



RA

Diagnosing and Treating Rheumatoid Arthritis

An understanding of the causes of RA and the development of new treatments for RA have greatly improved the outcomes for patients over the past 20 years.

By Ronale Tucker Rhodes, MS

The National Institutes of Health (NIH) estimates that there are at least 80 autoimmune diseases.¹ Of those, rheumatoid arthritis (RA) is the most common, according to a study conducted in 2011,² with rates higher than psoriasis, Crohn's disease, type 1 diabetes, lupus and multiple sclerosis.³ One in 28 women (3.6 percent) and one in 59 men (1.7 percent) will develop RA in their lifetime.² Today, approximately 1.3 million people in the U.S. have been diagnosed with RA.³

RA was first described in the 1800s. Its name was coined by British rheumatologist Alfred Baring Garrod in 1859.⁴ Back then, RA was referred to as a "wasting disease" because the chronic inflammation associated with RA that causes weight loss and loss of appetite resulted in people with RA being rail-thin. In addition, because it was believed that exercise caused more damage to joints, people with RA didn't exercise, causing their muscles to atrophy. Today, how RA is diagnosed and treated has changed considerably; new medicines curb inflammation, and exercise is part of treatment.⁵

What Is RA?

RA is an autoimmune disease in which the body's immune system mistakenly attacks its tissues, specifically the synovium, a thin membrane that lines the joints. The attack causes fluid buildup in the joints, causing pain in the joints and inflammation that is systemic — meaning it can occur throughout the body, including the organs.

It is a chronic disease that can't be cured. Most people with RA experience intermittent bouts of intense disease activity called flares. In some, the disease is continuously active and gets worse over time, while others enjoy long periods of remission.⁶

RA affects about 1 percent of the world population, occurring in 860 out of 100,000 people.³ Nearly three times as many women have the disease as men. In women, RA most commonly begins between ages 30 and 60, while in men, it often occurs later in life.⁶

Causes of RA

The exact cause of RA is unknown, but it is believed to be caused by a combination of genetic, environmental

and hormonal factors.⁷ In addition, there does appear to be some association with primary immunodeficiency diseases (PIs).

According to a study in *Arthritis and Rheumatism*, about 40 percent of RA risk comes from an inherited tendency.⁸ While the inheritance pattern is unclear because many genetic and environmental factors appear to be involved, it is believed that having a close relative with RA likely increases a person's risk of developing the condition.⁹

Variations in dozens of genes that have been identified as risk factors for RA are known or suspected to be involved in immune system function. The most significant genetic risk factors for RA are variations in human leukocyte antigen (HLA) genes, especially the HLA-DRB1 gene. The proteins produced from HLA genes help the immune system distinguish the body's own proteins from proteins made by foreign invaders (such as viruses and bacteria). Changes in other genes appear to have a smaller impact on an individual's overall risk of developing RA.⁹

Environmental factors may trigger RA in people who are at risk, although how is unclear. Potential triggers include changes in sex hormones (particularly in women), occupational exposure to certain kinds of dust or fibers, traffic pollution, viral or bacterial infections, smoking, obesity and proximity to the equator.

Traffic pollution is thought to play a role since pollution through particulates (microscopic particles that can be inhaled deep into the lungs) is linked with inflammation. Harvard researchers conducted a study in 2009 of more than 90,000 U.S. women and found that those who lived within 0.031 miles of a major road had the highest risk of RA compared with those who lived farther away.⁵

In a study at New York University School of Medicine, researchers tested fecal samples (which reflect the population of gut bacteria) from 114 residents of the New York City area, some who were healthy, some who had been living with RA for years, some who had been recently diagnosed with RA and others who had psoriatic arthritis. Those who were recently diagnosed with RA were especially important since they had not yet been treated for the condition. In that group, a bacterium named *Prevotella copri* (*P. copri*), which is linked to an inflammatory response, was present in 75 percent of patients' intestines, whereas it only appeared in 37 percent of patients living with either RA or psoriatic arthritis and in 21 percent of healthy controls. This last number is similar to the prevalence of *P. copri* that previous studies have found in the general population. While the results don't establish a specific

cause of RA, they do show that the bacterium and the disease tend to occur together.¹⁰

Long-term smoking is a well-established risk factor for developing RA; it is also associated with more severe signs and symptoms in people who have the disease. Scientists from the Karolinska Institute and Karolinska University Hospital found that smoking just a few cigarettes each day can more than double a woman's risk of RA. In the study, data were gathered and examined from the Swedish Mammography Cohort, which included 34,000 women between the ages of 54 and 89, 219 of whom had RA. Results showed that even light smoking is linked to an elevated risk of RA. And, the risk increases more than twofold when a person smokes one to seven cigarettes each day. In addition, after comparing the people who had never smoked to women who had smoked for up to 25 years, the researchers discovered that length of smoking time also increases the probability of developing RA. After quitting, the risks of RA were lowered by one-third after 15 years. Yet, compared with those who had never smoked, this risk was still considerably higher 15 years after quitting.¹¹

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Researchers at the Mayo Clinic recently found that obese individuals were 25 percent more likely to develop RA than people of normal weight. The study included 813 patients with RA and 813 controls. Both groups had extensive medical history available prior to their diagnosis (mean 32.2 years), and approximately 30 percent of each group was obese at diagnosis. The history of obesity was significantly associated with developing RA. Between 1985 and 2007, the incidence of RA rose by an increment of 9.2 per 100,000 among women. Obesity accounted for 4.8 per 100,000 (52 percent) of this increase.¹² Eric Matteson, a rheumatologist at the Mayo Clinic who led the study, said the link between RA and

obesity is more than just stress on the joints from being heavy. “The link, we think, has to do with the activity of the fat cells themselves,” says Matteson, who adds that it’s the fat cells that stoke the fire of inflammation. “We have recognized in the past several years that fat cells are important mediators of inflammation,” Matteson says. “They are immunologically active, and they produce proteins that are inflammatory.”¹³

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Interestingly, the farther individuals are from the equator, the greater their risk of RA. And, living at a higher latitude earlier in life — between the ages of 15 and 30 — seems to increase the risk of RA. In a 2010 study of nearly 10,000 women, RA risk was higher for those living in the Northeast and Midwestern U.S., compared with women who lived west of the Rockies. The researchers noted that the increased risk at high latitudes could be due to lack of sunlight, which seems to resonate with a 2004 study that tracked more than 29,000 women and found that those with the lowest intake of vitamin D had the highest risk of developing RA. While it’s not proven that vitamin D plays a role, other autoimmune diseases such as multiple sclerosis have also been tied to vitamin D intake.⁵

Some PIs are associated with a higher incidence of certain autoimmune arthritis syndromes. For instance, patients with common variable immunodeficiency can develop severe RA.¹⁴ In addition, about 25 percent to 33 percent of patients with IgA deficiency develop autoimmune diseases, including RA.¹⁵

Symptoms of RA

RA tends to begin slowly with minor symptoms that come and go, usually on both sides of the body, and progresses over a period of weeks or months. Symptoms

of the condition vary from person to person and can change from day to day. Some individuals feel unusually fatigued weeks or months before any other symptoms become obvious, which is sometimes accompanied by a general feeling of ill health or even depression.

Early signs of RA are morning stiffness and stiffness after any period of prolonged inactivity like napping or sitting that lasts for several hours, as well as stiffness in one or more of the smaller joints (usually in the fingers and wrists, although individuals may also experience pain in the knees, feet, ankles or shoulders) that occurs at any time of day, whether active or not, and comes on slowly, although it can come on suddenly and affect multiple joints over the course of one or two days. Joint stiffness is often followed by joint tenderness or pain during movement or while at rest. Other early warning signs include a low-grade fever that accompanies joint pain and inflammation; numbness, tingling or a burning feeling in the hands or a squeak or crackling noise as damaged cartilage grinds against joints; decreased range of motion; dry mouth; dry, itchy or inflamed eyes; eye discharge; difficulty sleeping; chest pain when breathing; rheumatoid nodules (hard bumps of tissue under the skin on the arms, most commonly the elbows or fingers); and loss of appetite and/or weight loss.¹⁶

Most people with RA experience some progression of the disease during their lives, but each person responds to the disease differently depending on how advanced the RA is at the time of diagnosis, the person’s age at the time of diagnosis and how “active” the disease is. Generally, there are a few common patterns. About 5 percent to 10 percent of people have long remissions with near-disappearance of symptoms that can last years and even decades without an actual cure. Approximately 15 percent of people have intermittent symptoms of low or no symptoms that can last months between flare-ups. Unfortunately, the majority of people have progressive RA, the most common and serious form, which requires a long-term treatment plan and a coordinated medical team to manage the treatment and slow or stop progression.

Signs of progressive RA include having long-duration or high-intensity disease activity (flares); being diagnosed at a young age, which means the RA has more time to become active in the body; having rheumatoid nodules; having active inflammation that shows up in tests of joint fluid or in blood tests; having had a lot of damage on X-rays upon diagnosis; and having elevated blood tests for the rheumatoid factor (RF) or citrulline antibodies.¹⁷

Diagnosing RA

No single test exists to diagnose RA. Instead, a diagnosis begins by reviewing the history of the patient's symptoms and examining the joints for inflammation, tenderness, swelling and deformity, as well as looking at the skin for rheumatoid nodules. The inflammation in the joints is what helps to distinguish RA from common types of arthritis that are not inflammatory such as osteoarthritis or degenerative arthritis. The distribution of inflammation is also important; in RA, the small joints of the hands and fingers, wrists, feet and knees are typically inflamed in a symmetrical distribution (affecting both sides of the body). If only one or two joints are inflamed, other tests are usually conducted to exclude arthritis due to infection or gout. If rheumatoid nodules are detected, a diagnosis of RA can often be confirmed.

A blood test is often conducted to reveal specific antibodies associated with RA. Eighty percent of people with RA have the RF antibody, which can be found with a blood test. However, there are people who have RA who don't have the RF antibody; these individuals are known as having seronegative RA. Fifty percent to 75 percent of people with RA have citrulline antibody (also referred to as anticitrulline antibody, anticyclic citrullinated peptide antibody and anti-CCP antibody). This antibody is particularly useful in diagnosing RA when the RF antibody is not present in a blood test. It is believed that citrulline antibodies represent the earlier stages of RA, and they have been associated with more aggressive forms of the disease. Last, an antibody called the antinuclear antibody (ANA) is often found in people with RA.

Doctors will also look at the blood test for sedimentation (sed) rate, which is a crude measure of inflammation in the joints, C-reactive protein that shows the measure of inflammation in the body, and anemia, which is common in people with RA. It should be noted that RF, ANA, sed rate and C-reactive protein tests can be abnormal in other systemic autoimmune and inflammatory conditions, so abnormalities in these tests alone are not sufficient to diagnose RA.

Finally, X-rays, bone scans and an MRI can be useful to determine whether there is swelling of soft tissues early in the disease, as well as to monitor the progression of the disease and joint damage.¹⁸

In 2010, the American College of Rheumatology (ACR) developed a new classification system (www.rheumatology.org/ACR/practice/clinical/classification/ra/ra_2010.asp) based primarily on X-rays of joints to focus on features at earlier stages of disease that are associated with persistent and/or

erosive RA, rather than defining the disease by its late-stage features. The goal is to refocus attention on the important need for earlier diagnosis and therapy to prevent or minimize the occurrence of complications from RA.¹⁹

Treating RA

Treating RA consists of both pharmacologic and non-pharmacologic therapies. Pharmacologic therapies comprise several classes of agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), nonbiologic and biologic disease-modifying antirheumatic drugs (DMARDs), immunosuppressants and corticosteroids.²⁰ NSAIDs help manage the chronic pain, inflammation and swelling associated with RA, but they do not slow RA progression, which is why they are usually used along with DMARDs and biologics.²¹

Early therapy with DMARDs has become the standard of care because they are capable of both retarding disease progression more efficiently than later treatment, as well as of inducing more remissions.¹⁶ Some DMARDs are used more often than others. Methotrexate is the most commonly used because it has been shown to work as well or better than any other single medicine, and it is also relatively inexpensive and generally safe. Plaquenil (hydroxychloroquine) and Azulfidine (sulfasalazine) are used for mild RA. While they are not as powerful as other DMARDs, they usually cause fewer side effects. Minocin (minocycline) is an antibiotic that may help RA by stopping inflammation. And, Arava (leflunomide) works about as well as methotrexate and can work even better in combination with it, with side effects similar to methotrexate.

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Biologics are the newest drugs for RA and are either injected under the skin or given directly into a vein. When used with methotrexate, they help most people with RA. These include Actemra (tocilizumab), Enbrel (etanercept), Humira (adalimumab), Kineret (anakinra), Orencia (abata-

cept), Remicade (infliximab), Rituxan (rituximab), Cimzia (certolizumab) and Simponi (golimumab). Biologics work by neutralizing the immune system's signals that lead to joint damage, and are thought to have fewer side effects than other DMARDs.²²

In 2012, the ACR updated its recommendations for the use of nonbiologic and biologic DMARDs to treat RA. As part of its recommendations, "Patients with active disease should be monitored every three months, and treatment should be adjusted if there is no improvement in six months. Methotrexate is recommended as first-line therapy; sulfasalazine or leflunomide can be substituted if there are contraindications to methotrexate. Anti-tumor necrosis factor agents are no longer the only biologics recommended for patients with an insufficient response to methotrexate; all biologics are considered similarly effective. And, biologics should be combined with DMARDs."²³

Many people with RA also have other autoimmune disorders.

High doses of intravenous immune globulin (IVIG) are sometimes used to treat RA. However, there is controversy over whether IVIG is effective in reducing symptoms and improving the functional capability of RA patients. In one study that evaluated the long-term treatment of RA with high doses of IVIG in 10 patients, the researchers concluded that "IVIG may be a valid, tolerable, alternative combination drug for maintenance therapy of RA."²⁴ Yet, while more recently there are case reports of a beneficial effect of IVIG for RA patients, clinical trials have not shown any beneficial effect.²⁵

Many nonpharmacologic agents can treat RA, including exercise, diet, massage, counseling, stress reduction, physical therapy and surgery. Surgical treatments include synovectomy, tenosynovectomy, tendon realignment, reconstructive surgery or arthroplasty, and arthrodesis.¹⁷ Surgery is more likely to be more successful in the early course of deformity.²⁶

In pregnant patients with RA, no special obstetric monitoring is needed beyond what is performed for usual obstetric care. However, some medications such as Arava used to treat RA can have adverse effects on the fetus and

may have to be discontinued several months before conception is planned.²⁰

Complications of RA

Both the autoimmune process that causes RA and the medications prescribed to treat it can affect the skin, eyes, heart, blood vessels, blood cells, lungs and other organs.

One-fifth of people with RA develop rheumatoid nodules that appear as bumps under the skin. RA patients also can develop inflammation of the blood vessels, known as vasculitis, that can cause changes to the skin and surrounding tissues that can appear as ulcers, and that also can affect the body's organs, including the eyes, heart and nerves. Inflammation of the episclera, a thin membrane that covers the sclera, or white of the eye, is also common.

Pericardial effusion, in which fluid is collected between the pericardium and the heart, is another complication of RA that occurs in some people, usually during flares or periods of heightened disease activity. Persistent pericarditis can lead to thickening and tightening of the membrane, which can interfere with the heart's ability to work properly. Recent research shows that people with RA have an increased risk of heart attack and stroke.

Most with active RA experience a reduction in blood cells, or anemia, that can result in fatigue, rapid heart beat, shortness of breath, dizziness, leg cramps and insomnia. And, because active inflammation also can lead to high levels of blood platelets, medicines used to suppress the immune system can lead to low levels of blood platelets, a condition called thrombocytopenia.

Inflammation also can affect the membrane lining in the lungs, leading to pleuritis and fluid collection, as well as interstitial lung disease and pulmonary hypertension. Treatments such as methotrexate can also cause lung problems.²⁷

Many people with RA also have other autoimmune disorders. Sjögren's syndrome often develops in the presence of another autoimmune disease such as RA. Sjögren's is a condition in which the immune system attacks lacrimal glands that produce tears and can cause the eyes to feel gritty and dry, and if left untreated, can lead to infection and scarring of the conjunctiva and cornea.^{27,28} Approximately 20 percent to 30 percent of people with RA also have fibromyalgia. And, corticosteroids used to treat RA may increase type 2 diabetes risk by increasing blood sugar levels.⁵

Finally, a recent study shows that the number of people with RA who are depressed is higher than previously thought. Conducted at the Arthritis Research UK Centre

for Genetics and Genomics at the University of Manchester, the researchers found that anxiety and depression in RA patients are common (28 percent to 44 percent) and much higher than in the general population (6.6 percent).²⁹

Improving RA Outcomes

Over the last several decades, research has greatly increased our understanding of the immune system, genetics and biology, which has led to considerably improved outcomes for patients with RA. NIH funds medical research at universities and medical centers across the U.S., which has led to important genetic discoveries and new therapies. Scientists are also increasingly understanding how and why RA develops, why some people get it and others do not, and why some get it more severely. This information is enabling people with RA to remain active far longer than was possible 20 years ago. And, with research being conducted with new technologies such as stem cell transplantation and novel imaging techniques, RA patients can expect greater improvements in the foreseeable future.³⁰ ■

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