



Michael J. Dunn, MD

Arthritis efforts at Medical College aimed at damage control, prevention

By Michael J. Dunn, MD, Dean and Executive Vice President,
Medical College of Wisconsin

For the 43 million Americans affected by arthritis, pain is an all-too-common part of daily life. The irreparable damage the disease often causes, however, drives the search for effective treatment and prevention measures.

The challenge is joined by researchers at the Medical College of Wisconsin's Arthritis Institute, directed by Lawrence M. Ryan, MD, Chief and Will & Cava Ross Professor of Medicine (Rheumatology). These College faculty members are steadfastly pursuing novel solutions to not only the aches and pains, but also the underlying destructive elements of arthritis.

As a group, the Rheumatology Division at the Medical College is focused most intently on Calcium Pyrophosphate Dihydrate (CPPD) Crystal Deposition disease. In this type of arthritis, pyrophosphate crystals form in the synovial fluid or articular tissues. Clinically, the CPPD crystals cause acute attacks of gout-like arthritis, or pseudogout. But more significantly, the crystals can cause and amplify osteoarthritis in weight-bearing joints. Osteoarthritis ultimately results in a complete loss of the cartilage surface in joints and exposure of the subchondral bone. The degenerative nature of osteoarthritis has an enormous negative impact on patients' quality of life, which is why finding solutions to CPPD Deposition disease is a priority for

Medical College researchers who aim to halt the domino effect of the disease.

With funding from the National Institutes of Health (NIH), Dr Ryan's research is directed at discovering what leads to pyrophosphate generation in chondrocytes. Murine ankylosis protein (ANK) is an ion channel found in cartilage cells that generates extracellular pyrophosphate, which can cause CPPD crystals to form. Doctor Ryan believes adenosine triphosphate (ATP) may be transported through ANK channels to the outside of chondrocytes. He is studying how ATP exits the chondrocyte, where it can then interact with chondrocyte extracellular enzymes that generate pyrophosphate from ATP.

Ikuko Masuda, MD, PhD, Assistant Professor of Medicine (Rheumatology) is studying the role of nucleoside triphosphate pyrophosphohydrolase (NTPPPH) through an NIH grant. NTPPPH is the ectoenzyme that breaks down ATP into pyrophosphate. Theoretically, inhibition of NTPPPH could prevent CPPD crystal formation, which would represent a significant treatment option for patients with this disease, especially if crystal production is stopped prior to the onset of osteoarthritis. Similarly, limiting substrate for NTPPPH by blocking ANK channels would decrease pyrophosphate production and CPPD formation.

These lines of research could have considerable impact on the elderly population, as prevalence of crystal formation increases with age. The crystals themselves provide no value to the body and the cause of their formation is unknown.

Ann K. Rosenthal, MD, Associate Professor of Medicine (Rheumatology) conducts related research of the enzyme transglutaminase, which acts as a regulator, controlling how much pyrophosphate the chondrocytes produce. Transglutaminase also modifies the matrix around cartilage, making it a more fertile soil for crystal growth. Her work is funded by both the NIH and Veterans Affairs.

Clinical researchers in the Medical College's Rheumatology Division are searching for new solutions to disease in the spirit of the founder of the College's Arthritis Institute, Daniel McCarty, MD. Doctor McCarty first described CPPD crystal arthritis and pioneered the use of combination chemotherapy to treat rheumatoid arthritis at the Medical College. This led to the advancement of using biologic agents to treat arthritis. For example, we now use etanercept, a protein that binds tumor necrosis factor (TNF), a molecule implicated in producing the inflammation and damage in joints affected with rheumatoid arthritis. College researchers are at the forefront of analyzing the use of biologic agents to

treat joint disease in an effort to further develop more effective and less toxic interventions.

Mary E. Cronin, MD, Associate Professor of Medicine (Rheumatology), has been involved in testing a biologic agent for the treatment of lupus nephritis and in studying a novel marrow ablative treatment for uncontrolled lupus. Mary Ellen Csuka, MD, Associate Professor of Medicine (Rheumatology), has been involved in studying biologic agents for the treatment of vascular spasm and skin thickening in scleroderma.

These medical interventions may someday revolutionize patient care for joint disease. Meanwhile, current patients who have been unsuccessful with non-operative treatments often seek surgical intervention at the Froedtert & Medical College clinics, located at Froedtert Hospital.

Most patients get complete pain relief from joint replacement surgery, says James T. Ninomiya, MD, Associate Professor of Orthopaedic Surgery. The Medical College employs leading-edge techniques to improve outcomes for arthritis patients. For example, College physicians use a minimally invasive surgical procedure for hip replacements. The incision can be less than 3 inches long, compared with the previous length of more than a foot. This results in less pain, faster recovery, and a quicker return to patients' previous lifestyles.

The success of these procedures is enhanced via expert diagnosis. Guillermo F. Carrera, MD, Professor and Chief of Diagnostic Radiology, is an international authority on radiologic techniques to evaluate joint disease. The Radiology Department has recently imple-

mented a completely digital image archiving and viewing system, which speeds interpretations and improves the ability to consult with rheumatologists and orthopaedic surgeons on complex cases with multimodality studies. New advances in magnetic resonance imaging and high-resolution, small-parts ultrasound show great promise for evaluating diseases of articular cartilage and muscle, as well as for directing diagnosis and treatment in patients with arthritis.

From the laboratory to the clinic, the Medical College of Wisconsin is impelling progress in the field of joint disease. Hopefully, thanks in part to these efforts, arthritis will one day cease to be such a pain.



The mission of the *Wisconsin Medical Journal* is to provide a vehicle for professional communication and continuing education of Wisconsin physicians.

The *WMJ* (ISSN 1098-1861) is the official publication of the Wisconsin Medical Society and is devoted to the interests of the medical profession and health care in Wisconsin. The managing editor is responsible for overseeing the production, business operation and contents of *WMJ*. The editorial board, chaired by the medical editor, solicits and peer reviews all scientific articles; it does not screen public health, socioeconomic or organizational articles. Although letters to the editor are reviewed by the medical editor, all signed expressions of opinion belong to the author(s) for which neither the *WMJ* nor the Society take responsibility. The *WMJ* is indexed in Index Medicus, Hospital Literature Index and Cambridge Scientific Abstracts.

For reprints of this article contact the *WMJ* Managing Editor at 866.442.3800 or e-mail wmj@wismed.org.

© 2003 Wisconsin Medical Society