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# Research in Progress

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**Adult Respiratory Distress Syndrome is a form of lung injury for which there is no cure and for which the mortality rate is 50 percent. Pulmonary Center researchers are investigating cell interactions that may lead to more successful therapies for this condition. See story on page 5.**

## Arthritis Center researchers seek to unlock mysteries of frustrating ailments

Few diseases have been as frustrating to both physicians and patients as the more than 100 disorders grouped under the heading of arthritis.

While some arthritic conditions, like bursitis, tend to be localized and short-lived, others, such as rheumatoid arthritis, may be long-lasting and debilitating.

In addition, in only a few instances are causes known. And while there are effective treatments for some types of arthritis, cures in most instances are not yet in sight.

Researchers at Boston University School of Medicine's Arthritis Center, however, are helping to unravel many of the unknowns of arthritis. By using epidemiological research techniques and clinical studies, the researchers hope to gain new knowledge about the extent and origins of various arthritic conditions and to improve diagnosis and treatment methods.

This *Research in Progress* special report focuses on three examples of diseases in which Arthritis Center researchers are working to shed more light:

• **Rheumatoid arthritis**—A research group headed by Robert Meenan, M.D., M.P.H., has developed and employed a comprehen-



*Researchers at the School of Medicine's Arthritis Center are making great inroads against arthritis, a group of diseases that affect one in 10 Americans. (Photo by Bradford F. Herzog)*

sive questionnaire that is helping rheumatoid arthritis patients and others communicate to their physicians basic but hard-to-measure aspects of their disease: how much pain is the condition causing, how is it affecting their mental state, how much is the condition interfering with the patient's ability to lead a normal life.

• **Fibrositis**—Don L. Goldenberg, M.D., and his colleagues have helped to characterize this perplexing condition, which usually strikes women in their child-bearing years and has often been dismissed as a psychosomatic disorder. The research group has demonstrated that the condition has a clearly defined set of symptoms, and has

done studies pointing the way to more effective treatments.

• **Osteoarthritis**—A team led by David Felson, M.D., M.P.H., is analyzing data from the renowned Boston University-Framingham Heart Study to better understand the origins of osteoarthritis, which results from the deterioration of the cartilage in joints and is the most common form of arthritis.

### **AIMS: A useful tool to measure patient's progress**

Physicians seeking to measure the impact of an arthritic condition on their patients often employ a variety *continued on page 2*

### Arthritis research... continued from page 1

of clinical tests. Among the tests used to evaluate the painful inflammatory condition of the joints known as rheumatoid arthritis, for example, are examinations of painful joints, x-rays and laboratory tests.

Such tests, however, do not really tell the physician how a patient is feeling, said Robert Meenan, M.D., M.P.H., an associate professor of medicine. And these tests generally are not considered especially relevant by patients, either.

"Patients tend not to focus on results of such tests," explained Meenan. "They are more interested in how the disease is affecting them: Can they reach up to get a can out of a kitchen cabinet? Can they walk upstairs?"

Physicians, of course, can try to gauge an arthritic condition's impact by talking to their patients. It is difficult to learn much of value in that regard, however, from a brief conversation in the office or on the phone.

Now, however, Meenan and his associates have developed an approach that substantially increases the amount of useful information that patients impart to their doctors.

The research group's technique is deceptively simple. Its centerpiece is a patient questionnaire called the Arthritis Impact Measurement Scales (AIMS). Examples of its 66 questions include: "Do you have to stay indoors most of the day because of your health?" "Can you easily button clothing?" "How much of the time during the past month have you felt downhearted and blue?" and, "During the past month how many times have you had to take medication for your arthritis?"

The questions, while basic in nature, are aimed at eliciting some very specific information about the impact of arthritic conditions on a patient.

"We're trying to get a handle not just on the patient's ability to func-



Robert F. Meenan, M.D., M.P.H., holds copy of AIMS questionnaire that he and colleagues created as a clinical tool for assessing pain and function in patients with arthritis. (Photo by Bradford F. Herzog)

tion, but also on his or her health status," explained Meenan. "We're looking at the extent of pain, the patient's psychological status and even some crude measures of social activity—for example, how the patient interacts with family and friends."

To check the validity of the AIMS questionnaire, Meenan and his associates recently collaborated with a University of Utah research group that was conducting a clinical trial to compare two methods for administering gold to rheumatoid arthritis patients: orally and by injection.

According to Meenan, the trial established that oral gold, while not as effective as injectable gold, can significantly help some patients without deleterious side effects that can accompany injectable gold therapy. For the BUSM group's purposes, however, the key finding was that the AIMS questionnaire proved to be a highly accurate measure of the effectiveness of the therapies.

The AIMS questionnaire subse-

quently has been widely recognized as an important new tool for clinical research in arthritis, and it is being used by a number of investigators across the country and abroad.

The BUSM group now is testing whether physicians will rely on the AIMS results in treating patients, as they do x-rays or blood tests. The investigators have identified 10 physicians around the country who treat large numbers of rheumatoid arthritis patients. The BUSM researchers have had some of those patients fill out the AIMS questionnaire, and are sending computerized summaries of the results to the physicians involved.

"We're studying whether having that information available influences the way physicians deal with their patients," said Meenan. "For example, if the AIMS instrument shows a patient ranking very high on the scale for depression, will that encourage the physician to make a referral to a psychiatrist? Or, if the patients say they're having trouble walking up stairs, will that make the doctor think about recommending physical therapy?"

"Our ultimate goal is to show that outcomes will improve when doctors regularly use the AIMS questionnaire to follow their patients who have arthritis," he added.

### Fibrositis: Shedding light on a baffling condition

Until recently, fibrositis was one of the most elusive and confusing forms of arthritis. Thanks to the efforts of Arthritis Center researchers and of investigators elsewhere, however, much is being learned about the origins and the nature of this condition.

"Patients who have fibrositis will complain of muscle pain, and will tell the doctor that they can't sleep well and that they feel tense a lot of the time," said Don L. Goldenberg, M.D., an associate professor of medicine. "Yet the doctor will find none of the classic signs of arthritis, and blood

tests will be normal."

The apparent vagueness of the symptoms has prompted many physicians to write off the disease as psychogenic. In fact, said Goldenberg, there probably is some relation between mental and physical well-being in this condition. Many of those who suffer from the condition describe themselves as perfectionists, and say that their symptoms get worse when they are under pressure or work long hours.

Research by Goldenberg's group and by investigators elsewhere, however, has made it clear that fibrositis—also known as fibromyalgia—is a distinct condition with a specific set of symptoms.

One of the key findings is that fibrositis produces a specific pattern of muscle pain. Areas affected include muscles of the neck, shoulder, back, hips, arms, and, less commonly, the knees and ankles.

Other symptoms may include fatigue, irritable bowel syndrome, stiffness and headaches. Sleep disorders also are common. In fact, said Goldenberg, a group of Canadian

investigators found that they could induce fibrositis symptoms in test subjects by depriving them of stage 4 sleep, which is the deepest and most restful form of sleep.

"We also find that many patients with fibrositis suffer from depression," explained Goldenberg. "This usually has preceded the development of the physical symptoms, though whether that means the biochemical changes associated with depression are linked to fibrositis is unclear."

The increasing understanding of fibrositis has led to a recognition of how widespread the condition is. Goldenberg said the condition may account for roughly 5 percent of the visits to general medical clinics in the nation each year.

Research also has revealed effective ways to treat fibrositis. A recent clinical study by Goldenberg's group, for example, has helped clarify the usefulness of an antidepressant, amitriptyline, and an anti-inflammatory agent, naproxen, in treating the condition.

"We administered the agents together to some of the patients, individually to others, and had a control group that was given two placebos," explained the rheumatologist. "The patients who received both agents showed the most progress, with a general improvement in the way they felt and in their ability to sleep, and also a reduction in pain."

The group treated with the antidepressant alone and in such a small dose that it should not have improved any possible depression, however, also showed a marked improvement in a variety of symptoms, including sleep disorders. That finding, said Goldenberg, lends support to the theory that sleep problems underlie at least some cases of fibrositis.

While the BUSM group plans to explore further the link between sleep disorders and fibrositis, they also are investigating other issues as well. Among them: Does the fact that the condition often appears just

before menopause indicate that hormonal changes may bring it on? And, does the frequent appearance of fibrositis in combination with rheumatoid arthritis and other inflammatory conditions mean it shares a common origin with such disorders?

"The research we've done to date suggests that fibrositis may not have a single cause," added Goldenberg, "but instead may be a syndrome that occurs in connection with a lot of different kinds of physical and psychological conditions."

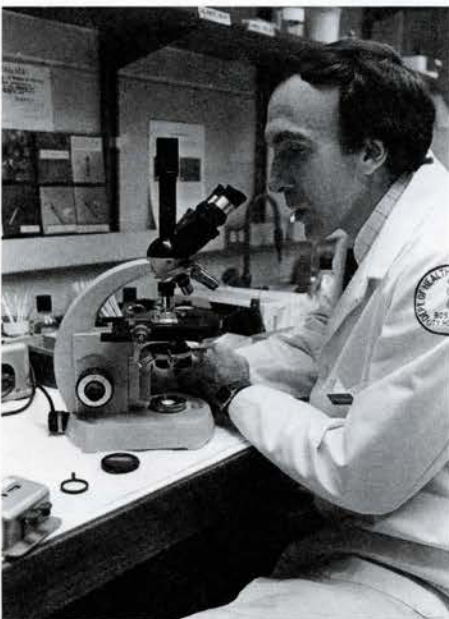
### Osteoarthritis: A 35-year study provides new insight

A third group of Arthritis Center investigators is making use of the renowned Boston University-Framingham Heart Study to explore the factors that may predispose patients to osteoarthritis, with the hope that their work may eventually lead to strategies for preventing the condition.

Osteoarthritis results from the deterioration of the cartilage in joints. As many as two of every 10 men and women over 50 are sufferers. In most, the condition is relatively mild. In some, however, the pain is so severe that they find it impossible even to walk.

According to David T. Felson, M.D., M.P.H., an assistant professor of medicine, the knee and the back are the areas most commonly affected, but osteoarthritis also can strike the hips, the fingers and other joints. "There's evidence that if osteoarthritis is affecting one site, that increases the likelihood of finding it at other sites as well," said the rheumatologist.

Many patients can be treated with medications and physiotherapies, but for the most severely afflicted, there is a highly effective remedy: artificial joints. But joint replacement is an expensive and potentially risky procedure, noted Felson, and thus is available to only a small percentage of osteoarthritis sufferers.



Don L. Goldenberg, M.D., in his lab. (Photo by Bradford F. Herzog)



David Felson, M.D., M.P.H., talks with patient about her arthritis, which affects her hands and knees. (Photo by Bradford F. Herzog)

Earlier studies of the so-called risk factors for osteoarthritis have pinpointed at least one such factor. "When you get muscle tears and cartilage injuries—the kinds of things that happen when you're playing football—there's no question that these predispose you to osteoarthritis in later life," said Felson.

There also is strong evidence that being seriously overweight increases the risk of the condition. The evidence regarding other potential risk factors, however, is less conclusive. "One of the questions is whether people who put repetitive pressure on their knees, like the cop on the beat, are at risk for osteoarthritis," said Felson. "We really don't know the answer."

Similarly, there is little scientific evidence about whether factors like smoking and diet can affect the risks of developing osteoarthritis. More generally, said the researcher, there is a basic question about whether osteoarthritis is caused solely by mechanical problems, like injuries, or whether the body's metabolic activities also play a role.

One bit of evidence pointing

toward at least some role for metabolic factors is the buildup of certain crystals in the joints that often accompanies osteoarthritis.

"It could be that there's a vicious cycle involved, in which damage to the cartilage produces metabolic changes that in turn produce more damage," said Felson. "At this point, however, we really have no way of knowing whether such a cycle exists."

In pursuit of answers to such questions, Felson's group is analyzing the frequency of osteoarthritis of the knee among participants in the Framingham Heart Study. These are men and women whose health patterns and lifestyles have been tracked for 35 years. Although the size of the study group has diminished from 5,300 to roughly 2,300, its members still offer a potentially valuable guide to the risk factors for osteoarthritis.

One reason is that they now range in age from 60 to over 90, which is a prime period for the emergence of osteoarthritis. A second is that the Framingham staff has monitored many of the factors that the BUSM

group wants to analyze: weight, diet, smoking habits, work histories and exercise patterns, among others.

The Study participants are brought in every two years for lab tests and interviews. "In the most recent two-year cycle," said Felson, "we had the Study's staff ask participants about specific symptoms, such as knee pain and lack of mobility. We also had them ask about sports injuries and other types of trauma."

In addition, the Framingham staff performed physical and x-ray examinations of the participants' knees.

In preliminary analyses, the investigators found that about 20 to 25 percent of the participants have osteoarthritis. That is a higher percentage than expected, said Felson, adding that it may reflect the advanced average age of the Study participants.

Planned next are a series of computer analyses aimed at uncovering evidence that particular types of activities, diets or habits predispose people to osteoarthritis.

"At this point, we have no idea what we'll find," noted Felson. "It's conceivable there will be no significant correlations. On the other hand, if we discovered that most of the osteoarthritis sufferers smoke more than the non-sufferers, or that most of them held jobs that involved a lot of walking, that would really help us start to sort out what causes this condition."

—Richard P. Anthony

#### Suggested Further Readings

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## BUSM researchers find cell interactions key to respiratory distress syndrome

Adult Respiratory Distress Syndrome (ARDS) is a form of lung injury for which there is as yet no cure, for which life-support care is available only in hospital intensive care units, and for which mortality remains at a depressing 50 percent, despite tremendous innovation in respiratory-care technology.

ARDS usually develops in association with pneumonia or such conditions as trauma, sepsis or drug overdose. The lungs become edematous when water and protein get into the gas-exchange spaces and prevent normal oxygenation of the blood.

Although improved ventilator techniques can sometimes help sustain a patient long enough for the lung to regain its normal functioning, frequently the damage is irreversible. For doctors to be able to fully treat ARDS patients, research at the cellular level, such as that which is under way in the Pulmonary Center at Boston University School of Medicine, must first uncover what causes the damage to the lung and how the damage occurs.

Why is the lung so susceptible to vascular injury? "From a systemic point of view, the lung, like the gut and the skin, is one of the places where we interact with our environment," said Sharon Rounds, M.D., an assistant professor of medicine at BUSM. "Toxic gases, for example, are inhaled directly into the lung and cause damage.

"The lung is the center of the blood circulation," she elaborated. "All the output of the heart's right ventricle goes through the lung circulation with every beat. It is a vast circulation with an enormous surface area; if there is some circulating toxic substance, such as gram-negative

bacteria, the lung would very likely come into contact with it."

According to Rounds, studies over the last 10 years have shown two factors to be crucial in the development of ARDS. First, endothelial cells—the cells that line blood vessels in the lung—are somehow altered to allow fluid to leak out of the vascular space and into the airways and alveoli. Second, studies in laboratory animals have shown that a type of white blood cell called polymorphonuclear neutrophils have the capacity to produce toxins in the process of fighting infection. These toxins, unfortunately, can also injure the lung tissue.

Rounds and her colleagues, who have been studying the disease since 1980, judged that in light of these two factors, some kind of interaction between neutrophils and endothelial cells might be an important early step in the development of ARDS. Because the lung is a complex organ composed of 40 different cell types, Rounds has focused her research on pure endothelial cell cultures to better see how neutrophil damage to endothelium might occur without the influence of other cell types.

Her early studies showed that thi-

ourea, a water-soluble toxic chemical compound that produces ARDS in rats, does influence the function of endothelial cells in pure cultures. The compound causes the cells to release a substance called a chemoattractant that stimulates neutrophils to "crawl."

"This was our first demonstration of endothelial cells influencing the function of other blood cells," said Rounds.

Subsequently, the researchers looked at the effects on endothelial cells of such agents normally found in the body as angiotensin II and histamine, powerful vasoactive compounds that affect vascular tone. The group's research results to date show that both angiotensin II and histamine also cause endothelial cells to release neutrophil chemoattractant.

"This is very exciting because thiourea, after all, is a rat poison but histamine and angiotensin II are important endogenous vasoactive substances," Rounds said. "We are now working to identify the chemical nature of the neutrophil chemoattractant produced by endothelial cells."

In the last year or so, Rounds has turned her attention to another aspect of endothelial cell-neutrophil



Sharon Rounds, M.D., studies CT-scan images of the lung. (Photo by Gustav Freedman)

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interaction—that of neutrophil adherence. The ability of neutrophils to stick to the surface of endothelial cells is another crucial, early step in neutrophil damage to the cell lining of the lung vasculature.

A recently completed study, presented by Rounds and pulmonary fellow Marta Render, M.D., last spring at the annual meeting of the Federation of American Societies of Experimental Biology, examined what effects the stage of endothelial cell culture development has on neutrophil-endothelial cell interactions. They found that neutrophils have a markedly decreased ability to adhere to the surface of mature endothelial-cell cultures. In such cultures, individual cells are positioned closely together to make a seamless lining such as that found in healthy blood vessels. Young cell cultures, however, in which endothelial cells are actively multiplying and dividing and have more space between cells, display a markedly greater neutrophil adherence.

"This suggests an analogy in vivo in which a mature, undamaged endothelial cell layer is naturally protected against neutrophil attack. If you wound a blood vessel (for example, with toxic gas or a bacterial infection) and cause a part of the endothelium to be lost, the remaining endothelial cells will grow over the wound to repair it. And yet in this state they are more susceptible to neutrophil attack. So, in addition to releasing chemoattractant, another aspect of endothelial-cell injury that can exacerbate lung damage is the

enhanced adherence of neutrophils to the surface of endothelial cells that are replicating in order to repair vascular damage," Rounds said.

The next step for Rounds is to understand the mechanisms of neutrophil adherence to endothelium. Her guess is that adherence involves changes in the surface coating of endothelial cells, called the glycocalyx. The glycocalyx is a thin layer of glycoprotein that covers the surface of all cell membranes and may modulate interactions between cells.

Said Rounds, "What I'm trying to do now is to determine whether changes in the glycocalyx are responsible for the movement of neutrophils toward endothelial cells. Are changes in endothelial glycocalyx part of the normal functioning of the cells or do they arise as a result of some injury? My hypothesis is that something happens to the endothelium that changes the nature of the glycocalyx and permits injury to occur so that a very subtle injury can set off a chain of events that can lead to ARDS.

"Although I can see a lot of potential for clinical application of these insights, I think we have a long way to go before we fully understand which patients would be appropriate to treat and how. There are some

drugs, for example, that prevent neutrophil chemoattractant from being released by endothelial cells. However, a lot of laboratory and animal work needs to be done before you could even consider taking that step with people," said Rounds.

Rounds' pulmonary circulation group is just one of several groups in the Pulmonary Center who are studying the effects of injury on such lung cell types as epithelial cells, fibroblasts and lymphocytes. Other researchers at the Center who collaborate with Rounds in her cell studies are David Center, M.D., an associate professor of medicine, and Harrison Farber, M.D., an assistant professor of medicine. Rounds' research is supported by funds from the National Heart, Lung, and Blood Institute and the American Heart Association.

—Caroline H. Lupfer

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