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April 2013

Handout on Health: Rheumatoid Arthritis

This publication is for people who have rheumatoid arthritis, as well as for their family members, friends, and others who want to find out more about this disease. The publication describes how rheumatoid arthritis develops, how it is diagnosed, and how it is treated, including what people can do to help manage their disease. It also highlights current research efforts supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and other components of the U.S. Department of Health and Human Services' National Institutes of Health (NIH). If you have further questions after reading this publication, you may wish to discuss them with your doctor.

What Is Rheumatoid Arthritis?

Rheumatoid arthritis (RA) is an inflammatory disease that causes pain, swelling, stiffness, and loss of function in the joints. It occurs when the immune system, which normally defends the body from invading organisms, turns its attack against the membrane lining the joints.

Features of Rheumatoid Arthritis

- Tender, warm, swollen joints
- Symmetrical pattern of affected joints
- Joint inflammation *often* affecting the wrist and finger joints closest to the hand
- Joint inflammation *sometimes* affecting other joints, including the neck, shoulders, elbows, hips, knees, ankles, and feet
- Fatigue, occasional fevers, a loss of energy

- Pain and stiffness lasting for more than 30 minutes in the morning or after a long rest
- Symptoms that last for many years
- Variability of symptoms among people with the disease

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Rheumatoid arthritis has several features that make it different from other kinds of arthritis.

(See box "[Features of Rheumatoid Arthritis.](#)")

For example, rheumatoid arthritis generally occurs in a symmetrical pattern, meaning that if one knee or hand is involved, the other one also is. The disease often affects the wrist joints and the finger joints closest to the hand. It can also affect other parts of the body besides the joints. (See "[What Happens in Rheumatoid Arthritis?](#)") In addition, people with rheumatoid arthritis may have fatigue, occasional fevers, and a loss of energy.

The course of rheumatoid arthritis can range from mild to severe. In most cases it is chronic, meaning it lasts a long time—often a lifetime. For many people, periods of relatively mild disease activity are punctuated by flares, or times of heightened disease activity. In others, symptoms are constant.

Who Has Rheumatoid Arthritis?

Scientists estimate that about 1.5 million people, or about 0.6 percent of the U.S. adult population, have rheumatoid arthritis.¹ Interestingly, some recent studies have suggested that although the number of new cases of rheumatoid arthritis for older people is increasing, the overall number of new cases may actually be going down.

¹According to the National Arthritis Data Workgroup, the actual number of new cases of rheumatoid arthritis is lower than previous estimates because of changes in the classification for the condition, as cited in Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, Liang MH, Kremers HM, Mayes MD, Merkel PA, Pillemer SR, Reveille JD, Stone JH, for the National Arthritis Data Workgroup. Estimates of the Prevalence of Arthritis and Other Rheumatic Conditions in the United States. Part I. Arthritis Rheum 2008;58(1):15-25.

Rheumatoid arthritis occurs in all races and ethnic groups. Although the disease often begins in middle age and occurs with increased frequency in older people, older teenagers and young adults may also be diagnosed with the disease. (Children and younger teenagers may be diagnosed with juvenile idiopathic arthritis, a condition related to rheumatoid arthritis.) Like some other forms of arthritis, rheumatoid arthritis occurs much more frequently in women than in men. About two to three times as many women as men have the disease.

What Happens in Rheumatoid Arthritis?

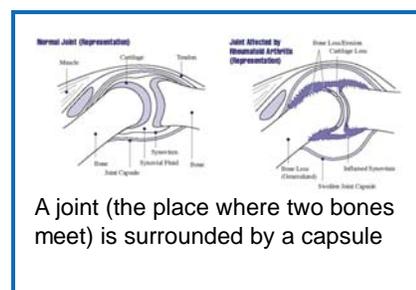
Rheumatoid arthritis is primarily a disease of the joints. A joint is the point where two or more bones come together. With a few exceptions (in the skull and pelvis, for example), joints are designed to allow movement between the bones and to absorb shock from movements like walking or repetitive motions. The ends of the bones are

covered by a tough, elastic tissue called cartilage. The joint is surrounded by a capsule that protects and supports it ([see illustration](#)). The joint capsule is lined with a type of tissue called synovium, which produces synovial fluid, a clear substance that lubricates and nourishes the cartilage and bones inside the joint capsule.

Like many other rheumatic diseases, rheumatoid arthritis is an autoimmune disease (*auto* means self), so-called because a person's immune system, which normally helps protect the body from infection and disease, attacks joint tissues for unknown reasons. White blood cells, the agents of the immune system, travel to the synovium and cause inflammation (synovitis), characterized by warmth, redness, swelling, and pain—typical symptoms of rheumatoid arthritis. During the inflammation process, the normally thin synovium becomes thick and makes the joint swollen puffy, and sometimes warm to the touch.

As rheumatoid arthritis progresses, the inflamed synovium invades and destroys the cartilage and bone within the joint. The surrounding muscles, ligaments, and tendons that support and stabilize the joint become weak and unable to work normally. These effects lead to the pain and joint damage often seen in rheumatoid arthritis. Researchers studying rheumatoid arthritis now believe that it begins to damage bones during the first year or two that a person has the disease, one reason why early diagnosis and treatment are so important.

Some people with rheumatoid arthritis also have symptoms in places other than their joints. Many people with rheumatoid arthritis develop anemia, or a decrease in the production of red blood cells. Other effects that occur less often include neck pain and dry eyes and mouth. Very rarely, people may have inflammation of the blood vessels (vasculitis), the lining of the lungs (pleurisy), or the sac enclosing the heart (pericarditis).



that protects and supports it. The joint capsule is lined with a type of tissue called synovium, which produces synovial fluid that lubricates and nourishes joint tissues. In rheumatoid arthritis, the synovium becomes inflamed, causing warmth, redness, swelling, and pain. As the disease progresses, the inflamed synovium invades and damages the cartilage and bone of the joint. Surrounding muscles, ligaments, and tendons become weakened. Rheumatoid arthritis also can cause more generalized bone loss that may lead to osteoporosis (fragile bones that are prone to fracture).

How Does Rheumatoid Arthritis Affect People's Lives?

Rheumatoid arthritis affects people differently. Some people have mild or moderate forms of the disease, with periods of worsening symptoms, called flares, and periods in which they feel better, called remissions. Others have a severe form of the disease that is active most of the time, lasts for many years or a lifetime, and leads to serious joint damage and disability.

Although rheumatoid arthritis is primarily a disease of the joints, its effects are not just physical. Many people with rheumatoid arthritis also experience issues related to:

- depression, anxiety
- feelings of helplessness
- low self-esteem.

Rheumatoid arthritis can affect virtually every area of a person's life from work life to family life. It can also interfere with the joys and responsibilities of family life and may affect the decision to have children.

Fortunately, current treatment strategies allow most people with the disease to lead active and productive lives. These strategies include pain-relieving drugs and medications that slow joint damage, a balance between rest and exercise, and patient education and support programs. In recent years, research has led to a new understanding of rheumatoid arthritis and has increased the likelihood that, in time, researchers will find even better ways to treat the disease.

What Causes Rheumatoid Arthritis?

Scientists still do not know exactly what causes the immune system to turn against the body's own tissues in rheumatoid arthritis, but research over the last few years has begun to piece together the factors involved.

Genetic (inherited) factors: Scientists have discovered that certain genes known to play a role in the immune system are associated with a tendency to develop rheumatoid arthritis. (See "[What Research Is Being Conducted on Rheumatoid Arthritis?](#)" for recent genetic developments.) For the genes that have been linked to rheumatoid arthritis, the frequency of the risky gene is only modestly higher in those with rheumatoid arthritis compared with healthy controls. In other words, individual genes by themselves confer only a small relative risk of disease. Some people who have these particular genes never develop the disease. These observations suggest that although a person's genetic makeup plays an important role in determining if he or she will develop rheumatoid arthritis, it is not the only factor. What is clear, however, is that more than one gene is involved in determining whether a person develops rheumatoid arthritis and how severe the disease will become.

Environmental factors: Many scientists think that something must occur to trigger the disease process in people whose genetic makeup makes them susceptible to rheumatoid arthritis. A variety of factors have been suggested, but a specific agent has not been identified.

Other factors: Some scientists also think that a variety of hormonal factors may be involved. Women are more likely to develop rheumatoid arthritis than men. The disease may improve during pregnancy and flare after pregnancy. Breastfeeding may also aggravate the disease. Contraceptive use may increase a person's likelihood of developing rheumatoid arthritis. This suggests hormones, or possibly deficiencies or changes in certain hormones, may promote the development of rheumatoid arthritis in a genetically susceptible person who has been exposed to a triggering agent from the environment.

Even though all the answers are not known, one thing is certain: rheumatoid arthritis develops as a result of an interaction of many factors. Researchers are trying to understand

these factors and how they work together.
(See [“What Research Is Being Conducted on Rheumatoid Arthritis?”](#))

How Is Rheumatoid Arthritis Diagnosed?

Rheumatoid arthritis can be difficult to diagnose in its early stages for several reasons. First, there is no single test for the disease. In addition, symptoms differ from person to person and can be more severe in some people than in others. Also, symptoms can be similar to those of other types of arthritis and joint conditions, and it may take some time for other conditions to be ruled out. Finally, the full range of symptoms develops over time, and only a few symptoms may be present in the early stages. As a result, doctors use a variety of the following tools to diagnose the disease and to rule out other conditions:

Medical history: The doctor begins by asking the patient to describe the symptoms, and when and how the condition started, as well as how the symptoms have changed over time. The doctor will also ask about any other medical problems the patient and close family members have and about any medications the patient is taking. Accurate answers to these questions can help the doctor make a diagnosis and understand the impact the disease has on the patient's life.

Good communication between patient and doctor is especially important. For example, the patient's description of pain, stiffness, and joint function and how these change over time is critical to the doctor's initial assessment of the disease and how it changes over time.

Physical examination: The doctor will check the patient's reflexes and general health, including muscle strength. The doctor will also examine bothersome joints and observe the patient's ability to walk, bend, and carry out activities of daily living. The doctor will also look at the skin for a rash and listen to the chest for signs of inflammation in the lungs.

Laboratory tests: A number of lab tests may be useful in confirming a diagnosis of rheumatoid arthritis. Following are some of the more common ones:

- **Rheumatoid factor (RF):** Rheumatoid factor is an antibody that is present eventually in the blood of most people with rheumatoid arthritis. (An antibody

is a special protein made by the immune system that normally helps fight foreign substances in the body.) Not all people with rheumatoid arthritis test positive for rheumatoid factor, and some people test positive for rheumatoid factor, yet never develop the disease. Rheumatoid factor also can be positive in some other diseases; however, a positive RF in a person who has symptoms consistent with those of rheumatoid arthritis can be useful in confirming a diagnosis. Furthermore, high levels of rheumatoid factor are associated with more severe rheumatoid arthritis.

- **Anti-CCP antibodies:** This blood test detects antibodies to cyclic citrullinated peptide (anti-CCP). This test is positive in most people with rheumatoid arthritis and can even be positive years before rheumatoid arthritis symptoms develop. When used with the RF, this test's results are very useful in confirming a rheumatoid arthritis diagnosis.
- **Others:** Other common laboratory tests include a white blood cell count, a blood test for anemia, which is common in rheumatoid arthritis; the erythrocyte sedimentation rate (often called the sed rate), which measures inflammation in the body; and C-reactive protein, another common test for inflammation that is useful both in making a diagnosis and monitoring disease activity and response to anti-inflammatory therapy.

X rays: X rays are used to determine the degree of joint destruction. They are not useful in the early stages of rheumatoid arthritis before bone damage is evident; however, they may be used to rule out other causes of joint pain. They may also be used later to monitor the progression of the disease.

How Is Rheumatoid Arthritis Treated?

Doctors use a variety of approaches to treat rheumatoid arthritis. These are used in different combinations and at different times during the course of the disease and are chosen according to the patient's individual situation. No matter what treatment the doctor and patient choose, however, the goals are the same: to relieve pain, reduce inflammation,

slow down or stop joint damage, and improve the person's sense of well-being and ability to function.

Good communication between the patient and doctor is necessary for effective treatment. Talking to the doctor can help ensure that exercise and pain management programs are provided as needed, and that drugs are prescribed appropriately. Talking to the doctor can also help people who are making decisions about surgery.

Goals of Treatment

- Relieve pain
- Reduce inflammation
- Slow down or stop joint damage
- Improve a person's sense of well-being and ability to function.

Current Treatment Approaches

- Lifestyle
- Medications
- Surgery
- Routine monitoring and ongoing care.

Health behavior changes: Certain activities can help improve a person's ability to function independently and maintain a positive outlook.

- **Rest and exercise:** People with rheumatoid arthritis need a good balance between rest and exercise, with more rest when the disease is active and more exercise when it is not. Rest helps to reduce active joint inflammation and pain and to fight fatigue. The length of time for rest will vary from person to person, but in general, shorter rest breaks every now and then are more helpful than long times spent in bed.

Exercise is important for maintaining healthy and strong muscles, preserving joint mobility, and maintaining flexibility. Exercise can also help people sleep well, reduce pain, maintain a positive

attitude, and manage weight. Exercise programs should take into account the person's physical abilities, limitations, and changing needs.

- **Joint care:** Some people find using a splint for a short time around a painful joint reduces pain and swelling by supporting the joint and letting it rest. Splints are used mostly on wrists and hands, but also on ankles and feet. A doctor or a physical or occupational therapist can help a person choose a splint and make sure it fits properly. Other ways to reduce stress on joints include self-help devices (for example, zipper pullers, long-handled shoe horns); devices to help with getting on and off chairs, toilet seats, and beds; and changes in the ways that a person carries out daily activities.
- **Stress reduction:** People with rheumatoid arthritis face emotional challenges as well as physical ones. The emotions they feel because of the disease—fear, anger, and frustration—combined with any pain and physical limitations can increase their stress level. Although there is no evidence that stress plays a role in causing rheumatoid arthritis, it can make living with the disease difficult at times. Stress also may affect the amount of pain a person feels. There are a number of successful techniques for coping with stress. Regular rest periods can help, as can relaxation, distraction, or visualization exercises. Exercise programs, participation in support groups, and good communication with the health care team are other ways to reduce stress.
- **Healthful diet:** With the exception of several specific types of oils, there is no scientific evidence that any specific food or nutrient helps or harms people with rheumatoid arthritis. However, an overall nutritious diet with enough—but not an excess of—calories, protein, and calcium is important. Some people may need to be careful about drinking alcoholic beverages because of the medications they take for rheumatoid arthritis. Those taking methotrexate may need to avoid alcohol altogether because one of the most serious long-term side effects of methotrexate

is liver damage.

- **Climate:** Some people notice that their arthritis gets worse when there is a sudden change in the weather. However, there is no evidence that a specific climate can prevent or reduce the effects of rheumatoid arthritis. Moving to a new place with a different climate usually does not make a long-term difference in a person's rheumatoid arthritis.

Medications: Most people who have rheumatoid arthritis take medications. Some medications (analgesics) are used only for pain relief; others, such as corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs), are used to reduce inflammation.² Still others, often called disease-modifying antirheumatic drugs (DMARDs), are used to try to slow the course of the disease. Common DMARDs include hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine. Other DMARDs—called biologic response modifiers—may be used in people with more serious disease. These are genetically engineered medications that help reduce inflammation and structural damage to the joints by interrupting the cascade of events that drive inflammation. Currently, several biologic response modifiers are approved for rheumatoid arthritis, including abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab, and tofacitinib. They work in one of several ways:

- Etanercept, golimumab, infliximab, adalimumab and certolizumab, reduce inflammation by blocking tumor necrosis factor (TNF), a cytokine or immune system protein that triggers inflammation during normal immune responses.
- Anakinra works by blocking a cytokine called interleukin-1 (IL-1) that is seen in excess in people with rheumatoid arthritis.
- Rituximab stops the activation of a type of white blood cell called B cells. This reduces the overall activity of the immune system, which is overactive in people with rheumatoid arthritis.
- Abatacept blocks a particular chemical that triggers the overproduction of white blood cells called T cells that

play a role in rheumatoid arthritis inflammation.

- Tocilizumab works by blocking a cytokine called interleukin 6 (IL-6) to reduce inflammation in people with rheumatoid arthritis,

Another DMARD, tofacitinib, from a new class of drugs call jak kinase (JAK) inhibitors, fights inflammation from inside the cell to reduce inflammation in people with rheumatoid arthritis.

²Warning: NSAIDs can cause stomach irritation or, less often, they can affect kidney function. The longer a person uses NSAIDs, the more likely he or she is to have side effects, ranging from mild to serious. Many other drugs cannot be taken when a patient is being treated with NSAIDs because NSAIDs alter the way the body uses or eliminates these other drugs. Check with your health care provider or pharmacist before you take NSAIDs. Also, NSAIDs sometimes are associated with serious gastrointestinal problems, including ulcers, bleeding, and perforation of the stomach or intestine. People age 65 and older, as well as those with any history of ulcers or gastrointestinal bleeding, should use NSAIDs with caution.

For many years, doctors initially prescribed aspirin or other pain-relieving drugs for rheumatoid arthritis, and waited to prescribe more powerful drugs only if the disease worsened. In recent decades this approach to treatment has changed as studies have shown that early treatment with more powerful drugs—and the use of drug combinations instead of one medication alone—may be more effective in reducing or preventing joint damage. Someone with persistent rheumatoid arthritis symptoms should see a doctor familiar with the disease and its treatment to reduce the risk of damage.

The person's general condition, the current and predicted severity of the illness, the length of time he or she will take the drug, and the drug's effectiveness and potential side effects are important considerations in prescribing drugs for rheumatoid arthritis.

Many of the drugs that help reduce disease in rheumatoid arthritis do so by reducing the inflammation that can cause pain and joint damage. However, in some instances,

inflammation is one mechanism the body normally uses to maintain health, such as to fight infection and possibly to stop tumors from growing. The magnitude of the risk from the treatment is hard to judge because infections and cancer can occur in people with rheumatoid arthritis who are not on treatment, and probably more commonly than in healthy individuals. Nevertheless, appropriate caution and vigilance are justified.

Surgery: Several types of surgery are available to patients with severe joint damage. The primary purpose of these procedures is to reduce pain, improve the affected joint's function, and improve the patient's ability to perform daily activities. Surgery is not for everyone, however, and the decision should be made only after careful consideration by the patient and doctor. Together they should discuss the patient's overall health, the condition of the joint or tendon that will be operated on, and the reason for, as well as the risks and benefits of, the surgical procedure. Cost may be another factor.

Following are some of the more common surgeries performed for rheumatoid arthritis:

- **Joint replacement:** Joint replacement involves removing all or part of a damaged joint and replacing it with synthetic components. Joint replacement is available for a number of different joints, but the most commonly replaced joints are the hips and knees. Joint replacement surgery is done primarily to relieve pain and improve or preserve function.

Although joint replacement traditionally involved a large incision and long recovery, new minimally invasive surgeries are making it possible to do some forms of joint replacement with smaller incisions and a shorter, easier recovery.

Artificial joints are not always permanent and may eventually have to be replaced. This may be an important consideration for young people.

- **Arthrodesis (fusion):** Arthrodesis is a surgical procedure that involves removing the joint and fusing the bones into one immobile unit, often using bone grafts from the person's own pelvis. Although the procedure limits

movement, it can be useful for increasing stability and relieving pain in affected joints. The most commonly fused joints are the ankles and wrists and joints of the fingers and toes.

- **Tendon reconstruction:** Rheumatoid arthritis can damage and even rupture tendons, the tissues that attach muscle to bone. This surgery, which is used most frequently on the hands, reconstructs the damaged tendon by attaching an intact tendon to it. This procedure can help to restore hand function, especially if the tendon is completely ruptured.
- **Synovectomy:** In this surgery, the doctor actually removes the inflamed synovial tissue. Synovectomy by itself is seldom performed now because not all of the tissue can be removed, and it eventually grows back. Synovectomy is done as part of reconstructive surgery, especially tendon reconstruction.

Routine monitoring and ongoing care:

Regular medical care is important to monitor the course of the disease, determine the effectiveness and any negative effects of medications, and change therapies as needed.

Monitoring typically includes regular visits to the doctor. It also may include blood, urine, and other laboratory tests and x rays.

People with rheumatoid arthritis may want to discuss preventing osteoporosis with their doctors as part of their long-term, ongoing care. Osteoporosis is a condition in which bones become weakened and fragile. Having rheumatoid arthritis increases the risk of developing osteoporosis for both men and women, particularly if a person takes corticosteroids. Such patients may want to discuss with their doctors the potential benefits of calcium and vitamin D supplements or other treatments for osteoporosis.

Alternative and complementary therapies:

Special diets, vitamin supplements, and other alternative approaches have been suggested for treating rheumatoid arthritis.

Research shows that some of these, for example, fish oil supplements, may help reduce arthritis inflammation. For most, however, controlled scientific studies either have not been conducted on them or have found no definite benefit to these therapies.

As with any therapy, patients should discuss the benefits and drawbacks with their doctors before beginning an alternative or new type of therapy. If the doctor feels the approach has value and will not be harmful, it can be incorporated into a person's treatment plan. However, it is important not to neglect regular health care.

Who Treats Rheumatoid Arthritis?

Diagnosing and treating rheumatoid arthritis requires a team effort involving the patient and several types of health care professionals.

The primary doctor to treat arthritis may be an **internist**, a doctor who specializes in the diagnosis and medical treatment of adults, or a **rheumatologist**, a doctor who specializes in arthritis and other diseases of the bones, joints, and muscles.

As treatment progresses, other professionals often help. These may include the following:

- **Orthopaedists:** Surgeons who specialize in the treatment of, and surgery for, bone and joint diseases.
- **Physical therapists:** Health professionals who work with patients to improve joint function.
- **Occupational therapists:** Health professionals who teach ways to protect joints, minimize pain, perform activities of daily living, and conserve energy.
- **Dietitians:** Health professionals who teach ways to use a good diet to improve health and maintain a healthy weight.
- **Nurse educators:** Nurses who specialize in helping patients understand their overall condition and implement their treatment plans.
- **Psychologists:** Health professionals who seek to help patients cope with difficulties in the home and workplace that may result from their medical conditions.

What You Can Do: The Importance of Self-Care

Although health care professionals can prescribe or recommend treatments to help patients manage their rheumatoid arthritis, the real key to living well with the disease lies with

the patients themselves. Research shows that people who take part in their own care report less pain and make fewer doctor visits. They also enjoy a better quality of life.

Self-management programs teach about rheumatoid arthritis and its treatments, exercise and relaxation approaches, communication between patients and health care providers, and problem solving. Research on these programs has shown that they help people:

- understand the disease
- reduce their pain while remaining active
- cope physically, emotionally, and mentally
- feel greater control over the disease and build a sense of confidence in the ability to function and lead full, active, and independent lives.

What Research Is Being Conducted on Rheumatoid Arthritis?

Over the last several decades, research has greatly increased our understanding of the immune system, genetics, and biology. This research is now showing results in several areas important to rheumatoid arthritis. Scientists are thinking about rheumatoid arthritis in exciting ways that were not possible even 10 years ago.

The National Institutes of Health (NIH) funds a wide variety of medical research at its headquarters in Bethesda, MD, and at universities and medical centers across the United States. One of the NIH institutes, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), is a major supporter of research and research training in rheumatoid arthritis through grants to individual scientists, Specialized Centers of Research, Multidisciplinary Clinical Research Centers, and Multipurpose Arthritis and Musculoskeletal Diseases Centers.

Following are examples of research in rheumatoid arthritis supported by the Federal Government through the NIAMS and other parts of NIH.

Genetics

Researchers are studying genetic factors that

predispose some people to developing rheumatoid arthritis, as well as factors connected with disease severity. Over the past decade, NIAMS-supported research in this area has led to several important genetic discoveries including the following:

Variation in a gene involved in controlling T-cell activation doubles rheumatoid arthritis risk:

The variation—called a single nucleotide polymorphism (SNP)—is located within a gene that codes for PTPN22, an enzyme known to be involved in controlling the activation of white blood cells called T cells that play an important role in the body's immune system. Where the SNP is present in one or both copies of a person's genes for this enzyme, T cells and other immune cells respond too vigorously, causing increased inflammation and tissue damage. Scientists say the implications of this finding go beyond a better understanding of rheumatoid arthritis risk; it may also help explain why different autoimmune diseases tend to run in families. Other studies have the same SNP with type-1 diabetes and juvenile arthritis.

Genetic variation increases risk of rheumatoid arthritis and lupus:

Separate research found a SNP in a large segment of the *STAT4* gene increases the risk of both rheumatoid arthritis and another autoimmune disease, systemic lupus erythematosus (lupus). The *STAT4* gene encodes a protein that plays an important role in the regulation and activation of certain cells of the immune system. One variant form of the gene was present at a significantly higher frequency in rheumatoid arthritis patient samples from the North American Rheumatoid Arthritis Consortium (NARAC)—a consortium formed to collect, analyze, and make available clinical and genetic data on 1,000 sibling pairs with rheumatoid arthritis—as compared with controls. Scientists replicated that result in two independent collections of rheumatoid arthritis cases and controls.

Twin study shows genetic differences in rheumatoid arthritis:

Because identical twins have the exact same genes at conception, scientists believe that changes in the genes after the genome is constructed may account for why one of a twin pair can have rheumatoid arthritis while the other does not. To better understand what those changes might be, scientists have used a sophisticated technique called microarray to examine the expression of

more than 20,000 genes at a time in 11 pairs of disease-discordant identical twins (meaning one twin had the disease, the other did not). The examination led to the detection of differences in expression of 827 genes. The most significantly overexpressed gene was laeverin, an enzyme that breaks down certain types of proteins; second was 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2), important in a steroid pathway linked to inflammation and bone erosion; and third was cysteine-rich angiogenic inducer 61 (Cyr61), which is known for its role in angiogenesis, the formation of new blood vessels. The scientists say their findings are exciting because they offer new insights into the mechanisms by which rheumatoid arthritis is mediated.

Genetic region associated with rheumatoid arthritis risk:

Using the relatively new genome-wide association approach, which makes it possible to analyze between 300,000 and 500,000 single nucleotide polymorphisms, researchers in the United States and Sweden identified a region of chromosome 9 containing two genes relevant to chronic inflammation: *TRAF1* (encoding tumor necrosis factor receptor-associated factor 1) and *C5* (encoding complement component 5). Scientists say it is not yet known how the genes in the TRAF1-C5 region influence rheumatoid arthritis risk, but they hope that by learning more about the genes and their role in the disease, they may find clues to influencing treatment of the disease.

Rare gene variants associated with

rheumatoid arthritis: Another genome-wide association scan was used to determine that rare variants of a gene that encodes the enzyme sialic acid acetyltransferase (SIAE) are associated with several autoimmune diseases, especially rheumatoid arthritis and type 1 diabetes. This discovery suggests that SIAE plays an important role in autoimmunity. They also highlight the promise that rare variant analysis holds for unraveling complex, multigene diseases.

New Therapies

Researchers continue to identify molecules that appear to play a role in rheumatoid arthritis and thus are potential targets for new treatments. The path between identifying the molecule and developing a drug that targets it is long and difficult. Fortunately, this path has

been successfully negotiated and new drugs have emerged that successfully reduce symptoms and damage in rheumatoid arthritis. Researchers continue to identify more candidate drugs, with hopes that these will have fewer side effects or will cure more patients.

Tofacitinib, approved for the treatment of rheumatoid arthritis in 2012, is from a new class of drugs developed to target Janus kinases. One member of this family, JAK3, was discovered in the early 1990s by a National Institutes of Health laboratory in the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). Subsequent studies carried out at the National Heart, Lung, and Blood Institute (NHLBI), in collaboration with the NIAMS, showed that genetic defects in JAK3 can cause severe combined immunodeficiency. This discovery led to the idea that drugs blocking Janus kinases would suppress the immune system and might be protective against the damaging inflammation of rheumatoid arthritis and certain other autoimmune diseases.

Understanding Joint Destruction

Advances in understanding the processes that lead to joint destruction are bringing NIAMS-supported researchers a step closer to new therapies to stop the destructive process. In one such study, researchers found a factor they suspect plays a crucial role in joint destruction: an adhesion molecule on cells of the synovium called cadherin-11. Adhesion molecules allow individual cells to stick together to form tissues. At normal levels, cadherin-11 enables the cells (synoviocytes) to adhere together to form the lining layer of the synovium. But when overgrowth of the synovium occurs, cadherin plays a key role in the destructive behavior of the synovium; namely, eroding the cartilage, which causes permanent destruction to the joint. In studies of mice prone to a disease similar to human rheumatoid arthritis, blocking cadherin-11 prevented cartilage destruction. The next step is to determine whether an agent to block an excess of the molecule has the same beneficial effect in people with rheumatoid arthritis.

In other research, scientists found that a lack of apoptosis (programmed cell death) contributes to a proliferation of cells in the joint lining and the failure to eliminate immune cells that react against self. In animal studies, mice

lacking two proteins that mediate the process of apoptosis developed arthritis.

Other NIAMS-funded research has led to a better understanding of autoantibodies and how they cause joint damage. Studying the joints of patients with rheumatoid arthritis, researchers found that anti-CCP and rheumatoid factor antibodies from the joints actually bound to a lot of products associated with joint cartilage and also to histones, intracellular proteins from the cell nucleus that associate with DNA in the formation of chromosomes. The histone deposits may be derived from cells that died and spilled their contents, a result of the disease condition. Furthermore, they found that cartilage in RA is actually coated with histones, regardless of whether RA was active or not. Cartilage from joints of people with osteoarthritis (OA) were not covered in histones. The researchers hypothesize that histones on the cartilage bind with antihistone antibodies, contributing to joint-damaging inflammation in rheumatoid arthritis.

Preventing Related Problems

Having rheumatoid arthritis does not make people immune to other medical problems. Thus, reducing the risk of problems that can be associated with rheumatoid arthritis is a focus of NIAMS research. One recent study showed that treatment with hydroxychloroquine, a medication used to treat rheumatic diseases and malaria, reduced the incidence of diabetes in people with rheumatoid arthritis. People with rheumatoid arthritis who took the medication for more than 4 years showed a reduction in risk of diabetes of up to 77 percent.

More information on research is available from the following websites:

- [NIH Clinical Research Trials and You](#) was designed to help people learn more about clinical trials, why they matter, and how to participate. Visitors to the website will find information about the basics of participating in a clinical trial, first-hand stories from actual clinical trial volunteers, explanations from researchers, and links to how to search for a trial or enroll in a research-matching program.
- [ClinicalTrials.gov](#) offers up-to-date information for locating federally and

privately supported clinical trials for a wide range of diseases and conditions.

- [NIH RePORTER](#) is an electronic tool that allows users to search a repository of both intramural and extramural NIH-funded research projects from the past 25 years and access publications (since 1985) and patents resulting from NIH funding.
- [PubMed](#) is a free service of the U.S. National Library of Medicine that lets you search millions of journal citations and abstracts in the fields of medicine, nursing, dentistry, veterinary medicine, the health care system, and preclinical sciences.

Hope for the Future

Scientists are making rapid progress in understanding the complexities of rheumatoid arthritis: how and why it develops, why some people get it and others do not, why some people get it more severely than others. Results from research are having an impact today, enabling people with rheumatoid arthritis to remain active in life, family, and work far longer than was possible 20 years ago. There is also hope for tomorrow, as researchers begin to apply new technologies such as stem cell transplantation and novel imaging techniques. (Stem cells have the capacity to differentiate into specific cell types, which gives them the potential to change damaged tissue in which they are placed.) These and other advances will lead to an improved quality of life for people with rheumatoid arthritis.

For More Information

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National Institutes of Health**

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Toll Free: 877-22-NIAMS (877-226-4267)
TTY: 301-565-2966
Fax: 301-718-6366
Email: NIAMSinfo@mail.nih.gov
Website: <http://www.niams.nih.gov>

Other Resources

National Institute of Allergy and Infectious Diseases (NIAID)

Website: <http://www.niaid.nih.gov/Pages/default.aspx>

**National Center for Complementary and Alternative Medicine
National Institutes of Health**

Website: <http://nccam.nih.gov>

American Academy of Orthopaedic Surgeons (AAOS)

Website: <http://www.aaos.org>

American College of Rheumatology

Website: <http://www.rheumatology.org>

Arthritis Foundation (AF)

Website: <http://www.arthritis.org>

Key Words

Analgesics. Medications designed to relieve pain. Pure analgesics do not have an effect on inflammation.

Anti-CCP antibodies. Antibodies to cyclic citrullinated peptide (anti-CCP). A positive test for the antibodies is useful for confirming a diagnosis of rheumatoid arthritis. In fact, tests for the antibodies can be positive years before the development of symptoms.

Apoptosis. Programmed cell death. This is a mechanism by which the body rids itself of old or unhealthy cells. A problem with this mechanism can allow cells that react against the body's own tissues to survive.

Arthrodesis. A surgical procedure that involves removing the joint and fusing the bones into one immobile unit, often using bone grafts from the person's own pelvis. Although the procedure limits movement, it can be useful for increasing stability and relieving pain in affected joints. The most commonly fused joints are the ankles and wrists and joints of the fingers and toes.

Autoimmune disease. A disease in which the immune system, which is designed to protect the body from foreign invaders, mistakenly sees the body's own tissues as foreign and makes autoantibodies against them, leading to tissue destruction.

Biologic response modifiers. Genetically engineered medications that help reduce

inflammation and structural damage to the joints by interrupting the cascade of events that drive inflammation.

C-reactive protein. A protein produced by the body during the process of inflammation. A positive blood test for the protein indicates the presence of inflammation in the body. The test may be used in diagnosing rheumatoid arthritis and monitoring disease activity and the response of treatment.

Cartilage. A tough, elastic tissue that covers the ends of the bones where they meet to form joints. In rheumatoid arthritis, the inflamed synovium invades and destroys joint cartilage.

Collagen. A family of fibrous proteins that are components of cartilage. Collagens are the building blocks of skin, tendon, bone, and other connective tissues.

Corticosteroids. Powerful anti-inflammatory hormones made naturally in the body or man made for use as medicine. Corticosteroids may be taken orally to relieve the systemic inflammation of rheumatoid arthritis or injected directly into an inflamed joint to temporarily reduce inflammation and relieve pain.

COX-2 inhibitors. A subclass of nonsteroidal anti-inflammatory drugs (NSAIDs) that are formulated to relieve pain and inflammation with less risk of gastrointestinal ulcers. For information about the risk posed by NSAIDs, see "NSAIDs" in the "[How Is Rheumatoid Arthritis Treated?](#)" section.

Diabetes. A disease that affects the body's ability to produce or use insulin, resulting in an inability to control the level of sugar in the blood. If not properly treated, high blood sugar levels can eventually lead to problems such as kidney disease, heart disease, and blindness.

Dietitian. A health professional who teaches ways to use a good diet to improve health and maintain a healthy weight.

Disease-modifying antirheumatic drugs (DMARDs). A class of medications used in the treatment of rheumatoid arthritis. DMARDs do more than ease the symptoms of rheumatoid arthritis like some other treatments. They often slow or stop the course of the disease to help prevent joint damage.

Erythrocyte sedimentation rate (sed rate). A blood test used to detect and monitor inflammation. It is measured by recording the

rate at which red blood cells fall and form sediment at the bottom of a test tube.

Flare. A period of heightened disease activity. In rheumatoid arthritis, a flare may be characterized by increased fatigue; fever; and painful, swollen, and tender joints.

Hydroxychloroquine. An anti-inflammatory drug used in the treatment of rheumatoid arthritis, malaria, and lupus.

Immune system. A complex network of cells and tissues that work in concert to protect the body against invaders such as viruses and bacteria.

Joint capsule. A tough membrane sac that holds the bones and other joint parts together.

Ligaments. Tough bands of connective tissue that attach bones to each other, providing stability.

Lupus. A chronic inflammatory condition in which the immune system attacks the skin, joints, heart, lungs, blood, kidneys and brain. Also called systemic lupus erythematosus.

Muscles. Bundles of specialized cells that contract and relax to produce movement when stimulated by nerves.

Nonsteroidal anti-inflammatory drugs (NSAIDs). A class of medications available over the counter or with a prescription that ease pain and inflammation.

Nurse educator. A nurse who specializes in helping patients understand their overall condition and implementing their treatment plans.

Occupational therapist. A health professional who teaches ways to protect joints, minimize pain, perform activities of daily living, and conserve energy.

Orthopaedist. A surgeon who specializes in the treatment of, and surgery for, bone and joint diseases. Also called orthopaedic surgeon.

Pericarditis. Inflammation of the pericardium, the thin sac-like membrane that surrounds the heart. Pericarditis can be caused by rheumatoid arthritis.

Physical therapist. A health professional who works with patients to improve joint function.

Pleurisy. Inflammation of the pleura, the linings surrounding the lungs. Pleurisy can be caused by rheumatoid arthritis.

Psychologist. A health professional who seeks to help patients cope with difficulties in the home and workplace that may result from their medical conditions.

Rheumatoid arthritis. A form of arthritis in which the immune system attacks the tissues of the joints, leading to pain, inflammation, and eventually joint damage and malformation. It causes swelling and redness in joints, and may make people feel sick, tired, and feverish. Rheumatoid arthritis may also affect skin tissue, the lungs, the eyes, or the blood vessels.

Rheumatoid factor (RF). An antibody that is present eventually in the blood of most people with rheumatoid arthritis. Not all people with rheumatoid arthritis test positive for rheumatoid factor, and some people test positive for rheumatoid factor, yet never develop the disease. Rheumatoid factor also can be positive in some other diseases.

Synovectomy. Removal of the synovium (joint lining). As a treatment for rheumatoid arthritis, synovectomy is much less common than it once was because not all of the tissue can be removed, and it eventually grows back. Synovectomy is done as part of reconstructive surgery, especially tendon reconstruction.

Synovium. A thin membrane inside the joint capsule that secretes synovial fluid. In rheumatoid arthritis, the synovium is attacked by the immune system.

Synovial fluid. A fluid secreted by the synovium that lubricates the joint and keeps the cartilage smooth and healthy.

Tendons. Tough, fibrous cords that connect muscles to bones.

Vasculitis. Inflammation of the blood vessels. Vasculitis can occur as a complication of rheumatoid arthritis.

X ray. A procedure in which low-level radiation is passed through the body to produce a picture called a radiograph. X rays of joints affected by rheumatoid arthritis are used to determine the degree of joint destruction.

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The mission of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), a part of the U.S. Department of Health and Human Services' National Institutes of Health (NIH), is to support research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases; the training of basic and clinical scientists to carry out this research; and the dissemination of information on research progress in these diseases. The NIAMS Information Clearinghouse is a public service sponsored by NIAMS that provides health information and information sources. Additional information can be found on the NIAMS Website at www.niams.nih.gov.

For Your Information

This publication contains information about medications used to treat the health condition discussed here. When this publication was developed, we included the most up-to-date (accurate) information available. Occasionally, new information on medication is released.

For updates and for any questions about any medications you are taking, please contact

U.S. Food and Drug Administration

Toll Free: 888-INFO-FDA
(888-463-6332)

Website: <http://www.fda.gov>

For additional information on specific medications, visit Drugs@FDA at

www.accessdata.fda.gov/scripts/cder/drugsatfda. Drugs@FDA is a searchable catalog of FDA-approved drug products.

For updates and questions about statistics, please contact

Centers for Disease Control and Prevention's National Center for Health Statistics

Website: <http://www.cdc.gov/nchs>

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