

THE SAVVY WOMAN PATIENT

How and Why Sex Differences
Affect Your Health

Society for Women's Health Research

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CAPITAL SAVVY SERIES



CHAPTER 5

Autoimmunity

What Is the Immune System?

The immune system is your body's front line of defense against bacteria, viruses, and other foreign invaders. The first barrier is actually your skin; invaders can enter when you get a cut or other injury. (You can also get infections from airborne pathogens, which enter the body through mucosal surfaces such as the respiratory tract.) Once inside the body, bacteria and other intruders encounter cellular patrols, the neutrophils and macrophages, which are dispatched by the bone marrow. There are billions of these cells circulating in your bloodstream and patrolling your tissues at any given time. Macrophages (which literally means "big eaters") suck in the intruder, chew it up, and destroy it with enzymes within the cell. They can also send a chemical alarm that calls into action white blood cells, known as lymphocytes, to search out the rest of the invaders of foreign cells (antigens).

There are several types of lymphocytes. Helper T cells identify and eliminate antigens and signal other lymphocytes, the B cells, to produce proteins, called antibodies, that attach to each specific antigen to mark it for destruction. The effect is almost like a game of paintball or laser tag. Some antibodies stick to the surface of an antigen like a glowing target; other antibodies may actually attack. There are also cytotoxic (cell-killing) T cells that produce molecules that destroy cells marked as antigens and suppressor T cells that dial down the intensity of other immune responses. T cells are supposed to tolerate the body's own (self) antigens. Self-reactive T cells also exist and are usually eliminated in your thymus gland. But sometimes by accident these rogue T cells are not eliminated. When this happens, B cells get a signal to produce autoantibodies, antibodies that attach to and can provoke an attack on the body's own tissues. In susceptible women, this can result in autoimmune disease.

During their assault on foreigners, macrophages and white blood cells also produce chemicals that not only destroy the invaders (or the cell marked by a self-antigen), but cause inflammation as well. Inflammation normally helps to heal injuries in the body, but in some autoimmune diseases, such as rheumatoid arthritis (RA), inflammation

continues for too long and can become destructive. Many of the medications used to treat autoimmune disease, such as corticosteroids, are designed to dampen inflammation and adjust the immune system reactions that provoke it. In addition, the body produces a number of chemicals, or cytokines, that promote inflammation, notably tumor necrosis factor alpha (TNF α) and interleukin-1 (IL-1). Drugs specifically designed to inhibit these cytokines, such as TNF α blockers etanercept and infliximab, are used to treat multiple autoimmune diseases, including RA and Crohn's disease. Other antibodies, proteins, and chemicals are involved in autoimmune diseases, and scientists are working on treatments to inhibit them as well.

What Is Autoimmune Disease?

Autoimmune disease results when the immune system accidentally launches an attack on the body's own organs and/or tissues. Autoimmune diseases can affect almost any area of the body. Some antibodies or T cells attack tissue in an organ or gland. In RA, excessive inflammation causes the lining of the joints to become swollen, inflamed, and painful, eventually destroying the joint itself. In systemic lupus erythematosus, the skin, kidneys, brain, and lungs all can be targets of inflammatory and destructive molecules. Even your blood can be affected; autoantibodies can cause dangerous blood clots in antiphospholipid syndrome or speed up the normal turnover of platelets in the spleen in immune thrombocytopenia, causing bleeding and heavy periods. Other autoimmune diseases affect the pancreas (type 1 diabetes), adrenal glands (Addison's disease), connective tissues (scleroderma), skin (psoriasis), and muscles (myasthenia gravis).

Because these diseases affect multiple body systems (often at the same time), and women may have more than one disease (as many as four to five diseases), there may be a wide range of early symptoms. Illnesses often overlap and mimic each other. For example, fatigue and joint pain can be symptoms of RA, lupus, and autoimmune thyroid disease. Symptoms can also come and go, creating a time lag between the symptoms experienced and the clinical signs of disease needed to make a diagnosis.

If you have early RA, for instance, your joints may be red and painfully swollen for weeks, but on the day you see your doctor, your joints may look perfectly normal. The gap between when a disease develops and when a formal diagnosis is made can be considerable. The signs of autoimmune disease can be vague, or they may be misdiagnosed and treated as another condition. Many women have been told that their symptoms are "all in their head." A survey by the American Autoimmune Related

Diseases Association (AARDA) found that more than 45 percent of patients were labeled hypochondriacs in the earliest stages of their illness. Women may spend years bouncing from specialist to specialist, spending thousands of dollars before they get a correct diagnosis. By that time, there may be major damage to joints or organs. Ongoing research is looking for blood markers and other techniques to diagnose these diseases earlier, before major damage occurs.

Risk Factors

GENETICS

There are more than 80 autoimmune diseases, and genetics links many of them. Some share common genes; for example, scientists in Britain recently discovered a single gene that may increase susceptibility to type 1 diabetes, Hashimoto's thyroiditis, and Graves' disease. Researchers in Japan found a genetic defect shared by RA, psoriasis, and lupus. Because of the shared genes phenomenon and the fact that these diseases run in families, scientists have now come to think of autoimmunity as a single category of disease.

Many scientists do not believe that a single specific gene leads to autoimmune disease, but rather that several genes can increase a woman's susceptibility. The Multiple Autoimmune Disease Genetics Consortium (MADGC) was established to study the genes of family members of people with RA, lupus, MS, autoimmune thyroid disease, type 1 diabetes, psoriasis, inflammatory bowel disease, and Sjögren's syndrome.

ENVIRONMENT

A number of environmental factors, including drugs, viruses (such as Epstein-Barr virus), bacteria, and even food, also appear to trigger autoimmune diseases in susceptible people. For example, gluten, a protein in wheat and other grains, triggers an autoimmune reaction in the small intestine leading to celiac disease (celiac sprue). Recent research suggests that exposure to toxins such as asbestos may provoke autoimmunity as well.

WHY YOUR SEX MATTERS

Another factor linking autoimmune diseases is their strong prevalence in women; 75 percent of those affected by these diseases are women. In some cases, that proportion tops 90 percent.

Female-Male Ratios in Selected Autoimmune Diseases

Hashimoto's thyroiditis	10:1
Graves' disease	9:1
Sjögren's syndrome	9:1
Systemic lupus erythematosus (SLE)	9:1
Rheumatoid arthritis	2.5:1
Scleroderma	3:1
Multiple sclerosis (MS)	2:1

Source: Baron-Faust, Rita, and Jill P. Buyon. *The Autoimmune Connection*. New York: McGraw-Hill, 2003.

Why are women affected more often than men? For one thing, women have stronger immune responses than men and tend to produce more antibodies and autoantibodies. Female hormones, particularly estrogen, may play a role. Estrogen can stimulate certain immune responses; it may act partly as an on-off switch in some autoimmune diseases, and it may affect other hormones that influence autoimmunity. For example, some autoimmune diseases such as Hashimoto's thyroiditis or myasthenia gravis may arise (or worsen) during pregnancy, while RA and multiple sclerosis get better. Some disease symptoms flare when estrogen is elevated during the first part of the menstrual cycle; in MS and myasthenia gravis, symptoms can worsen premenstrually when progesterone spikes. Other diseases, such as Sjögren's syndrome, often occur after menopause, when estrogen levels are low.

An example of a hormone that can be influenced by estrogen is corticotropin-releasing hormone (CRH), which releases stress hormones when you are under stress or pregnant. These stress hormones affect immune activity. Research indicates that when these stress hormones are high, susceptible women may be more likely to develop some autoimmune diseases, including lupus, and when these hormones are low, susceptible women may be more likely to develop other autoimmune diseases, including RA and multiple MS.

On the other hand, women produce androgens (male hormones), such as testosterone, that may have a protective effect. In recent years, scientists have found that women with lupus and Sjögren's have low levels of testosterone. The androgen dehydroepiandrosterone (DHEA) is even used as a treatment for lupus, and androgen eye drops are being tested for alleviating dry eyes in women with Sjögren's.

Autoimmunity may also have roots in women's ability to carry a fetus in the womb. A fetus is technically half a "foreign" body, because it contains genes and proteins from the mother and the father. During pregnancy, a woman's immune system does not attack the non-self-antigens.

After delivery, studies show that fetal cells can remain in the mother's circulation for more than 20 years. Since these cells no longer enjoy privileged status; they may confuse the immune system and provoke an immune reaction akin to the rejection of a transplanted organ. Evidence of these persistent fetal cells (referred to as microchimerism) has been found in women with scleroderma, Sjögren's, and autoimmune thyroid and liver diseases. Women may also develop autoimmune diseases in greater numbers because they are exposed to possible triggers more often.

This chapter explores seven of the most common autoimmune diseases, all of which are more common in women than in men and discusses two associated disorders. Two other autoimmune diseases—autoimmune hepatitis and primary biliary cirrhosis—are discussed in chapter nine.

Rheumatoid Arthritis

WHAT IS RHEUMATOID ARTHRITIS?

More than two million Americans—about 75 percent of them women—are affected by rheumatoid arthritis (RA), a chronic inflammation of the lining of the joints (synovium). Although it can occur at any age, women typically first notice symptoms between the ages of 30 and 50. RA is the most common rheumatic autoimmune disease and can lead to permanent joint damage and can cause chronic pain, loss of function, and disability. RA can also be a systemic disease, affecting other parts of the body.

RISK FACTORS

RA appears to be caused by a combination of genetic vulnerability, environmental triggers, and hormonal influences. People with the genetic marker, a portion of DNA that is used to identify an individual disease or trait, known as HLA-DR4, appear to have an increased risk of developing RA and of having more severe disease. Some of the suspected environmental triggers include Epstein-Barr virus and bacteria, including streptococci (which causes strep throat and rheumatic fever), salmonella (which causes food poisoning), *Escherichia coli* (*E. coli*, which causes urinary tract infections), *Helicobacter pylori* (which causes stomach ulcers), and *Borrelia burgdorferi* (which causes Lyme disease). Cigarette smoking is also linked to RA.

WHY YOUR SEX MATTERS

While women are two to three times more likely to get RA than men, men tend to be affected more severely. Studies show that women who

have never had a child are twice as likely to develop RA as women who have. The disease often improves during pregnancy (when estrogen levels are high) but worsens after delivery (when estrogen levels drop). The peak age for RA appears to be after age 40, when estrogen levels are fluctuating or declining. Recent research suggests that if RA is diagnosed after menopause, it may progress at a faster rate. This has spurred research into the role that estrogen may play in RA; some scientists are studying whether oral contraceptives might be protective.

Women with RA may have reduced fertility, which can predate their diagnosis. Some drug treatments used for RA can also affect fertility. Menopausal symptoms in women with RA can be treated with low-dose estrogen, but hormone therapy needs to be individualized (as it does for any menopausal woman).

The risk of premature atherosclerosis (thickening of artery walls by cholesterol-laden plaques) and coronary artery disease is greater among women with RA. Some research indicates that women under age 50 with RA have three times the risk of death from heart attack and congestive heart failure as healthy women of the same age. Corticosteroids such as prednisone, one of the mainstays of RA therapy, can also increase cholesterol and the risk of diabetes, infections, and osteoporosis. Women taking corticosteroids may need bone-building drugs or cholesterol-lowering medications. In addition, RA has been linked to low bone density independent of corticosteroid therapy.

SYMPTOMS

The first symptoms of RA may include swelling, stiffness (often worse in the morning), and general aching of the joints. RA affects joints on both sides of the body, in contrast to osteoarthritis, a disease of wear and tear that may strike joints in one area. The joints affected by RA also may be warm or red. Other common symptoms are fatigue, weakness, muscle pain, and depression.

In 50 percent of women, symptoms come on gradually and can wax and wane. As the disease progresses, inflamed cells in the joint release enzymes that can digest bone and cartilage, often causing the joint to lose its shape and alignment and increasing pain and loss of movement. Early diagnosis and treatment are important in minimizing joint destruction, so it is essential to see a doctor if telltale symptoms persist for a number of weeks.

Around 20 percent of women with RA may develop raised, firm lumps just under the skin, known as rheumatoid nodules. These nodules often occur in areas where there is repeated pressure on the skin, such as the elbows. Because RA can be systemic, these nodules may arise in the eyes, heart, or lungs.

Up to half of women with RA may develop inflammation in the lining of the lungs (pleurisy), making it painful to take a deep breath. Inflammation may also develop around the sac enclosing the heart (pericarditis); symptoms include chest pain, dry cough, and fever. Even blood vessels may become inflamed in RA; a sign of this vasculitis can be tiny broken blood vessels in the nail bed.

DIAGNOSIS

Doctors may need to perform several tests to diagnose RA properly. The work-up will most likely include a complete medical history, physical exam, and lab tests and x-rays. During the physical exam, your doctor will look for evidence of joint swelling, tenderness, redness, misalignment, or loss of motion. Expect to describe your pain, including the times of day it is most and least severe. Blood tests include a test for an antibody called rheumatoid factor (RF); approximately 70 to 80 percent of people with RA have positive tests for rheumatoid factor (but it may not be detected early on in RA). It is important to note that RF can be present in other conditions (including lupus and even infections), so testing positive is only one factor in making a diagnosis. Other blood tests look for evidence of inflammation, including an erythrocyte sedimentation rate (ESR or SED rate), which measures the speed at which red blood cells fall to the bottom of a test tube, and C-reactive protein (CRP), which is elevated with systemic inflammation. A complete blood count may reveal anemia, a low red blood cell count, which often occurs in RA. X-rays are used to determine the degree of joint erosion, cartilage loss, and joint distortion.

TREATMENT

Your doctor will prescribe treatments to attack RA on several fronts: to relieve pain and reduce inflammation and to stop or slow joint damage. The choice of medications takes into account how severe your symptoms are and how far the disease has progressed. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to combat pain. These include aspirin and its chemical cousins, ibuprofen and naproxen, diclofenac, and indomethacin, and newer NSAIDs, called COX-2 inhibitors. However, COX-2 drugs carry an increased risk of heart attack and stroke and should not be used if you have or are at increased risk for cardiovascular disease. Recent studies show that all NSAIDs also carry slight cardiovascular risks and should not be used at high doses for prolonged periods.

Corticosteroids such as prednisone are used to combat inflammation and modulate immune overreactivity. Disease-modifying antirheumatic

drugs (DMARDs), including methotrexate and leflunomide, may be used to slow joint destruction. The newest DMARDs are “biologic” agents that inhibit the cytokines that promote inflammation and joint destruction. These include the TNF α blockers.

Joint replacement surgery is often needed for RA patients with severely damaged joints. Just about any joint in the body can now be replaced, and the surgery dramatically improves function and pain. Exercise and stress reduction are important for RA patients. Patients and their health care providers are turning increasingly to alternative and complementary therapies such as massage and acupuncture.

FUTURE APPROACHES TO RA TREATMENT

Researchers are looking at agents that block the processes by which arthritis begins. One strategy being tested is the use of cancer drugs, such as rituximab, to selectively destroy B cells that contribute to the disease process of RA. Another biological drug being tested for RA, alefacept, targets specific T cells.

Stem cell transplantation is another novel therapy under study. Stem cells are primitive cells in the bone marrow that can multiply into specific blood cells. In this experimental treatment, a patient’s immune system is destroyed with high doses of chemotherapy drugs and then reconstituted with stem cells from the person’s own red blood cells (autologous stem cells).

Studies are also being done on new markers that could be used to diagnose RA earlier, before joint destruction has begun (or perhaps in women at high risk before the disease process is fully underway). One such experimental test looks for autoantibodies, called cyclic citrullinated peptides (CCPs); one study found that 93 percent of those who tested positive for CCPs went on to develop RA after three years, but only 25 percent of those who tested negative developed the condition.

Autoimmune Thyroid Disease

The thyroid is a small, butterfly-shaped gland in your neck that plays a major role in your body. Thyroid hormones influence almost every organ and regulate metabolism, the rate at which your body turns food into energy. Endocrinologists often liken thyroid disease to living in a house with a broken thermostat. Having excess thyroid hormones turns up metabolism and body heat and causes weight loss, heat intolerance, and anxiety. Low levels of thyroid hormone turn down metabolism and make you feel cold, tired, and depressed.

WHAT ARE THYROID DISEASES?

Autoimmune thyroid diseases are actually the most common of all autoimmune diseases, affecting 10 million Americans. Hashimoto's thyroiditis results from an underactive thyroid gland and affects women 10 times more often than it does men. Graves' disease, which results from an overactive thyroid, is five times more common in women.

RISK FACTORS

In Hashimoto's thyroiditis, T cells attack cells in your thyroid gland, causing inflammation that interferes with thyroid hormone production. In Graves' disease, antibodies attack the receptors for thyroid-stimulating hormone (TSH), triggering overproduction of thyroid hormones. Researchers do not yet know what triggers these processes. Some theories include excess iodine in the diet, fetal cells that persist in a woman's blood circulation after pregnancy, and even severe stress.

Family history is a major risk factor; if you have close relatives with autoimmune thyroid disease, you are five to 10 times more likely to develop it than the average person. Autoimmune thyroid diseases also occur frequently with other autoimmune conditions such as RA and lupus. In some cases, other endocrine disorders such as adrenal insufficiency and type 1 diabetes may be risk factors for autoimmune thyroid disease.

WHY YOUR SEX MATTERS

Estrogen and progesterone can both exacerbate thyroid inflammation. Women with Hashimoto's disease often have heavier menstrual periods that last for longer than a week. Hashimoto's can disrupt the normal hormonal communication between the ovaries and endocrine glands, causing the ovaries to fail to ovulate, even though the uterine lining continues to be stimulated. As a result bleeding can occur between periods. Women with Graves' disease may have a decreased menstrual flow and a shorter cycle.

Both Hashimoto's disease and Graves' disease can lead to infertility and miscarriage. However, women who have trouble conceiving because of thyroid disease often regain fertility after being treated. Untreated hyperthyroidism can also lead to bone loss, since excess thyroid hormones activate bone-eating cells.

Autoimmune thyroid disease improves during pregnancy and worsens in the year after giving birth. If a woman has mild thyroid inflammation, pregnancy may tip the balance; there's also an increased risk of Graves' disease during the postpartum period. Thyroid function should be

checked before, during, and after pregnancy. Your obstetrician will use TSH tests to tell whether your thyroid hormone dose needs to be increased as your pregnancy progresses.

The fetus relies in part on maternal thyroid hormones, especially before the 10th week of pregnancy, when the fetal thyroid begins to develop. In Graves' disease, autoantibodies can cross the placenta and cause temporary neonatal hyperthyroidism. Women with untreated thyroid deficiency during pregnancy may be up to four times more likely to have children with lower IQ scores as well as deficits in motor skills and attention, language, and reading abilities. Fortunately, all newborns in the United States are tested for thyroid hormone levels.

Postmenopausal hormone therapy can affect thyroid hormones; women taking estrogen or estrogen and progestins need to have their TSH levels monitored and the dose of replacement thyroid hormone (levothyroxine) adjusted if needed. Women over age 65 can be at increased risk of subclinical hypothyroidism, so TSH testing and possible replacement thyroid hormones may be necessary for this age group.



Burnout or What?

By Peggy McCarthy, owner and CEO of a company that creates educational programs for health professionals and the public

I was 57 years old and owned my own business. I had been traveling because of my job about 70 percent of the time. In the past year I had had three weekends free, and at home, because much of the work involved weekend meetings. I often made two cross-county trips a week. I had been living this lifestyle for about 15 years.

It was the holiday time at the end of the year, time when I usually tried to retreat to my home for a few days of rest and relaxation. But this year, I suddenly realized after a few days of rest that I was not bouncing back in my usual way. Normally I am a high-energy, very positive person. This particular year I realized I was depressed. I knew that I had been working far too hard and had far too much on my plate, too many responsibilities. Maybe I had finally burned out and was ready for a change.

After a week at home, I made the decision that I would meet with a counselor to discuss my future plans. I thought I might sell my business or simply close it down. I had never really been depressed in my life, and the feeling was not comfortable. I knew I was not able to make good decisions feeling this way, so I gave myself a year in which I would think, discuss, and make plans. Whatever I ended up doing, I wanted it to be

done “gracefully.” I did not want to inconvenience my staff or my clients in any way.

It took me about a month to interview potential therapists. I wanted someone I felt I could work well with. In fact, before I hire any medical person to work with me as my physician or therapist, I always interview him or her. I find this works the best with any professional consultant, be it medical, legal, financial, or other.

By February I had engaged a really lovely woman as my therapist, and I went for my first hourly session with her. She asked me to describe what was going on in my life. I spent the hour talking about my work and the projects we were developing. At the end of the session she said, “I don’t think you are burned out. Yes, you are working too many hours but you obviously love what you do and get tremendous pleasure out of doing it. I think you may have a medical problem that is causing this depression. Have you ever had your thyroid checked?”

Lights flashed for me!!! Three years earlier I had to have a physical for an insurance policy. The insurance doc who did the physical had briefly mentioned that my thyroid was a bit enlarged on one side. I was too busy and didn’t give it another thought until this particular February afternoon with my therapist.

A week later I had been diagnosed with Hashimoto’s disease and began therapy with thyroid hormone. Within a few weeks all signs of the depression that I was feeling had gone away. However, I continued seeing the therapist for some time. I realized I could not continue to live the lifestyle I was living without having other, potentially more serious physical consequences from the abuse my body was taking.

Since that time I have cut my travel to a maximum of three trips per month. I started doing yoga when I was in my 20s and had been diagnosed with Raynaud’s disease, another autoimmune disease, just like Hashimoto’s. I began doing yoga again, daily. I had always had a healthy diet but had put on extra pounds, so I lost some weight. I made it a priority to walk as much as possible, something that was harder to find time to do on the west coast than in New York where I had lived previously. And I continue to plan for my next phase of life, knowing that I still want to move into it as gracefully as possible.

(Reprinted with permission by Peggy McCarthy)

SYMPTOMS OF HASHIMOTO’S THYROIDITIS

An underactive thyroid slows metabolism and decreases production of body heat; the most common symptoms are weight gain and intolerance

to cold. Other common symptoms include fatigue, constipation, dry skin, hair loss, heavy and irregular menstrual periods, and difficulty concentrating. Some of these symptoms may appear suddenly and others, especially hair loss (on any area of the body), may be very gradual. Depression is a key symptom of Hashimoto's that is often overlooked, and persistent depressive symptoms may warrant TSH tests. Major depression is a separate illness and does not occur with thyroid disease.

However, thyroid hormones can interact with the mood stabilizer lithium used as a long-term treatment for bipolar disorder, making it less effective. It's not clear why, but lithium itself may cause the thyroid to become underactive as a side effect, so thyroid hormone levels need to be monitored in women taking this drug.

SYMPTOMS OF GRAVES' DISEASE

An overactive thyroid increases metabolism, causing weight loss. Also, because your body needs more blood for increased energy use, your heart pumps faster causing a rapid pulse, palpitations, and sometimes an irregular heartbeat. Your gastrointestinal system may also speed up, resulting in more frequent bowel movements. Increased metabolism causes your body to produce more heat, which may cause you to feel warm and flushed and have increased sweating. People with Graves' disease may find it hard to fall or stay asleep, and sleep loss can lead to fatigue. They may also have muscle weakness, especially in the hips, thighs, and shoulders. Hyperthyroidism can also cause a person to feel more energetic, even hyperactive or jumpy, to be irritable, or to experience mood swings. Menstrual flow can become lighter, and some women can lose their period altogether.

Roughly half of the women with Graves' disease develop eye inflammation and protruding eyes (Grave's orbitopathy). Eye muscles can become weakened from increased pressure behind the eye and hamper eye movement, leading to impaired or double vision. Graves' orbitopathy can also damage the optic nerve. In some cases, the eyelids may not close completely during sleep, causing the cornea to become dry and prone to ulceration. Fortunately, less than 1 percent of people with Graves' disease have serious or permanent eye problems.

DIAGNOSIS

Both a physical exam and blood tests are needed to diagnose thyroid disease. The thyroid may enlarge (goiter) in both Hashimoto's and Graves' diseases. Your doctor will physically examine the thyroid, often while you are swallowing water, to get a sense of the gland's size and texture.

Blood tests to measure TSH are the best indicators of thyroid function. Low TSH indicates hyperthyroidism; elevated TSH signals hypothyroidism. Other blood tests can determine the existence of thyroid antibodies; up to 80 percent of women with Hashimoto's have antithyroid antibodies. If you have a goiter, a test to measure radioactive iodine uptake may be done to look for abnormal thyroid function. If nodules are present, ultrasound can be used to image the gland, and a thyroid scan can determine if overactive thyroid nodules are causing Graves' disease.

TREATMENT

Hashimoto's is easily treated with synthetic replacement thyroid hormones. However, it may take some time to find just the right dose, and yearly blood tests are needed to ensure thyroid hormones remain at the right level. While 10 percent of women with Hashimoto's thyroiditis have a spontaneous remission, others may have progressive thyroid failure and will need increased doses of medication. Even with careful monitoring, women with Hashimoto's run a slight risk of having excess thyroid hormones and should be checked (especially after menopause) for bone loss and heart rhythm problems.

Treatment for Graves' disease involves calming down the overactive thyroid or destroying the gland so that it does not pump out excess thyroid hormones. This can be achieved with antithyroid drugs or radioactive iodine or by surgically removing the gland. After the gland is destroyed, replacement thyroid hormones are given. Until these replacement hormones become fully effective and are adjusted properly, beta blockers, such as propranolol, may be needed. Such drugs block the effects of thyroid hormones, slow elevated heart rate, and lessen anxiety. In many cases, eye inflammation and protrusion in Graves' disease are mild and do not require therapy. If orbitopathy is more severe, corticosteroids may be prescribed to reduce inflammation and lessen swelling. Swollen eye tissue can be removed with surgery, and swollen muscles around the eye can be repaired; surgery to enlarge the bony opening around the eyes is done only if other treatments are unsuccessful.

What Is Sjögren's Syndrome?

As many as four million Americans—about 90 percent of them women—may have Sjögren's syndrome, in which the immune system attacks the body's moisture-producing glands and tissues. These include the lacrimal glands that produce tears and the salivary glands as well as mucus membranes in the nose and vagina. In some cases, Sjögren's can also affect the

kidneys, gastrointestinal (GI) tract, lungs, liver, and blood vessels. In 50 percent of cases, Sjögren's syndrome occurs alone (primary Sjögren's), and 50 percent of the time it occurs in the presence of another autoimmune disease such as RA, lupus, scleroderma, or thyroid disease.

Sjögren's develops when moisture-producing glands are damaged by activated immune cells, making them less able to respond to signals from the brain to produce tears or saliva. In addition, inflammatory cytokines may damage the nerves and neurotransmitters (chemical substances in the brain) that stimulate the tear ducts or salivary glands. The dry eyes that characterize Sjögren's are also caused by damage to tiny glands behind the eyelashes (called meibomian glands) that secrete an oil that prevents tears from evaporating too quickly.

RISK FACTORS

Like RA and other autoimmune disorders, Sjögren's can also run in families. Although it can develop at any age, it is most prevalent after age 40. Like other autoimmune diseases, Sjögren's syndrome appears to be influenced by genetic vulnerability, environmental triggers (such as the Epstein-Barr virus), and hormones.

WHY YOUR SEX MATTERS

The underlying cause of evaporative dry eye may be low levels of male hormones. Androgens decline after menopause, although not to the extent that estrogen production drops. Researchers are studying androgen therapy as a treatment for primary Sjögren's and androgen eye drops for dry eye symptoms. Studies have shown that estrogen therapy appears to worsen dry eye.

Women with Sjögren's syndrome often experience vaginal dryness, which can lead to painful intercourse. Vaginal lubrication does not come from moisture-producing glands but from fluid that is passed from the bloodstream through the vaginal walls. Vaginal dryness in Sjögren's patients is often mistaken for menopause-related vaginal atrophy or degeneration. Symptoms related to dryness can be helped by moisturizers. Lubricants can make sex more comfortable. Local estrogen therapy in the form of creams, a ring, or suppository tablet also helps dryness by reversing the atrophy of vaginal tissues that occurs after menopause.

SYMPTOMS

The hallmarks of Sjögren's syndrome are dry eyes, dry mouth, and fatigue. Classic dry eye symptoms include a dry, gritty, or burning sensation; itch-

ing; light sensitivity; eyelids that stick together; and mucus accumulation in the corners of the eyes on awakening. Women with dry mouth may have difficulty chewing or swallowing, burning mouth or tongue, and increased dental decay (due to low saliva production). Sjögren's can also cause swollen parotid glands (the largest of the salivary glands, in front of the ears), joint pain, dry nose, and fatigue and can lead to peripheral nerve problems, lung inflammation, and kidney dysfunction. Women with Sjögren's may also have a slightly increased risk of lymphoma, a malignancy of the lymph glands, so swollen lymph nodes should be investigated.

DIAGNOSIS

Because symptoms of Sjögren's syndrome, such as joint pain and fatigue, may overlap with those of RA and other autoimmune diseases, it is often misdiagnosed or missed altogether. Physicians may treat dry eye and overlook other symptoms, such as dry mouth or dry vagina, which may signal Sjögren's. Dentists may see women with dry mouth and numerous cavities and never ask if they suffer dry eyes as well. A woman may visit her doctor for menopausal symptoms in her late 40s and not be diagnosed with Sjögren's syndrome until much later. In fact, the average time from the onset of symptoms to a diagnosis can sometimes exceed six years.

During a work-up, blood tests are performed to check for specific autoantibodies, including RF and antinuclear antibodies (ANAs), present in 70 percent of patient with Sjögren's, as well as variety of autoimmune diseases including lupus (see page 58). Your sedimentation (SED) rate will be measured, and you will be given tests to look for elevation in normal blood proteins known as immunoglobulins, common in people with Sjögren's syndrome.

For women with dry eyes, special tests are performed to measure tear production and the volume of tears produced. The most common of these is the Schirmer's test, in which small pieces of filter paper are placed between your eyeball and lower lid to measure the amount of moisture produced within five minutes. A slit-lamp examination uses a special lamp and a magnifying device to reveal the normal layer of tears along the lower eyelid, which may appear thickened. Another test, called rose bengal staining (involving a harmless vegetable dye), helps to determine the quality of the oily layer of tear film and its distribution over the surface of the eye. Other tests may be done to assess the condition of the cornea.

A dentist or oral pathologist can measure saliva production in dry mouth. This is done by putting an acidic or sour substance in the mouth to stimulate saliva production. In some cases, a biopsy of the tiny salivary glands in the lower lip may be needed to detect immune cell infiltration.

TREATMENT

The symptoms of Sjögren's syndrome are treated individually. Over-the-counter (OTC) and prescription medications are available to relieve the dry eye and dry mouth symptoms. OTC products include preservative-free artificial tears, artificial saliva, saline nasal sprays, and vaginal lubricants. An ophthalmologist may recommend eyedrops containing cyclosporine for dry eye. In some cases, tiny silicone plugs (punctal plugs) are inserted in the tear ducts to prevent tears from draining away. Non-drug strategies include the use of a humidifier and protective goggles to prevent tear evaporation.

Two oral prescription drugs are used to treat dry mouth, pilocarpine hydrochloride and cevimeline, which are taken after meals to improve salivary flow. Studies suggest they may also improve dry eye and dryness in other areas of the body. Artificial saliva can provide topical relief for dry mouth.

Other manifestations of Sjögren's, such as kidney or lung problems, are treated separately with medication.

FUTURE APPROACHES TO SJÖGREN'S SYNDROME

One promising avenue of therapy for dry eye is eyedrops containing androgens. The National Institutes of Health is also exploring the use of androgens, in the form of dehydroepiandrosterone (DHEA), to treat primary Sjögren's syndrome. Some medications used to treat RA may also be useful in Sjögren's.

What Is Systemic Lupus Erythematosus?

As many as 1.5 million people, 90 percent of them women, may have systemic lupus erythematosus (SLE), a chronic inflammatory disease that can affect almost any organ or organ system of the body, including the skin, joints, lungs, blood, and kidneys. It is the leading cause of kidney disease in young women. Around 10 percent of patients initially develop a form of lupus that involves only the skin, discoid lupus, but then go on to develop systemic lupus. In some cases, lupus is mild and can be managed with medications. In others, lupus can cause serious and potentially life-threatening problems. It can affect just about any area of the body; antibodies may attack not only the cells in various organs but also parts of cells, including the DNA and cell nuclei.

Recent animal research reveals that antibodies to DNA (and other autoantibodies) bind to specific receptors on the surface of cells, called

Fc receptors. A specific Fc receptor appears to be defective in lupus, allowing accumulation of damaging antibodies, which may help set the stage for lupus. In addition to antibodies, structures, called immune complexes, play a major role in lupus. Immune complexes are lattice-like structures formed when antibodies bind to their targets. They can build up in blood vessels and cause inflammation and blockages. Immune complexes are normally cleared partly by proteins, called complement, but women with lupus may produce too little complement to keep up with immune complex formation, or the complement they produce is used up too quickly. The resulting accumulation of immune complexes can cause damage to blood vessels and organs such as the kidneys. Low levels of androgens may also factor into lupus.

RISK FACTORS

Risk factors for SLE appear to be a combination of genetic vulnerability and environmental triggers, including infections, certain drugs and antibiotics (especially those in the sulfa and penicillin groups, which may worsen lupus), and ultraviolet light.

While some studies suggest a role for microchimerism, other research suggests that maternal cells that get into a fetus's blood circulation and persist into adult life may increase the risk of developing lupus. Biopsies of heart muscle have found maternal cells in babies with neonatal lupus; however, this research is highly speculative.

So far, researchers have identified about a dozen genes that are associated with lupus, and some of these genetic defects appear to run in families. About 10 percent of lupus patients have a close relative with the disease, and about 5 percent of the children born to women with lupus will develop it. Lupus most often occurs in women between the ages of 15 and 40, but it can occur in both sexes and at any age. African Americans, American Indian, and Asian American women develop SLE more frequently than Caucasians.

WHY YOUR SEX MATTERS

Since there is some increased risk of lupus becoming more active during or immediately after pregnancy, pregnant women or those trying to become pregnant should be monitored closely. Women with lupus run a higher risk of getting pre-eclampsia, a dangerous form of high blood pressure during pregnancy. Antiphospholipid syndrome (APS), an autoimmune disease that promotes clotting, can coexist with lupus and complicate pregnancy. Additionally, women with central nervous system, kidney, or heart and lung involvement may be at greater risk during

a pregnancy and require close medical supervision. The good news is that most women who are in remission for six months before becoming pregnant do well during their pregnancy.

Antibodies in the mother's blood travel across the placenta during pregnancy to protect the growing fetus from infection. But bad antibodies travel along with the good ones, so women with lupus who have certain antibodies (anti-SSA/Ro and SSB/La) may give birth to children with neonatal lupus, which is usually temporary. Neonatal lupus is a misnomer; it is not a systemic disease like SLE. Most often, neonatal lupus only causes a skin rash that resolves without treatment within eight months after birth.

In two percent of women with anti-SSA/Ro antibodies, neonatal lupus can cause a permanent condition, called congenital heart block, in which there is a blockage in the electrical signal that travels from one part of the heart to another. In congenital heart block, an area in the middle of the heart, called the AV node, which is critical to transmitting electrical impulses that regulate heartbeat, is damaged by maternal autoantibodies (or other yet unknown factors). This causes an abnormally slow heartbeat in the newborn, requiring a pacemaker. In less than 20 percent of these cases, the condition can be fatal. Some babies may have both heart block and the skin rash. The proportion of women with anti-SSA/RO antibodies whose babies will develop a neonatal lupus rash is unknown. However, as mentioned earlier, the rash is transient and usually disappears by eight months, when the mother's antibodies are cleared from the baby's circulation.

LUPUS AND THE HEART

Lupus poses an increased risk for cardiovascular disease in women, especially before age 45. But the factors that cause this increased risk of premature atherosclerosis are unclear. Some studies indicate that the natural estrogen found in women's bodies, which is usually protective against cardiovascular disease, may promote blood clotting in younger women with lupus who have antiphospholipid antibodies.

SYMPTOMS

The most common symptoms of SLE include achy or swollen joints, prolonged fatigue, fever, anemia, and skin rashes, including the telltale butterfly-shaped rash across the cheeks and nose. Additional symptoms may include chest pain on deep breathing, sensitivity to sunlight, hair loss, and Raynaud's phenomenon (a condition where fingers turn white or blue in the cold due to spasms in tiny blood vessels that restrict blood flow).

DIAGNOSIS

Lupus is often perceived as difficult to diagnose, because its signs and symptoms can accumulate over time. Many physicians refer to the criteria established by the American College of Rheumatology (ACR). While the ACR criteria are mostly used for clinical trials, they can aid in a diagnosis. To meet the criteria, a woman must have four or more of the following symptoms (not necessarily at the same time):

- ◆ a rash over the nose and cheeks that looks like a butterfly (malar rash);
- ◆ red raised patches (discoid rash) on the skin (often on the scalp or earlobes);
- ◆ skin sensitivity to sunlight;
- ◆ ulcers (usually painless) in the nose or mouth;
- ◆ arthritis (tenderness, pain, and swelling) in two or more joints;
- ◆ inflammation of the lining of the lung or heart;
- ◆ excessive protein in the urine;
- ◆ blood cell disorders, including hemolytic anemia, a low white blood count, or thrombocytopenia (a low number of platelets—cells needed for clotting);
- ◆ positive test for antinuclear antibodies (ANAs); and
- ◆ evidence of other autoantibodies, including anti-double-stranded DNA antibodies (anti-dsDNA), anti-SSA/Ro, anti-SSB/La, and antiphospholipid antibodies (APLs);

Blood tests to detect antinuclear antibodies (ANAs) are positive in more than 95 percent of women with SLE. Recent studies suggest that these antibodies may actually be present for years before symptoms develop. However, women with other autoimmune diseases can also have ANAs, so a combination of other tests, a physical examination, and a detailed medical history are necessary to make a diagnosis. For example, since the kidneys can be involved in SLE, a urine dipstick test is important. This test measures the amount of protein in the urine, which can indicate if the kidneys are losing too much protein. A new screening test for lupus looks for molecules called SR proteins and may pick up the 20 percent of cases that might not be detected through standard screening tests. Whether it will prove to be helpful in diagnosing SLE awaits more study.

TREATMENT

Therapy for lupus centers on reducing symptoms and lowering the number and severity of disease flare-ups, halting the progression of the disease, and minimizing organ damage.

Nonsteroidal anti-inflammatory pain medications (NSAIDs) commonly are used to ease joint pain. They must be used with caution in lupus patients, since they can worsen kidney disease. Another mainstay of treatment includes corticosteroids and other drugs that suppress inflammation. (As in other autoimmune diseases, corticosteroids increase the risk of infections, diabetes, osteoporosis, osteonecrosis, and hypertension.) Many lupus patients are helped by antimalarial drugs, most commonly hydroxychloroquine, which help dampen inflammation. This drug is most useful for relieving discoid lesions, hair loss, joint pain, and perhaps even fatigue. Some studies suggest it may also have positive effects on bone mass and perhaps protect against blood clots and high cholesterol. Immunomodulating drugs, including azathioprine and cyclophosphamide, are used when there is more serious kidney or organ involvement. These drugs may help suppress the immune system by reducing the number of immune cells more active in lupus.

Women who have clotting problems (such as clots in leg veins) or antiphospholipid antibodies and who have suffered a blood clot are given anticoagulant medications.

Women may also be treated with DHEA, a natural steroid hormone. Research has found that many women with lupus have low levels of androgens, which may have anti-inflammatory properties. DHEA may be helpful for women with mild lupus, particularly those with skin rashes, hair loss, and joint pain. While DHEA is sold as a dietary supplement, a pharmaceutical-grade preparation has not shown clear-cut effectiveness in clinical trials, so it has yet to win U.S. Food and Drug Administration (FDA) approval for treating lupus.

Women with lupus are also cautioned to use sunscreens and avoid excessive sun exposure.

Regular monitoring of the disease is essential to detect increases in symptoms as well as development of new ones that could require a change in treatment.

FUTURE APPROACHES TO LUPUS

Researchers are investigating new drugs and biologicals that target specific cells of the immune system, with the hope of being able to obstruct or suppress the production of specific antibodies and harmful cytokines. Early research is also underway into correcting the defect in Fc receptors that allows accumulation of autoantibodies. Lab experiments in mice suggest that increasing the activity of these receptors could potentially reverse or halt part of the autoimmune process in lupus, paving the way for a future gene therapy.

Right now, results of a major study indicate that oral estrogens are safe

for carefully selected women with lupus. It was believed that hormones caused disease flares, and for years women with lupus were told to avoid estrogen. But the recently concluded Safety of Estrogens in Lupus Erythematosus, National Assessment (SELENA) trials found that hormone therapy did not significantly increase the rate of severe lupus flares and was associated with only a higher risk of mild and moderate flares. The SELENA trial also found that oral contraceptives did not increase severe, moderate, or even mild flares. With the exception of women with unstable SLE, or those at increased risk of clots, experts say birth control pills can be prescribed safely for women with lupus.

What Is Scleroderma?

The term scleroderma is taken from two Greek words, “sclero,” meaning hard and “derma,” meaning skin. Scleroderma affects up to 300,000 people in the United States, 80 percent of whom are women. In scleroderma, autoimmunity leads to excessive production of collagen in the skin and other connective tissues, causing hardening and scarring (fibrosis). Smaller blood vessels are also damaged by the disease, causing many of the complications, including high blood pressure. About two-thirds of women with scleroderma have localized scleroderma, which affects only the skin. The rest have a systemic form of the disease, affecting not only the skin, but also internal organs such as the lungs, kidneys, and esophagus. Systemic scleroderma can be widespread (diffuse) or limited, affecting just a few areas.

Scleroderma affects the tiny blood vessels in the fingers and other areas of the body, causing them to narrow and restrict blood flow. This frequently happens in the small blood vessels of the hands, making them extremely sensitive to cold, a problem called Raynaud’s phenomenon. In Raynaud’s, narrowed blood vessels go into painful spasms when exposed to the cold, causing a brief stoppage of blood flow that turns the fingers white, then blue, and then red as blood flow resumes. Raynaud’s occurs in most people with scleroderma, but it can also occur in RA and lupus as well as in otherwise healthy people. When blood vessels in the kidneys are narrowed, it leads to high blood pressure. Up to 40 percent of people with scleroderma develop pulmonary hypertension, or high blood pressure in the lungs.

In scleroderma, the immune system attacks cells that produce collagen, a substance that normally makes your skin elastic and supports the joints, ligaments, and tissues that surround internal organs. Collagen is usually made in small amounts, but the immune attack causes it to be overproduced, replacing normal tissue in the skin or other organs. Small blood

vessels in the skin and organs are also damaged early on in this process. It is not known what triggers the immune system attack.

With localized and systemic scleroderma, damage to small blood vessels within the skin can lead to skin ulcerations. Complications of scleroderma can range from very mild to life-threatening, depending on the areas affected. Chronic heartburn and gastroesophageal reflux disease (GERD) are frequent complications of scleroderma, due to fibrosis (or formation of scar tissue) of the esophagus. This damage leads to weakening of the valve that keeps acid in the stomach, causing the acid to back up into the esophagus. Systemic fibrosis can also affect the lungs and heart. Early diagnosis and proper treatment can minimize symptoms and lessen the risk of more serious complications.

RISK FACTORS

Scleroderma can develop at any age (even in childhood), but it most commonly arises between the ages of 25 and 55. A family history of scleroderma increases the risk; relatives of people with scleroderma have a two times greater risk of developing the disease. A family history of rheumatic diseases also appears to be a slight risk factor. Other risk factors include occupational exposure to silica dust, organic solvents such as polyvinyl chloride, and some drugs.

WHY YOUR SEX MATTERS

Female hormones are believed to play only a slight role, if any, in scleroderma. As in some other autoimmune diseases, fetal cells that persist in a woman's circulation after pregnancy may be a factor. One theory is that these fetal cells may provoke an immune reaction akin to the rejection of a transplanted organ, which leads to scleroderma. Researchers have found that women with scleroderma have 20 times the number of circulating fetal cells as women with children without scleroderma. However, since some patients have not been pregnant, microchimerism cannot explain all cases of scleroderma. It is, however, an interesting avenue for further research, since there are no other strong candidates (genetic or environmental) for potential triggers for the disease.

SYMPTOMS

Early symptoms of scleroderma can include puffy hands, joint pain, and Raynaud's phenomenon. As many as 95 percent of people with scleroderma experience Raynaud's. Other common symptoms include skin thickening on the hands and forearms (which eventually may cause the

hands to be frozen in a claw-like position); tight, mask-like tightening of facial skin; and ulcerations on fingertips or toes due to lack of blood supply. Because scleroderma can stiffen the esophagus, heartburn and difficulty swallowing are frequent symptoms. Shortness of breath may signal lung involvement. Scleroderma can also produce hair loss, abnormally dark or light patches of skin, widening of small blood vessels in the skin (telangiectasias), tiny calcium deposits in the skin (calcinosis), and fatigue. Symptoms of limited scleroderma have often been referred to as CREST—for calcinosis, Raynaud's, esophageal dysfunction, and telangiectasias. However, as understanding of the disease has progressed, this term has become less widely used.

DIAGNOSIS

A variety of tests, along with a complete physical examination, is needed to diagnose scleroderma. If there is tightness, thickening, or hardening of the skin, your physician may order a skin biopsy. Blood tests for anti-nuclear antibodies (ANAs) are positive in 85 percent of people with scleroderma; other antibody tests are less specific for the condition. Protein may appear in your urine if there is kidney involvement. Chest x-rays can reveal lung fibrosis, while pulmonary function tests can assess the severity of lung damage. If you have symptoms of GERD, gastrointestinal studies such as a barium swallow (which involves drinking a small amount of liquid containing barium, which appears white on x-rays) and endoscopy (using a fiberoptic scope) may be done to check for damage to the esophagus.

TREATMENT

There is no cure for scleroderma, but complications of the disease can be treated. Joint pain can be eased with nonsteroidal anti-inflammatory drugs. Thickened skin is treated with a variety of agents, including D-penicillamine, and moisturizers and lubricants can keep skin from tearing. If cracks or ulcers in the skin become infected, topical or systemic antibiotics are used. Physical or occupational therapy, including range-of-motion exercises, can help maintain hand flexibility. The arthritis that can occur in scleroderma is treated with some of the same drugs used to treat RA.

Raynaud's phenomenon can be treated with drugs to help dilate blood vessels, including calcium channel blockers and medications that improve blood flow, such as pentoxifylline, or clopidogrel to prevent blood clots.

Drugs that reduce stomach acid production, including proton pump inhibitors, are used to treat reflux and may also help heal the structures and

precancerous lesions in the esophagus that can result from GERD. People with GERD are also helped by lifestyle changes, including eating slowly, chewing food thoroughly, drinking plenty of water, not eating within two hours of going to bed, and sleeping with the head of the bed elevated.

High blood pressure and kidney problems in scleroderma are often treated with drugs, called angiotensin-converting enzyme (ACE) inhibitors, such as captopril or enalapril. Three new drugs have been approved to treat pulmonary hypertension in scleroderma: bosentan, which aids blood vessel function and two derivatives of prostaglandin (a substance that occurs naturally in the body), epoprostenol, and treprostinil. Immunosuppressants, drugs that inhibit immune cells, and certain anti-cancer agents (including cyclophosphamide) have been useful for pulmonary fibrosis and are being tested further.

FUTURE APPROACHES TO SCLERODERMA

Researchers are exploring the use of immunosuppressive agents that selectively target overproduction of collagen. Antibodies that inhibit growth factors to reduce collagen production are also being studied. Stem cell transplantation is another therapy under active investigation.

Studies show that many women with scleroderma remain sexually active, and sildenafil and other longer-acting drugs are being tested to improve problems with decreased sensation and vaginal lubrication caused by restricted blood flow.

What Is Multiple Sclerosis ?

Multiple sclerosis (MS), a chronic disease of the central nervous system, affects more than 400,000 people, two-thirds of whom are women. In MS, autoantibodies, immune cells, and inflammation eat away myelin, the protective tissue wrapped around nerve cell fibers in the brain and spinal cord; sometimes the nerve fiber itself is damaged or broken during the attack. The damage to myelin interferes with communication between nerve cells, causing symptoms ranging from dizziness and blurred vision to paralysis. As myelin is stripped away, it is replaced by scar (sclerotic) tissue at multiple sites around the nervous system (hence the name multiple sclerosis).

This is a gradual process, and myelin may regenerate itself in the beginning and inflammation can come in spurts; this may underlie relapsing-remitting MS, in which the disease worsens and then gets better. The majority of people with MS have the relapsing-remitting form. Around 10 percent of people have the primary-progressive form of MS, which is

characterized by a continual worsening of the disease. Half of those with relapsing-remitting disease eventually develop the progressive form (secondary-progressive MS). In rare cases (less than 5 percent), people have a progressive-relapsing form of MS.

RISK FACTORS

As with other autoimmune diseases, a combination of genetic vulnerability and environmental triggers (such as Epstein-Barr virus) may play a role in MS. There appears to be a genetic link with MS; several studies show that the risk of developing MS increases almost 20 times if a close family member has the disease. MS also seems to be more prevalent in people of northern European descent and uncommon in those of Asian descent. However, it is not clear whether this is due to genetic or environmental factors. And there are likely multiple genes involved.

A recent multinational study found that a variation in a gene that controls an inflammatory cytokine, called interferon (IFN) gamma, may play a role in MS. Unlike the beta interferons used to treat MS symptoms (see page 69), IFN gamma plays a role in the immune attacks that produce MS symptoms. One gene variant that causes high levels of IFN gamma to be produced (causing more attacks on myelin) was found to be more common in women, which may help to explain why more women have MS than men. In any case, genes are only part of the picture; the identical twin of a person with MS has only a one in three chance of developing the disease, and more than 80 percent of people with MS do not have a close relative with the disease.

Respiratory infections are known to trigger MS relapses, and there are dozens of potential viral suspects in MS, in addition to the Epstein-Barr virus (EBV) (which causes infectious mononucleosis). However, some of the strongest evidence is for EBV. Antibodies to EBV and other viruses (evidence we have had an infection) are elevated in people with MS, and EBV antibodies are increased during MS exacerbations. So far, however, there is no solid, scientific evidence that a virus actually causes MS.

WHY YOUR SEX MATTERS

Female hormones, especially estrogen, could play a role in MS. During pregnancy there are fewer MS relapses when estrogen is elevated. It is thought that estriol, a weak form of estrogen that is produced during pregnancy, may even help protect against MS. Early studies in animals show that testosterone may be protective, and researchers think this could explain why men develop MS less often and typically later in life than women. (However, when men get MS, it is usually more severe and

progressive.) A recent study from Italy indicates that the hormone testosterone is reduced in women suffering from MS, and that estrogen may help control nerve damage in MS. Studies are underway to study the effects of estriol on MS, and preliminary data have been positive.

MS does not appear to have any effect on a women's ability to get pregnant or to have a healthy pregnancy. And women with MS do not have any higher rate of birth defects. At this time it is not known whether the wide shifts in hormones during perimenopause or the decline in estrogen after menopause affect the severity or course of MS.

SYMPTOMS

MS can produce a wide variety of symptoms: the most common are actually fatigue and depression (as well as wide mood swings), which are not often associated with MS. (In fact, depression may be due to undiagnosed brain lesions.) Early symptoms that raise a red flag for MS include blurred or double vision or a sudden blindness in one eye. Many MS patients experience muscle weakness in their extremities and difficulty with coordination and balance, sometimes severe enough to impede standing or walking. People with MS can also experience abnormal nerve sensations such as numbness, prickling, or a "pins and needles" feeling. There can also be tremors, dizziness, and spasticity (involuntary movement of muscles or stiffness). Approximately half of all people with MS experience cognitive problems such as difficulties with concentration, attention, memory, and poor judgment, but such symptoms are usually mild and are frequently overlooked. Less commonly, people experience headaches, seizures, or speech and swallowing difficulties. Heat often makes symptoms worse. As the disease progresses, one may experience loss of bowel and bladder control, and in severe MS, paralysis may result.

DIAGNOSIS

Making a diagnosis of MS is not easy, and the symptoms often mimic those of other conditions. Specific diagnostic tests are required to rule out other diseases and establish a definitive diagnosis of MS. You can expect to have your reflexes, balance, coordination, and vision checked, and diagnostic tests performed. Magnetic resonance imaging (MRI) of the brain is the most frequently used test and can clearly show the white "plaques" (patches of scar tissue and inflammation) characteristic of MS. (An MRI may be done using the contrast agent gadolinium to spotlight areas of demyelination.) Several new MRI techniques may help quantify and characterize MS lesions that are too subtle to be detected using conventional MRI scans.

Other diagnostic tests include evoked potential tests, which measure how quickly and accurately your nervous system responds to certain stimulation, and a spinal tap, which checks your cerebrospinal fluid for antibodies and proteins that result from the breakdown of myelin.

The severity of MS is scored using the Extended Disability Status Score (EDSS), which measures vision, sensation, coordination, strength, and walking ability. A score of 0 indicates a normal neurological exam. A score of 1.0–1.5 indicates an abnormal neurological exam, but no disability; 2.0–2.5 shows mild disability; 3.0–3.5 shows mild to moderate disability; and someone with a score of 6.0 generally needs assistance from a cane to walk.

The National Multiple Sclerosis Society established criteria that require evidence (either on MRI or clinical signs) of two separate neurological disturbances occurring at least 30 days apart for a diagnosis of MS. However, a woman who experiences a single MS attack can be started on disease-modifying medications that can slow disease progression and potentially prevent permanent disability.

TREATMENT

There are now six disease-modifying drugs approved for relapsing-remitting MS. Three of these drugs are based on natural beta interferons, which have been shown to dampen immune reactions and improve MS exacerbations: interferon beta 1-a and interferon beta 1-b, all given by self-injection. Glatiramer acetate is a synthetic protein to which the immune system responds as it would myelin, so it acts as a “decoy” for attacks on myelin. Mitoxantrone is actually chemotherapy drug that suppresses the activity of T cells, B cells, and macrophages and seems to lessen attacks on myelin. It can also affect the heart, so patients must have normal cardiac function and regular cardiac tests to receive the drug, which is given intravenously. Some interferon products have begun to be used in some cases of secondary-progressive MS, and one of them and the glatiramer acetate are being tested against primary-progressive MS.

Since MS relapses, or “flares,” are due to inflammation in the central nervous system, the most common treatments for exacerbations are intravenous, high-dose corticosteroids, most commonly methylprednisolone. It is important to note that corticosteroids can increase the risk of atherosclerosis, diabetes, and osteoporosis.

Other treatments target MS symptoms, such as depression, pain, tremor, bladder or bowel dysfunction, and fatigue. Stimulants such as modafinil can help combat fatigue, as can the antiviral medication amantadine and antidepressants. Antiseizure medications and tricyclic antidepressants are effective for nerve pain, and antispasmodic drugs

and muscle relaxants are used to relieve spasticity. Physical therapy and exercise can help preserve function. One study of early MS patients found that six months of regular exercise (either practicing yoga or riding a stationary bicycle) improved energy levels.

Many people find aids such as foot braces, canes, and walkers help them remain independent and mobile. However, studies show that two of three people with MS are able to walk on their own 20 years after their diagnosis, and those numbers should improve as more and more people are treated earlier.

FUTURE APPROACHES TO MS

Investigators are continuing their search for early diagnostic tests for MS. A recent study revealed a distinct pattern of proteins and protein building blocks (peptides) in the blood of a small group of newly diagnosed MS patients, raising the hope that a simple blood test may be used one day to diagnose MS before any nerve damage is evident on MRI. In addition, a potential blood test for antimyelin antibodies is in clinical trials.

Preliminary research suggests that the cholesterol-lowering drugs called statins, which have anti-inflammatory properties, can modulate immune responses in MS patients. A recent review found that all statin drugs have side effects, including potentially serious muscle wasting, so they should not be taken in hopes of treating MS symptoms until more research is done to confirm their effects and determine the proper dose.

In addition, drugs used to treat Alzheimer's disease, such as donepezil, are being tested to see if they can improve the cognitive decline that can occur in MS. Scientists are also investigating ways to reverse the damage to myelin (and myelin-producing cells) or trigger myelin to regenerate.

Associated Disorders

Some women with autoimmune disease may also suffer from disorders such as fibromyalgia or chronic fatigue syndrome (which are not generally thought to be autoimmune). Since the symptoms are often similar, notably joint pain and fatigue, women with autoimmune diseases may be mistakenly diagnosed with these "fellow travelers" or the symptoms may be diagnosed as a disease flare.

WHAT IS FIBROMYALGIA SYNDROME?

Fibromyalgia syndrome (FMS), a disorder characterized by pain or hypersensitivity in the muscles, ligaments, and tendons of the body, affects

2–4 percent of women in the general population. Up to 25 percent of women with RA, lupus, and Crohn’s disease meet the American College of Rheumatology diagnostic criteria for FMS, which usually strikes women between the ages of 20 and 40.

RISK FACTORS

It is not known what causes fibromyalgia, but recent research suggests that pain sensitivity may be greater in women with FMS. Studies show that areas involved in processing pain and certain brain chemicals may be different in people with FMS. In vulnerable women, a stressor or trauma—such as a physical injury, an autoimmune disease, extreme emotional stress, or hormonal alterations (such as being hypothyroid)—may provoke a disturbance in the central nervous system. Studies also reveal higher levels of certain inflammatory cytokines in women with FMS. Fibromyalgia can run in families, and several genes may contribute to a predisposition to pain amplification. In some cases, FMS can arise after an infection, especially infectious mononucleosis and Lyme disease.

WHY YOUR SEX MATTERS

Around 2–4 percent of women in the general population may be affected by this disorder, and up to 25 percent of women with autoimmune diseases may also have FMS. Fibromyalgia symptoms also overlap with other disorders that can occur in women with autoimmune diseases, including chronic fatigue syndrome (CFS), irritable bowel syndrome, and interstitial cystitis. Women are more than twice as likely as men to experience depression during their lifetime, and the incidence of depression and anxiety in women with FMS may run as high as 40–70 percent.

SYMPTOMS

Women with FMS often complain of widespread, chronic pain and pain sensitivity around the body. Women with FMS may also suffer from fatigue, sleep disturbances, depression, anxiety, difficulty concentrating, and memory problems. Other symptoms can include migraine headaches, abdominal pain, bloating or alternating constipation and diarrhea, and temporomandibular jaw pain.

DIAGNOSIS

To meet the criteria for fibromyalgia set by the American College of Rheumatology, there must be a history of chronic widespread pain involv-

ing all four quadrants of the body, as well as areas overlying the bones of the skull, backbone, ribs, and chest, and pain produced by applying pressure at 11 of 18 specific “tender points” located at the neck, shoulders, lower back, hips, and knees.

A fibromyalgia work-up includes blood tests for liver, kidney, and thyroid function; a complete blood count; and a sedimentation rate or level of C-reactive protein to detect inflammation. Unless pain has come on suddenly or there is evidence to suggest an autoimmune disease, testing for autoimmune markers is not usually done. If there is pain and stiffness in weight-bearing joints, x-rays or other imaging may be done to look for evidence of arthritis, either RA or osteoarthritis.

TREATMENT

FMS can be treated with low doses of antidepressants, which reduce pain signals from nerves. These drugs include tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and antidepressants that also affect norepinephrine. However, numerous studies show that exercise may be the most effective prescription for treating FMS. Exercise not only helps to combat deconditioning and relieve pain, it may also act as an antidepressant. Physical therapy and other treatments for pain, including injections of cortisone or local anesthetic at tender points where pain radiates to other areas (trigger points), can reduce discomfort. Women with FMS are also helped by cognitive-behavioral therapy and learning relaxation techniques and other stress-reducing measures.

What Is Chronic Fatigue Syndrome?

While fatigue is a common symptom of many autoimmune diseases, chronic fatigue syndrome (CFS) is a separate disorder. CFS is characterized by prolonged, debilitating fatigue and multiple complaints, including headaches, muscle and joint pain, and difficulties with memory and concentration. It may affect as many as two million Americans, 75 percent of whom are women. The hallmark symptom, profound fatigue, can come on suddenly or gradually. While CFS can feel like the flu, its symptoms linger for at least six months and may even persist for years. While some patients recover fully, most recover partially or recover and relapse.

RISK FACTORS

CFS can occur with autoimmune diseases, but it is not believed to be autoimmune itself. The syndrome may involve as yet unknown interactions

between the immune and central nervous systems. Although researchers once thought that elevated antibodies to Epstein-Barr virus indicated a greater likelihood of developing CFS, further research has not shown this to be the case.

WHY YOUR SEX MATTERS

CFS affects women three times more often than men and occurs most often between the ages of 40 and 49, although it can occur at any age. There do not appear to be any risk factors associated with race or socioeconomic class. Some studies have shown, however, that allergies are significantly more common in people with CFS.

SYMPTOMS

CFS symptoms can include fatigue and weakness, muscle and joint aches, headaches, inability to concentrate, allergy-like symptoms, and tender lymph nodes. These symptoms plateau early and may linger or come and go frequently for more than six months. In about a third of cases, CFS develops after a bacterial or viral infection with flu-like symptoms. Other common symptoms include gastrointestinal complaints, skin rashes, dizziness, numbness and tingling in extremities, dry eyes, chills, or night sweats. Some CFS patients also report mild to moderate symptoms of anxiety or depression.

DIAGNOSIS

The criteria set by the CDC for a diagnosis include unexplained fatigue lasting at least six months, associated with a marked reduction in activity and not alleviated by rest. In addition, a person must have four of seven possible symptoms, including memory impairment, tender lymph nodes, muscle pain, pain in multiple joints, new-onset headaches, unrefreshing sleep, and malaise (feeling unwell) lasting more than 24 hours after exertion. If an autoimmune disorder is suspected, lab tests may be done.

TREATMENT

Since the underlying cause (or causes) is unknown, there is no specific treatment for CFS. Exercise (including tai chi, yoga, and stretching), cognitive behavioral therapy, nonsteroidal anti-inflammatory drugs, low-dose tricyclic antidepressants, and medications to combat fatigue have all been shown to be helpful. According to the CDC, other ther-

apies such as massage, acupuncture, chiropractic, and light therapy may also be beneficial. While many claims are made for herbal remedies and dietary supplements, they have not been evaluated in controlled trials.

—RITA BARON-FAUST



A Witness

By Kellie Martin, actor, producer, director, and spokesperson for the American Autoimmune Related Diseases Association

I'm a sister, a daughter, a stepdaughter, a wife, a potential mother, an actress, a woman and a friend. But most of all, I'm a witness to the havoc autoimmune diseases wreak on those they strike, the devastation they level on families and loved ones, and the terrible price we pay for one of the biggest problems associated with autoimmune diseases . . . getting a correct diagnosis in a reasonable amount of time before major damage is done.

I'm a witness to my sister, Heather. Heather and I were always best friends. For 19 years, I watched my little sister grow into a beautiful woman. I was there when she was born, and I was there when she died.

A few days after finishing her sophomore year at college, Heather couldn't get out of bed. The doctor said it was the flu. This doctor was new to my family. He'd never had to handle anything more than a sore throat for us.

When Heather's abdominal pain, fever, nausea, and insomnia got worse, the doctor prescribed an anti-nausea medication. She had a violent allergic reaction to it. She started to convulse. She lost control of her neck muscles, and her eyes rolled back in her head.

That was Heather's first visit to the emergency room, but she was treated only for the convulsions. They didn't deal with anything else . . . her stiff joints, intense muscle pain, fatigue, her inability to eat. She was so weak, she couldn't hold a spoon. Later, she couldn't eat because she had sores in her mouth, and it hurt her too much.

The following night, Heather had to go back to the emergency room for abdominal pain and horrible cramping in her legs. They gave her a painkiller and sent her home. The next day, my mom had to take her back again. They went to the emergency room three times in three days. Then they finally put Heather in the hospital. My mother had to beg the doctor to admit her.

At the hospital, the nurses took blood from Heather three times a day, and each day, a new specialist was called in to see her . . . an internist, an infectious-disease specialist, a hematologist. As a last resort, they gave Heather a test for lupus. But they still thought Heather had an unusual virus, so the doctors discharged her.

My mom and I carried Heather into the house and put her in bed. We knew she'd feel better in her own room with her dog, Sparky. She was relieved to be home, but she got weaker every day. It seemed like she was sent home, not to get better, but because no one knew how to help an incapacitated 19-year old who had been completely healthy two weeks earlier.

The doctor told us he believed that Heather had a virus that was attacking her joints and muscles. My mom asked if the results had come back from the lupus panel. The doctor said that he'd gotten a verbal response that the test was negative. He told us to go home and put a cool cloth on Heather's forehead for her fever. He smiled, patted her on the head and left.

That night, for the first time in her life, Heather crawled into bed with our mother. That was highly unusual; Heather wasn't afraid of anything. She was much more like a big sister, even though I'm three years older. Heather was the rock of our family.

We took Heather to another doctor's office, where her condition was diagnosed two minutes after her examination. The doctor looked really disturbed when he saw Heather's hospital charts and medical history. He ordered a second lupus panel because the first one never appeared in her file. The next day, Heather was admitted to the hospital because of dehydration and kidney failure—both caused by lupus.

We were given a list of treatments that Heather would be getting: steroids, vitamins, fluids. During her first week at the hospital, the blood vessels in Heather's lungs began to burst. Her breathing became more labored. The doctors also found that the lupus had affected Heather's liver and bone marrow. The list of treatments increased to antibiotics and chemotherapy.

Heather liked to be in control, and while her body was so out of control, she wanted to make decisions . . . even though she knew she had no choice. When they said she had to go into the intensive-care unit, it was her choice to go in. But, after that, nothing was her decision, because she was sedated from then on and her body started its descent.

The night before Heather went into ICU, though, she had an amazing burst of energy. It was exactly like the old Heather. She didn't want to rest, she wanted to talk . . . about school, basketball, friends, boyfriends, everything. She sang songs, talked on the phone. That night was such a gift.

I'm still trying to make sense of what happened to Heather. Because of her experience, I've gotten sort of a crash course in lupus and autoimmune disease. I've learned that my stepmother also has lupus, and that one of my best friends from college has just been diagnosed with scleroderma. Those are very close relations in my life.

You may think autoimmune disease hasn't touched your family. I'll bet that all you have to do is scratch the surface, and you'll find it has.

Until we can find a cure for autoimmune diseases, I'm told our best hope is early, prompt diagnosis. Something my sister was not fortunate enough to receive. But, something that is well within our reach.

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