

Unravelling the mysteries
of arthritis, a painful
condition affecting more
than 37 million
Americans, is the
mission of MU's Arthritis

Center Director
Dr. Gordon Sharp,
below, and the

In laboratories on every corner of campus, dozens of MU scientists are wrestling with some of the same questions. Why do autoimmune diseases — such as rheumatoid arthritis, lupus and scleroderma — trigger the human body to self-destruct? What causes the body's immune system to go haywire and attack its own tissues?

And how can doctors treat, or some day even prevent, these and other

rheumatic diseases? Finding an answer to those questions would make life easier for the 37 million Americans who have one of the more than 100 forms of arthritis.

Arthritis can be much more than the aches and pains of old age. Even young children can suffer from a juvenile form of rheumatoid arthritis. Arthritis can turn a person's daily routine into a painful obstacle course. Some forms, called autoimmune diseases, not only can destroy

'A' Team

STORY BY JOHN BEAHLER, PHOTOS BY ROB HILL



joints and bones, but also can attack the lungs, heart, kidneys and circulatory system. One out of five Missourians, — an estimated 1 million people — has arthritis.

"Normally, our immune system is a protective mechanism that attacks invaders such as viruses, bacteria and fungi," says Dr. Gordon Sharp, Curators' professor of medicine and the internationally known biomedical researcher who heads MU's Arthritis Center. "But with autoimmune diseases, the immune system is reacting with our normal cells and tissues, creating great havoc."

Although researchers at Mizzou don't have the final answers, they are in the front ranks of scientists around the world who are probing the mechanisms of autoimmunity. The center includes a core

of more than 80 faculty members, who span a rainbow of academic disciplines. They include experts in internal medicine, physical medicine and rehabilitation, pathology, orthopedic surgery, psychiatry, pediatrics, biochemistry, microbiology, molecular biology, statistics, nursing, psychology, journalism, and physical and occupational therapy.

Two thousand years ago, the Greeks believed arthritis was caused by a bodily humor that flowed from the brain. Today, researchers are targeting the incredibly complex cascade of biochemical events that churn through the body's cells.

Scientists at MU have made major breakthroughs. Basic research by Dr. Helen Braley-Mullen, professor of internal medicine and molecular microbiology and

immunology, is leading to a better understanding of the mechanisms that turn some immune cells into factories that pour out harmful antibodies.

MU researchers have mapped the surface of tiny snippets of nuclear proteins, locating the areas where antibodies attach. Dr. Robert Hoffman, associate professor of internal medicine, and his colleagues have found specific genes that may predispose a person to some forms of rheumatic disease.

Dr. Kim Wise, professor of molecular microbiology and immunology, recently received a major grant from the National Institutes of Health to continue his study of minute organisms called mycoplasmas. Wise, along with Hoffman and other collaborators, is exploring whether mycoplasmas are the "invaders" that trigger autoimmune reactions in some

Out of the blue

IT'S NORMAL to get the blues from time to time, but when those down-in-the-dumps feelings escalate into major depression there could be some serious consequences.

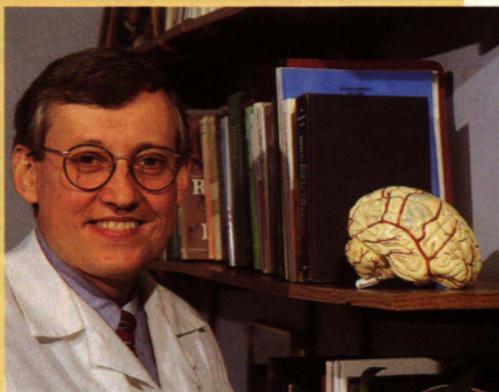
Depression can be a debilitating disease all by itself; combined with the chronic pain of arthritis there's a potential for severe disability, says Dr. Jerry Parker, associate professor of internal medicine.

Parker and other MU researchers are studying the relationship between depression and arthritis. They're asking if managing depression also reduces the disability of rheumatoid arthritis. It's an important question, because nearly one of five people with rheumatoid arthritis will develop major depression. Standard arthritis treatments don't focus on this secondary illness.

"People with rheumatoid arthritis live with quite a heavy psychological burden," says Parker, who is chief psychologist at the Truman Veterans Hospital in Columbia. "They must cope with severe pain and also with great uncertainty. The disease comes and goes in unpredictable ways; neither physicians nor patients can predict when or fully understand why."

Parker and his colleagues are using what's known as a "biopsychosocial" model. This approach recognizes that the biological aspects of a chronic disease like arthritis are entwined with psychological and sociological factors. There can be difficult adjustments in family relationships, for example, and often there are economic consequences as well. As a

Research by psychologist Jerry Parker and other Mizzou faculty is aimed at establishing the best ways to treat the millions of arthritis patients who suffer from depression.



group, people with rheumatoid arthritis earn only half what would be expected for their age and education level.

The study will treat patients with an antidepressive drug. One group will receive only the drug. Another set of patients will receive the drug in addition to "cognitive behavioral" counseling, which helps patients with depression replace pessimistic thought patterns with a more optimistic outlook. The idea is to help them break out of a cycle of isolation and inactivity.

Then researchers will look for different levels of disability and depression between the groups of patients. They'll also track the hormones and other blood chemicals that are markers for disease activity. Their findings could have an impact on treatments for arthritis and other chronic diseases that can help patients lead a more normal life.

rheumatic diseases. Other scientists are studying the impact of depression on rheumatoid arthritis. Still others are looking at the ways that aerobic exercise reduces the pain and swelling of arthritis.

Sharp, professor of internal medicine and pathology, is the glue that holds together this massive research and education effort. His soft-spoken civility doesn't match the description one colleague has for him: "Dr. Sharp is relentless as Ahab in search of the white whale."

There was no rheumatology program when Sharp came to MU in 1969. Over the next 25 years he helped build a center that is an international powerhouse of arthritis research. In recent years, he and members of his team have been awarded more than \$8 million in

research and education grants.

In his own biomedical research, Sharp has discovered some of the main serologic markers for a variety of rheumatic diseases. Using those markers, called "antinuclear antibodies," Sharp developed tests that allow doctors to diagnose and classify patients much earlier, when these diseases can be more easily controlled. He established the Antinuclear Antibody Laboratory at MU, and physicians from around the world now send more than 7,000 serum samples each year to be tested using the lab's latest techniques.

Perhaps even more important, Sharp has been a mentor to a whole generation of young arthritis researchers. He's also trained scores of badly needed rheumatology specialists.

"We know that we can't yet cure these diseases, but we have new drugs, as well

as physical therapy and occupational therapy approaches," Sharp says. "If they're used early on we can prevent some of the deformities and complications in many individuals, so it's important to diagnose them early."

"Right now, 95 percent of arthritis patients have to be cared for by family physicians and generalists, many of whom have not had much background and training in arthritis. There simply aren't enough rheumatologists to treat them all," he says.

Sharp made his mark early in the field of rheumatology. As a medical student at Johns Hopkins University, he realized that quite a few family members had significant problems with rheumatic disease. At Johns Hopkins, he worked with pioneer pathologist Arnold

Marian Minor, MSPH '79, PhD '89, assists Betty Overall of Columbia on a dynamometer, a device that tests muscle range and strength. Tom Smith, MA '93, takes the readout on a computer.



Keep them moving

From her first days as a physical therapist, Marian Minor has seen how devastating arthritis can be. "My first patient was a woman who had rheumatoid arthritis for 25 years and was terribly disabled," says Minor, MSPH '79, PhD '89. "She stayed in my mind because there just wasn't anything I could do for her. It was unsettling to feel so helpless and useless."

Medications and treatments for arthritis have improved dramatically since then. Minor, assistant professor of physical therapy, and her colleagues at the Missouri Arthritis Center have had a hand in rewriting the textbooks about the role exercise can play in treating arthritic diseases. Beginning in the mid-1980s, their research demonstrated that carefully controlled aerobic exercise is an effective treatment. In some cases of rheumatoid arthritis, exercise resulted in a 40 percent decrease in joint swelling.

Before that research, the prescription for the pain and complications of arthritis was plenty of rest. "When we started out, you didn't say aerobic and arthritis in the same sentence; that was radical stuff," Minor says.

affects the immune system in some way. We still have a lot to learn."

People from around mid-Missouri with arthritis have a special resource in the Health Connection, located in Columbia's Parkade Plaza. Sponsored by the Missouri Arthritis Rehabilitation Research and Training Center at MU, the Health Connection offers low-cost exercise programs for older adults, beginners and anyone with special needs. It also serves as a research laboratory where Minor and other Mizzou faculty and students study the effects of exercise on people with arthritis.

Minor, in collaboration with Dr. Joyce Mitchell, director of the Medical Informatics Group at MU, is working on another hurdle: getting the most up-to-date information into the hands of people with arthritis. This fall they hope to start testing an interactive computer program that lets people with osteoarthritis assess their own range of motion and strength. Then the computer puts together an individual exercise program and makes a 15-minute videotape for the patient to take home.

And there can be a bigger payoff beyond simply becoming more fit, Minor says. "Learning to exercise well and successfully helps people learn to solve other problems in their lives related to arthritis."

Rich, who was doing some of the first groundbreaking research in autoimmune diseases. After two years of research training at the National Institutes of Health, Sharp moved on to a residency and fellowship at Stanford.

It was at Stanford that he and his colleagues first recognized an unusual group of patients with symptoms that had overlapping features of a number of rheumatic diseases — lupus, scleroderma and polymyositis. Tests showed that they had extraordinarily high levels of novel antinuclear antibodies, which was not typical of other rheumatic diseases. Sharp and the others concluded that they were dealing with a distinct disease. In the late 1960s they began reporting on their work with the disease they called mixed connective tissue disease. Sharp's contributions to the research were

acknowledged when the condition became known in some countries as "Sharp's Syndrome."

"We thought then that it might be clinically important to identify these patients because they might require different treatment," Sharp says. "Second, these extraordinarily high levels of antinuclear antibodies, if studied in the lab, might yield some information that would give us a better understanding of the disease."

He was right on both counts. Patients with mixed connective tissue disease responded to corticosteroid drugs and, unlike lupus patients, they seldom had serious kidney disease. Studying the unusual antibodies connected with the disease was equally productive.

"There is no doubt that this concept has stimulated a tremendous burst of research

internationally, which has brought us to a clearer understanding of some of the probable factors involved in the disease," Sharp says. "It has helped us learn more about the mechanisms at work."

Continuing his work at MU, Sharp conducted a 15-year study that found patients with mixed connective tissue disease often experienced serious lung problems. In his first years at MU, he also went quietly to work building a research and training team that was soon recognized as an important contributor in uncovering basic information about autoimmune rheumatic diseases.

But Sharp didn't merely stay in the laboratory and the examining room. Another enormous contribution has been his efforts to fund basic research and



Exercise instructor Frances Deal Cheper, 73, leads the aerobic workout in the Health Connection, sponsored by Mizzou's Arthritis Rehabilitation Research and Training Center. Located in Columbia's Parkade Center, the Health Connection provides a range of low-cost exercise options for adults, whether or not they suffer from arthritis.

deliver that research to patients and doctors who need it most. In the mid-1970s, he was a member of the National Arthritis Commission that held public hearings throughout the nation, gathered information about arthritis and recommended a national plan of action to the U.S. Congress. The commission report was instrumental in establishing federally funded multipurpose arthritis centers all around the country, including one at MU.

Although those centers were a big first step, they didn't go far enough. "We came to the realization that they didn't have enough money to do community work," Sharp says. In the late 1970s, he and others went to the governor and state legislature for support. Sharp was chairman of a new state Arthritis Task Force, appointed by

Gov. Christopher "Kit" Bond. "We did the same thing that was done on a national level; we surveyed Missouri communities and held hearings and found out what problems are facing arthritis patients in Missouri."

In 1984 a new state law authorized a network of regional arthritis centers. In collaboration with the Arthritis Foundation, these centers brought treatment and education services to communities around the state. It's a unique undertaking; Missouri is still the only state with such a community-based arthritis effort. Many people call Sharp the father of these regional arthritis centers.

"Now a patient doesn't have to travel from Bethany, Mo., to Columbia or Kansas City, but can go to St. Joseph. A patient in the Bootheel doesn't have to go to St. Louis, but can go to Cape Girardeau.

The intent is to provide optimal treatment and care for patients as close as possible to their home communities," he says.

In 1988, the Arthritis Center, in collaboration with MU's Rusk Rehabilitation Center, received a grant to establish the nation's only arthritis rehabilitation, research and training center funded by the U.S. Department of Education. That support continued in 1993, with an additional \$3.3 million grant to continue support for research, training and dissemination of new information.

"With the federally funded arthritis centers and with the regional centers in Missouri, we now have the wherewithal to deal with people afflicted with arthritis," Sharp says. "We can improve their quality of life and help them become more functional." ■

Research promises hope for lupus patients

Women make up the vast majority of people who suffer from the autoimmune disease called systemic lupus erythematosus. That's why scientists have suspected for years that the female hormone estrogen somehow triggered the sporadic flares of the disease, which may be associated with bouts of skin rash, nervous disorders and joint pain.

Nearly two-thirds of lupus patients suffer from the mild form of the disease, but in severe cases lupus attacks the heart, lungs, brain and kidneys. The disease can flare up when women are pregnant, or when they take birth control pills which contain estrogen.

Now, a preliminary study by MU rheumatologists suggests that another hormone called prolactin may play a role in lupus. That finding holds out the promise of a new treatment, using a safer drug that has fewer side effects and that already is used to treat other illnesses. Prolactin is produced by the pituitary gland at the base of the brain and is the hormone that stimulates production of mother's milk. Scientists recently learned that prolactin also stimulates the body's immune system.

Using hybrid mice that spontaneously develop a lupus-like disease, Drs. Sara Walker and Robert McMurray, professor and assistant professor

of internal medicine, tested the theory that prolactin is involved in lupus. Some of the mice received doses of bromocriptine, a drug that lowers prolactin levels. In another group of mice, prolactin-producing pituitary glands were transplanted. The mice that received bromocriptine lived substantially longer and showed fewer signs of disease. The second group of mice developed high levels of prolactin and died prematurely from lupus.

In a small group of human patients, treatment with bromocriptine resulted in marked improvement. Results of the preliminary research are so encouraging that Walker and McMurray are developing a full-scale study to establish the effectiveness of bromocriptine in suppressing some forms of lupus. That, and other new treatments, give lupus patients new optimism.

"Every year, the outlook for living with lupus increases," Walker says. "We expect most people with lupus to be alive many years after the diagnosis is made.

Those are pretty good odds — almost better than driving a car every day."

By studying hybrid mice, Dr. Sara Walker and her colleagues are testing a theory that the human hormone prolactin plays a role in lupus.

