initiative; and
- > Ongoing user support, to provide the most appropriate form of the index to meet specific user needs.

Transcultural adaptation of WOMAC 3.1, in particular, has been a complex process spearheaded by the Health Outcomes Group in San Francisco, Calif. The impact of environmental challenges involved in, for example, stair climbing and transportation, are different in different parts of the world, and bathing and toileting habits also vary, but the WOMAC appears capable of tapping into global commonalities that exist in OA symptoms.

Validation

In comparative analyses against performance-based measurement techniques, the WOMAC has frequently been superior in performance. Likewise, in comparisons against other disease-specific measures the WOMAC has compared favorably, and against generic health status measures has often been superior in responsiveness.⁵

Traditionally, OA clinical trial data are analyzed at the group level. Recently, attention has focused on individual patient-reported outcomes. These can be considered in two general forms: responder criteria, in which each patient is classified as a responder or nonresponder to treatment, based on whether their change in health status exceeds a predefined threshold; and state-attainment criteria, in which patients are classified on the basis of when, whether, and/or for how long they achieve a certain predefined level of low symptom severity.

WOMAC data have contributed significantly to the development of both response and state attainment criteria. (Download a list of WOMAC's contributions to clinical criteria at www.TheRheumatologist.org under "Download Issues.")

Patient Participation, Focus Key

Patient involvement in estimating the clinical importance of improvement, and the acceptability of different levels of symptom severity is innovative, and meets the requirements for consumer involvement in decision making. The process also helps establish consumer-based definitions for response and state attainment in knee and hip OA.

An alternative method of benchmarking patients' health status is against normative values derived from WOMAC items and estimated from a survey of the general population. The first such survey targeting 24,000 members of the general public has been completed, and data from a second survey, targeting a further 36,000 members, are currently being analyzed.⁸ Once completed, age- and gender-specific normative values based on items in the WOMAC NRS3.1 should be specified from about 7,500 subjects for pain and stiffness and about 13,000 subjects for physical function.

The International Classification of Function (ICF) proposed by World Health Organization provides a conceptual framework for health status assessment. An ICF core set has been described for OA, and the WOMAC successfully mapped to the ICF framework.^{9,10} A model has been developed for predicting utility scores that closely approximate those derived by direct measurement, which has important implications for health economic analyses.¹¹

Collaboration Continues

The WOMAC also paved the way for rapid development of a comparable index for hand OA studies, termed the Australian/Canadian (AUSCAN 3.1)

Hand Osteoarthritis Index.¹² Like the WOMAC, the AUSCAN index is a tridimensional, self-completed, patient-centered health status questionnaire, encompassing pain, stiffness, and physical function.¹³ The AUSCAN Index contains five pain, one stiffness, and nine physical function items and has been validated in both five-point LK and 100-mm VA scaling formats; an 11-point NRS version is also available. The AUSCAN Index has been translated into 32 alternate-language versions, and is recognized in OARSI Guidelines for the conduct of clinical trials in hand OA. The concepts of OMERACT-OARSI Responder Criteria, AUSCAN 20-50-70 Responder Criteria, and BLISS (Pain) Index have recently been explored in hand OA patients, and appear applicable.¹⁴ For more information, visit www.auscan.org or www.womac.org.

The last 25 years of WOMAC development have involved an extensive collaboration, as well as the commitment of patients with knee and/or hip OA. In addition to providing a standardized tool for evaluating treatment response, WOMAC data have also been important in informing decisions regarding the proposal of response criteria and state-attainment criteria, as well as AUSCAN. The WOMAC and AUSCAN indices are well placed to meet current and emerging OA needs in clinical research and practice. Given the availability of response criteria (OMERACT-OARSI, MCII75, MPCI, WOMAC 20-50-70), state-attainment criteria (PASS75, BLISS), and population-based normative data, the opportunities for incorporating quantitative measurements into routine clinical practice are great and will hopefully improve outcomes.

THE RHEUMATOLOGIST

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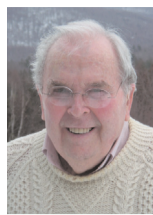
TABLE 1:

Versions of the WOMAC

When reading articles that reference the WOMAC, pay attention to which version, scaling format, and language form was used.

Version	Characteristics
WOMAC 5.0	Original form, five subscales (pain, stiffness, physical function, social function, and emotional function)
WOMAC 3.0	Three subscales (pain, stiffness, and physical function)
WOMAC 3.1	Version of WOMAC 3.0 refined for international use, standard form today
WOMAC 3.1S	Signal version
WOMAC SF3.1	Short-form version

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Dr. Bland

In Memoriam: John Bland, MD

>> By Paul Plotz, MD

John Hardesty Bland, MD, professor of medicine emeritus at the University of Vermont College of Medicine in Burlington, died on March 15, 2007. He was midway through his 90th year, fulfilling the prescription of his last book, *Live Long, Die Fast: Playing the Aging Game to Win*, published when he was 80. A consummate rheumatologist and wonderful bedside doctor and teacher, Dr. Bland was also one of the

genuine polymaths in the American medical world.

He was born in Globe, Ariz., and graduated from the Quaker-run Earlham College (remaining a practicing Quaker all his life) and from Jefferson Medical College in Philadelphia. He trained in medicine in Philadelphia and then at the University of Vermont. He learned rheumatology from three giants: Walter Bauer, MD, former chief of medicine at Mass-

achusetts General Hospital, Jonas Kellgren, MB BS, former chief of rheumatology at the University of Manchester, and Leon Sokoloff, MD, of the National Institutes of Health (NIH). He founded the rheumatology research unit at the University of Vermont and remained on the faculty from 1948 until his death.

As a medical resident, Dr. Bland became interested in the science of salt and water metabolism, just then being introduced into clinical practice from the physiological studies of Homer Smith, MD, and his colleagues. He studied and taught his fellow house officers this field. In 1952, he produced the first edition of his excellent text, *Clinical Use of Fluid and Electrolytes*. "See one, do one, teach one," writ large, was the pattern for many of his numerous enthusiasms.

He and Dr. Sokoloff published a splendid monograph on the musculoskeletal system in 1975, and Dr. Bland's superb *Diagnosis and Medical Management of Disorders of the Cervical Spine* was based on his deep knowledge of the literature, his own clinical experience, and more than 100 careful dissections of whole human cervical spines he had performed. He was elected a Master of the ACR in 1989.

Dr. Bland was a great outdoorsman—both active and contemplative. An acute observer of the natural world, he fell in love with mosses and lichens, published his lovely book, *Forests of Lilliput: The Realm of Mosses and Lichens* in 1971, and had been working on a field guide. A colleague recalled that, on outings, Dr. Bland would pick up a log or swim off to retrieve an interesting or instructive specimen.

Throughout his life, Dr. Bland had a remarkable career in sport. An excellent Nordic skier, he was a frequent medalist in National and World Masters Cross Country Ski championships. He served as a member of the medical advisory team of the US Nordic ski team and then as chief medical officer for Nordic Events at the Lake Placid Olympics. After a heart attack during a ski race at age 59, he took up marathoning and ran the grueling Boston marathon several times. He was also a competitive equestrian.

Dr. Bland loved teaching and writing for lay groups. He fervently believed in the reversibility of osteoarthritis of the hip and knee and of atherosclerotic arterial narrowing, and—while not exactly believing in immortality—prescribed his preferred alternative in *Live Long, Die Fast*.

He was driven by a childlike curiosity and possessed boundless good nature and a delightful sense of fun. He was a wonderful father, friend, physician, and teacher. His funeral was a sad and joyous remembrance attended by hundreds—family, medical friends old and young, patients, skiers, equestrians, marathon runners, and farmers—all in one way or another his colleagues. | THE RHEUMATOLOGIST |

Dr. Plotz is chief of the arthritis and rheumatism branch of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH in Bethesda, Md.

Th17 Cells Explained

The new kids on the block have rheumatologic ramifications

>> By Virginia Hughes

self-antigens, making them a crucial component of the development of inflammation and severe autoimmunity.

Research Background

The history, developmental properties, and potential therapeutic targets of Th17 cells were discussed by Daniel Cua, PhD, a researcher at Schering-Plough Biopharma/DNAX in Palo Alto, Calif., at the ACR/ARHP Annual Scientific Meeting in Boston last November. He also presented new data, published in the December issue of *Nature Immunology* (2007;8:1390-1397), showing how specific cellular environments can lead to the pathogenic properties of Th17 cells.

"There's so much work on Th17 cells coming out now, and so fast," Dr. Cua said. "It's really changing the way immunologists think about inflammatory diseases."

Practicing rheumatologists should pay attention to the new developments, he added, because the research will likely lead to effective therapies for autoimmune diseases. "There are no promises," he cautioned, "but if you understand the disease process, then it makes sense that you can better treat it."

Dr. Cua's research track started seven years ago when one of his colleagues at DNAX, Robert A. Kastelein, PhD, discovered another cytokine, interleukin 23 (IL-23). In pivotal genetic experiments, they found that animals lacking IL-23 were completely resistant to collagen-induced arthritis. In other words, as the DNAX team published in *Nature* (2003;421:744-748), IL-23 was required for joint inflammation.

The next step was figuring out how IL-23 worked at the cellular level. Claire Langrish, PhD, then a post-doc in Dr. Cua's lab, first investigated the nature of the cytokines the IL-23 cells were producing. "She uncovered that what was missing in the IL-23-resistant animal was in fact IL-17," Dr. Cua explained. IL-23 is required for the production of the cytokine interleukin 17, and it's IL-17 that's driving the resistance to inflammation.

IL-17, a cytokine secreted by activated T cells, was first discovered by French scientists in the early 1990s. By the time of Dr. Landrish's experiments, "we already knew IL-17 levels were elevated in patients with MS and RA," Dr. Cua explained, "and thought that they were probably highly pathogenic."

Dr. Cua said that at that time the field's dogma was that Th1 cells were the only ones responsible for the induction of the autoimmune disease cascade. But Dr. Landrish's experiments on Th17 "told us that there's another subset of T cells that could drive autoimmune disease," he said. "It made us completely rethink autoimmune pathogenesis."

RA Research Sheds Some Light

Around that time, Dr. Cua teamed up with Hiroshi Takayanagi, PhD, a researcher in the immunology department at the University of Tokyo, to explore Th17's possible role in RA. They knew that, as part of the pathogenesis of RA, activated T cells cause osteoclasts to destroy bone. What wasn't known was how the T cells initiate this process. After several years

of work, the team found that Th17 cells were responsible for linking T-cell activation with bone resorption, and that both IL-23 and IL-17 were crucial in the bone destruction phase of RA. They suggested that Th17 would be a powerful therapeutic target for RA (*J Exp Med.* 2006; 203:2673-2682).

"With this discovery, things really were beginning to make sense," Dr. Cua said, because it showed that there was another immune response—other than the Th1 pathway—that could be responsible for chronic inflammatory diseases. "The key message was that bone destruction is associated with IL-23/17 pathway."

The next phase of Dr. Cua's research, beginning about 2003, was to try to understand the cellular regulation of Th17 cells. He performed analyses of more than 30,000 genes to look for the genes responsible for producing the transcription factors that regulated Th17, and found about six that were "specifically expressed in IL-17-producing cells and had no known functions," he explained (*Nat Immunol.* 2007;8:950-957).

Making Sense of Th17

Finally, Dr. Cua discussed the possible non-pathogenic functions of Th17 cells. "A mentor told me once, 'You can't have a population of T cells whose only job is to induce autoimmune diseases. It doesn't make any sense,'" Dr. Cua recalled. So what useful purpose could Th17 cells have? Dr. Cua looked at where in the living organism the cells are normally expressed. The primary spot is mucosal tissue. "So we're basically saying that IL-17 cells are not always pathogenic. They have an important role in gut homeostasis," he said.

Which led to the next research question: What is the critical factor that causes a Th17 cell to become pathogenic?

Previous studies had shown that the signaling proteins TGF- β and IL-6 somehow work together to "turn on" the pathogenic functions of Th17 cells. But Dr. Cua's most recent experiments have shown that it's not TGF- β and IL-6, but IL-23 that drives Th17 cells to become pathogenic.

As more and more is learned about Th17 cells, the "new kids on the block," Dr. Cua is most optimistic about their growing clinical applications. He predicts that widespread treatment using some of these targets is still five to 10 years down the road. But he also mentioned specifically one drug—a monoclonal antibody to one of the molecular subunits of IL-23—that is currently being tested on

There's so much work on Th17 cells coming out now, and so fast. It's really changing the way immunologists think about inflammatory diseases.

—Daniel Cua, PhD

patients with psoriatic arthritis in phase-3 clinical trials. The randomized, double-blind trials have been going on since December 2005, with good results: patients receiving the therapy showed improvement in both arthritis and psoriasis skin lesions. As Dr. Cua said excitedly about the trials, "it actually gives you goose bumps." | THE RHEUMATOLOGIST |

Virginia Hughes is a medical writer based in New York City.

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HANDPICKED REVIEWS OF CONTEMPORARY LITERATURE

ANKYLOSING SPONDYLITIS

Gene Association Hints at Potential Ankylosing Spondylitis Treatment

>> By Maripat Corr, MD

Wellcome Trust Case Control Consortium, Australo-Anglo-American Spondylitis Consortium (TASC), et al. Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. Nat Genet. 2007;39(11):1329-1337.

Abstract

We have genotyped 14,436 nonsynonymous single nucleotide polymorphisms (nsSNPs) and 897 major histocompatibility complex (MHC) tag SNPs from 1,000 independent cases of ankylosing spondylitis (AS), autoimmune thyroid disease (AITD), multiple sclerosis (MS), and breast cancer (BC). Comparing these data against a common control dataset derived from 1,500 randomly selected healthy British individuals, we report initial association and independent replication in a North American sample of two new loci related to AS—ARTS1 and IL23R—and confirmation of the previously reported association of AITD with TSHR and FCRL3. These findings, enabled in part by increased statistical power resulting from the expansion of the control reference group to include individuals from the other disease groups, highlight notable new possibilities for autoimmune regulation and suggest that IL23R may be a common susceptibility factor for the major “seronegative” diseases.

Commentary

The new platforms for high-throughput genetic screening are rapidly expanding our knowledge of susceptibility loci for complex diseases. Investigators for the Wellcome Trust Case Control Consortium and the Australo-Anglo-American Spondylitis Consortium recently reported their findings from a large, genome-wide scan of four diseases. The strongest associations observed in the study were between SNPs in the major histocompatibility (MHC) encoding region and the three autoimmune diseases studied: AS, AITD, and MS. The genome-wide scan also identified and validated two new genes—ARTS1 (type I tumor necrosis factor receptor shedding aminopeptidase regulator) and IL23R (interleukin 23 receptor)—to be associated with AS.

Functionally, ARTS1 and IL23R represent interesting biological candidates for association with AS. The ARTS1 (also known as ERAAP, or ERAP1) gene encodes a type II integral transmembrane aminopeptidase with intra- and extracellular functions. In the endoplasmic reticulum, ARTS1 is involved in processing peptides to the optimal length for MHC class I presentation.^{1,2} This activity is intriguing because of the strong asso-

ciation of AS with the class I allele HLA-B27. A genetic association with the peptide loading process suggests a mechanistic link to HLA-B27 in developing disease. Alternatively, ARTS1 cleaves cell surface receptors for pro-inflammatory cytokines like IL-1, IL-6, and tumor necrosis factor (TNF), reducing the number of surface receptors and releasing soluble receptor antagonists.³⁻⁵ Potentially, a variant of ARTS1 with reduced ability to cleave surface receptors would prolong the interval that cells could receive signals from inflammatory cytokines.

Susceptibility to Crohn’s disease and psoriasis have also been reported to be associated with polymorphisms in the IL23R gene.^{6,7} This shared association suggests that there may be a common mechanism in the pathogenesis of seronegative spondyloarthropathies that lends itself to treatment. IL-23 shares the p40 protein subunit with IL-12 and plays a critical role in the generation of effector memory T cells and IL-17-producing T cells. These IL-17-producing T cells are critical in sustaining organ specific inflammation in several different mouse models of autoimmune disease. Targeting IL23R would theoretically also reduce IL-17 production. Therapeutic trials assessing the efficacy of IL12/23 inhibitors in Crohn’s disease are underway.^{8,9} The genetic link between AS and Crohn’s disease implies that clinical success using the IL12/23 inhibitors in Crohn’s disease may translate therapeutically to AS by targeting a common mechanism.

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FRACTURES

New Tool for Predicting Hip Fracture Risk

>> By Daniel Hal Solomon, MD, MPH

Robbins J, Aragaki AK, Kooperberg C, et al. Factors associated with 5-year risk of hip fracture in postmenopausal women. JAMA. 2007;298:2389-2398.

Abstract

Context: The 329,000 hip fractures that annually occur in the United States are associated with high morbidity, mortality, and cost. Identification of those at high risk is a step toward prevention.

TABLE 1:
Risk Factors for Hip Fracture

Risk Factors	Odds Ratio (95% CI)	P Value	Point Score
Age per each year	1.13 (1.11–1.15)	<.001	1/2 per year >50
Self-reported health			
Fair or poor vs. excellent	2.38 (1.66–3.40)	<.001	3
Good vs. excellent	1.22 (0.90–1.66)		1
Very good vs. excellent	1.11 (0.83–1.49)		0
Height per each inch	1.11 (1.07–1.16)	<.001	1/2 per inch >64
Weight per each pound	0.99 (0.98–0.99)	<.001	1 per 25 lb. <200
Fracture on or after age 55			
Not applicable vs. no	1.01 (0.51–2.02)	<.001	0
Yes vs. no	1.72 (1.41–2.10)		2
Race/ethnicity			White, 3
Unknown vs. white	1.00 (0.47–2.14)	<.001	
Asian/Pacific Islander vs. white	0.26 (0.10–0.70)		
American Indian vs. white	1.60 (0.50–5.10)		
Hispanic vs. white	0.32 (0.12–0.86)		
Black vs. white	0.41 (0.24–0.70)		
Physical activity			1
5–12 vs. ≤12	1.32 (1.04–1.67)	.004	
<5 vs. ≤12	1.26 (0.97–1.64)		
Inactive 0 vs. ≤12	1.64 (1.24–2.17)		
Smoking status			
Current vs. never	2.33 (1.71–3.18)	<.001	3
Past vs. never	0.96 (0.79–1.17)		0
Parent broke hip, yes vs. no	1.50 (1.20–1.87)	<.001	1
Corticosteroid use, yes vs. no	1.94 (1.16–3.25)	.01	3
Use of hypoglycemic agent, yes vs. no	1.74 (1.17–2.60)	.006	2

Source: JAMA. 2007;298:2389-2398.

Objective: To develop an algorithm to predict the five-year risk of hip fracture in postmenopausal women.

Design, setting, and participants: A total of 93,676 women who participated in the observational component of the Women's Health Initiative (WHI), a multiethnic longitudinal study, were used to develop a predictive algorithm based on commonly available clinical features. Selected factors that predicted hip fracture were then validated by 68,132 women who participated in the clinical trial. The model was tested in a subset of 10,750 women who had undergone dual-energy X-ray absorptiometry (DXA) scans for bone mass density assessment.

Main outcome measure: The prediction of centrally adjudicated hip fracture, measured by the area under the receiver operator characteristic (ROC) curves.

Results: During a mean (SD) follow-up of 7.6 (1.7) years, 1,132 hip fractures were identified among women participating in the observational study (annualized rate, 0.16%), whereas during a mean follow-up of 8.0 (1.7) years, 791 hip fractures occurred among women participating in the clinical trial (annualized rate, 0.14%). Eleven factors predicted hip fracture within five years: age, self-reported health, weight, height, race/ethnicity, self-reported physical activity, history of fracture after age 54 years, parental hip fracture, current smoking, current corticosteroid use, and treated diabetes. ROC curves showed that the algorithm had an area under the curve of 80% (95% confidence interval [CI], 0.77%–0.82%) when tested in the cohort of different women who were in the clinical trial. A simplified point score was developed for the probability of hip fracture. ROC curves comparing DXA-scan prediction based on a 10% subset of the cohort and the algorithm among those who participated the clinical trial were similar, with an area under the curve of 79% (95% CI, 73%–85%) versus 71% (95% CI, 66%–76%).

Conclusion: This algorithm, based on 11 clinical factors, may be useful to predict the five-year risk of hip fracture among postmenopausal women of various ethnic backgrounds. Further studies are needed to assess the clinical implication of the algorithm in general and specifically to identify treatment benefits.

Commentary

Hip fractures cause substantial morbidity, mortality, and related costs. While many pharmacologic agents have been developed for treating osteoporosis, an unacceptably high proportion of patients do not receive treatment until after a fracture, and many receive no treatment even after sustaining a fracture. Timely bone mineral density (BMD) testing can help identify at-risk individuals. However, most fractures occur in persons who do not have osteoporosis by t-score thresholds, pointing out the importance of non-BMD-related risk factors. Robbins and colleagues used the very large WHI datasets to develop and test a clinical prediction rule for hip fractures in postmenopausal women.

These investigators used data from nearly 100,000 women participating in the observational component of the WHI to identify eleven risk factors that were strong and significant predictors of hip fractures. These are listed in Table 1 (p. 22) and include older age, worse self-reported health, height above 64 inches, weight less than 200 pounds, fracture after 54 years of age, white race, physical inactivity, current smoking, parental history of hip fracture, corticosteroid use, and use of a hypoglycemic agent. Many of these risk factors have been well described in prior literature. These factors were then combined using a scoring system (available in a calculator form at <http://hipcalculator.fhcrc.org>) and compared with the five-year fracture rates.

The clinical prediction rule was found to be a good predictor of hip fractures within five years

with areas under the ROC curve (AUC) of approximately 0.80. The performance of the clinical prediction rule varied by the predicted five-year risk of hip fracture. For example, at low five-year predicted risk value (i.e., 0.1%), the rule was very sensitive but less specific. At higher five-year predicted risk values (i.e., 1%), the rule was very specific but less sensitive. The predictive ability of the rule was tested against BMD in a subset of women and found to have a slightly lower AUC, 0.71 versus 0.79. As expected, combining the clinical prediction rule with BMD information gave the best predictive information.

This study was well conducted and pursues an important clinical area. There are many non-

BMD risk factors that should be assessed when considering how to counsel women (and men) about their risk of a future fracture. This study informs us about some important factors and gives precise information about combining these factors for a precise estimate of risk. The clinical prediction rule and its calculation can easily be accessed and used via the Internet. However, because most drug treatment trials have not used such a risk calculator to define included populations, it is unclear how treatment will affect the calculated risks. I look forward to the day when clinical prediction rules are combined with treatment trials to better guide our therapeutic decision-making.

THE RHEUMATOLOGIST

METRICS IN RHEUMATOLOGY

RHEUMATOLOGY'S DIVERGENT THINKERS

OMERACT selects outcomes measures with an egalitarian process

>>By Gretchen Henkel

If rheumatology organizations could be assigned human characteristics, OMERACT (which stands for Outcome Measures in Rheumatology, formerly Outcome Measures in Rheumatology Clinical Trials) would be the family's divergent thinker. It has now been 16 years since the first international conference to achieve consensus about outcomes measures in rheumatology took place. Every two years since 1992, OMERACT has been providing an intellectual forum where an international community of clinicians, scientists, and regulatory, industry, and patient representatives sits down as equals to hammer out agreement on common endpoints to be used in clinical trials in the rheumatic diseases.

Like nurturing parents, OMERACT's five executive committee members are justifiably proud, and even a bit amazed, at the way in which OMERACT's unique organizational structure continues to build on its initial mission. Peter Brooks, MD, executive dean of health sciences at the University of Queensland in Brisbane, Australia, one of the original OMERACT founders and a current executive committee member, says, "Most organizations have to reinvent themselves after about a decade. But OMERACT doesn't seem to have had to do that. It's been 16 years and we're still going strong and still expanding."

Lee S. Simon, MD, associate clinical professor of medicine at Harvard Medical School in Boston and another executive committee member, says, "I'm involved in many other groups, and this has been the largest effort to be open of any group I've ever seen."

TR talked recently with several of the founders and members of OMERACT to solicit their reflections on the organization's purpose, accomplishments, and future opportunities and challenges.

Why the Need?

For a specialty in which international collaborations and a focus on outcomes seem relatively common today, why would an initiative such as OMERACT be needed? In 1990, it was a different story. At that time, outcomes measurement was a huge challenge in clinical trials, says Vibeke Strand, MD, clinical professor of medicine in the division of immunology at Stanford University in Palo Alto, Calif., and another OMERACT executive committee member. Researchers in North America used different trial endpoints from their colleagues in Europe and regulatory agencies did not accept results of trials from countries other than their own.

During post-graduate thesis work in clinical epidemiology under the supervision of Peter Tugwell, MSc, MD, at McMaster University, Maarten Boers, MSc, MD, PhD, identified 22 different outcomes



OMERACT Executive Committee members and spouses at a dinner held during the Malta conference. Clockwise from left: Rob Kew, OMERACT conference organizer; Mrs. Boers; Dr. Boers; Dr. Tugwell; Leanne Idzerda, OMERACT secretary; Dr. Brooks; Mrs. Tugwell; Dr. Simon; Jack Loftis, PhD; Dr. Strand.

measurements that had been used as endpoints in arthritis trials worldwide. (Both men would later become founding members and executive committee members of OMERACT.) This led to a key realization, explains Dr. Tugwell, professor of medicine at the University of Ottawa and the Institute of Population Health in Ontario, Canada: "How on earth were we going to come up with a recommendation for clinicians to use in clinical practice if everyone was using a different outcome?"

Dr. Boers, professor of clinical epidemiology and biostatistics at VU University Medical Centre in Amsterdam, The Netherlands, fondly recalls these early discussions with Dr. Tugwell. "The story that should go into folklore is that, as my thesis supervisor, he had made all kinds of scribbly remarks throughout my manuscript—his handwriting is famously difficult to read—and there were two remarks I could not read," says Dr. Boers. "One was 'Do a review on combination therapy,' and the other was 'Suggest a conference on outcomes measures.'"

Clinical researchers weren't the only ones challenged with disparities in outcomes measures. In discussions with regulatory agencies, Drs. Tugwell and Boers found that regulators, too, had expressed frustration with the Atlantic divide. "The idea was to get a small group of people together," Dr. Strand says. "We were trying to make sure that there would be consensus [about which outcomes measures to use] on both sides of the pond." OMERACT 1 took place in Maastricht, The Netherlands, in 1992, and was organized around a Delphi process to achieve consensus on outcomes measures in RA. Its objectives were:

- > To broaden consensus on the minimum number of outcomes measures to be included in all RA clinical trials;
- > To achieve consensus on criteria for minimum clinically important improvement in patients with RA, as well as minimum important differences between treatment groups in RA clinical trials; and
- > To determine whether aggregate outcomes measures or indexes are useful in assessing patients and trials.¹

The 92 conference attendees filled out preconference questionnaires and then took part in discussions and voting tallies throughout the meeting proceedings. And the rest, as they say, is history.

Dr. Tugwell recalls the tensions in that first meeting while trying to reach consensus on the top seven outcomes measures. "We had invited the top people," he says, "and asked them to 'take off the hat' of having developed an outcome measure—which most of them had—and, in the interest of science, be prepared to consider which outcome might be agreed to as the one everyone should use." Preliminary voting, done on electronic keypads, reflected an almost 50-50 split over which variables should be included, recalls Dr. Tugwell. "By the end of the conference, that bimodal voting had disappeared," he says, "and we got a unimodal agreement on the top seven outcomes—pain, tender joints, swollen joints, function, patient's global assessment, physician's global assessment, and acute phase reactant."

CAREER TIMELINE

1990—OMERACT concept is born.

1992—OMERACT 1, Maastricht, The Netherlands, Attendance: 102.

1996—OMERACT 3, Cairns, Australia, Attendance: 92.

1994—OMERACT 2, Ottawa, Canada, Attendance: 112.

1998—OMERACT 4, Cancun, Mexico, Attendance: 124.

How It Works

The initial premise for OMERACT 1 was based on this summary statement: "Clinical trials are only as credible as their endpoints." As many articles on OMERACT have emphasized, improving endpoint outcomes measurement requires a "data-driven, iterative alignment process."² The procedure for developing conference agendas has evolved over the years, and topics are generated by the grassroots membership, not its leadership. OMERACT exists as a structure, supplying parameters and expertise for members to achieve a certain level of presentation.

During the earlier years, topics could be generated using the Delphi process, guided by committees until mature enough for general discussion. Now, with so many topics vying for attention, the process is a staged one: initiatives now begin as special interest groups (SIGs), when small groups of experts conduct a literature review and validation studies. The next step is a workshop, where studies are presented that help formulate and select which of the Four D domains (discomfort, disability, dollar cost, death) will constitute the focus. Finally the topic is formally presented at an OMERACT conference as a module, when evidence from the literature and from targeted studies is presented. Final selection of relevant measures is voted upon by conference attendees, and must pass the OMERACT Filter of Truth, Discrimination, and Feasibility.² (See www.omeract.org for more information on the filter.) The process from special interest group to module can take several years, and is not for everyone, says Dr. Boers, "but if you don't have tools to measure what's working and what's not working, there will be no progress, whatever drugs you develop. So we see ourselves as the slightly zany toolkit for rheumatology!"

Notable Accomplishments

OMERACT didn't stop with reaching consensus on core sets of measures for RA. Other achievements include core sets of measures for osteoarthritis and osteoporosis, psoriasis/psoriatic arthritis, psychosocial measures, and a core set of data for cost-effectiveness evaluations. Workshops have been held for a wide range of conditions, including MRI in ankylosing spondylitis, fatigue, fibromyalgia, gout, low back pain, drug safety, and chemical biomarkers, among many others. When asked to highlight specific OMERACT accomplishments, all those interviewed praised the successful initiative of member John Kirwan, MD, professor of rheumatic diseases at the University of Bristol Rheumatology Unit (U.K.), to include patient representatives in the OMERACT process. (See "Patients as Research Partners," above right.) "We now have 29 different groups working under the OMERACT umbrella," Dr. Simon pointed out. "The product itself—all the supplements that have been published over the years—has been incredibly noteworthy."

Kenneth G. Saag, MD, professor of medicine and epidemiology, and director of the Center for Education and Research on Therapeutics of Musculoskeletal Disorders at the University of Alabama at Birmingham, has served as the ACR representative since OMERACT 6. "It has now broadened to take on more structure and a growing relationship with other, longer-standing international bodies, such as the ACR and EULAR," he says.

Dr. Saag is especially interested in watching the passion that worldwide experts bring to the OMERACT process. He points to a joint ACR/EULAR project to develop measures for gout response criteria that was seeded by the OMERACT process.

"Another huge benefit of OMERACT is that it has been a tremendous training vehicle for our junior faculty and fellows," he says. "Junior clinical investigators can spend one-on-one time with experienced, senior-level people from throughout the world."

Patients as Research Partners

The need to include patients' perspectives in the OMERACT research process was first acknowledged at OMERACT 5, held in Toulouse, France, in 2000, and patient representatives first attended as delegates at OMERACT 6, held in 2002 in Gold Coast, Australia. "When we had the first patient group," recalls Dr. Brooks, "it opened our minds to looking at outcomes measures in a different way. After all, they are the people who have to do these measures and fill in the questionnaires. I don't know of any other medical organization in the world that involves patients the way we do in measurement." It was the participation of patients that led OMERACT to include fatigue as an outcome measure for RA.³

"Getting the patient perspective has been a neglected area," says Dr. Saag. "We think we know what patients think is important, as we measure different aspects of their disease, but did we really ever bother to ask them?"

Pamela Richards, who lives in Bristol, U.K., and is the current chair of OMERACT's Patient Panel, dis-



Pamela Richards (front row at right) and the rest of the Patient Panel who attended OMERACT 8 in Malta in 2006.

tinctly recalls her reactions when she attended her first OMERACT conference. "It was quite an amazing experience just to be with so many people who were researching the condition I had, and interested in the nitty-gritty of it," she says. "My previous experience with doctors is that they would focus on the things they could do, but all of the other things I experienced were not in their textbooks and were not validated as being part of RA. Also, my experience of living with the condition every day had not been put to good use." That all changed, says Ms. Richards, when she attended OMERACT 7, held in Monterey Bay, Calif.

As with many others who have participated in the OMERACT process, Ms. Richards has found stimulation to initiate other projects.

"My passion is to focus on enabling other patients to become individual research partners," she says. "Not everyone can attend OMERACT. However, people around the world can have the same kind of purpose by participating in their own area, not just as 'token patients,' but in a very positive way [e.g., to help structure protocols for clinical trials]."

To that end, Richards (together with Maarten de Wit from The Netherlands) was instrumental in formulating an OMERACT glossary targeted for patient representatives to familiarize them with the OMERACT process. She has also co-produced a three-hour patient-training workshop, which will debut at EULAR in June. She anticipates helping to foster patient groups such as the one connected with Dr. Kirwan's department at Bristol, and credits her experiences with OMERACT as the catalyst for her activism. "These people are incredible academics, but they also recognize that patients are people. They see us [the patient representatives] as people they can work with, not just patients they treat."—G.H.

Tensions and Image Issues

Inclusion of industry representatives has been a contentious issue, but OMERACT's organizers have always strongly believed that true consensus about outcomes measures is possible only if all stakeholders are brought to the table. Dr. Saag believes inclusion of industry representatives enlivens the OMERACT process. "Therapeutic development is inherently a public-private partnership," he says. "Having all partners at the table when we are designing measurement sets that are to be used in clinical trials leads to a richer and more relevant discussion."

Dr. Boers suspects that some in the rheumatology community harbor an unspoken belief that "OMERACT is, in some way, an industry vehicle. We obviously feel that is not true. All you can do, of course, is just keep up the good and keep on showing that the results that come out of OMERACT are not industry results, but are scientific results." As an example, Dr. Strand points to the successes of the newer disease-modifying antirheumatic drug trials in RA as a direct result of OMERACT's efforts, acting with the ACR and EULAR in establishing consensus regarding outcomes measures.

Current Challenges

Executive committee members are aware that success could spoil the OMERACT process. Limiting the number of people at the meetings continues to be a challenge. OMERACT has "grown tremendously, and we're now trying to figure out how to try to limit the number of topics at each meeting," says Dr. Strand. The stepped plan (SIG to workshop to module) for consideration of meeting topics was one answer to the challenges of growth. After OMERACT 8, held in Malta, many attendees complained about the number of topics and the expanding meeting size.

Dr. Boers is concerned about losing flexibility

in meeting organization, and he worries about mentoring new leaders for the process. "The number of participants has doubled, but the number of experts who really know how to run a workshop has not doubled," he explains. "There is still a lack of seasoned experts to guide the process through. So, if you keep expanding, pretty soon the quality will go down."

Another challenge: bringing OMERACT's recommendations into the daily practice of rheumatology. Rheumatologists may recognize that use of outcomes measures is an essential part of good management, says Dr. Brooks, "but at the end of the day, very few of us actually know whether the treatments we are giving to patients are actually helping." He urges practicing rheumatologists to learn more about the OMERACT order and to help their patients understand more about measurements and the drugs they are taking.

Summing up the OMERACT experience, Dr. Brooks says, "There are many things you do in life, and I think—and I suspect the others feel as I do—that this is something that we are all pleased about and proud of, that we've been a part of this movement." | THE RHEUMATOLOGIST |

Gretchen Henkel writes the "Metrics in Rheumatology" series.

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2006—OMERACT 8, Malta. Attendance: 260.

2000—OMERACT 5, Toulouse, France. Attendance: 120.

2004—OMERACT 7, Monterey Bay, Calif. Attendance: 250.

2008—May 27–31. OMERACT 9, Kananaskis Village, Canada.