Sarcoidosis

Introduction

Sarcoidosis is a disease that causes inflammation of the body's tissues. Inflammation is a basic response of the body to injury and usually causes reddened skin, warmth, swelling, and pain. Inflammation from sarcoidosis is different. In sarcoidosis, the inflammation produces small lumps (also called nodules or granulomas) in the tissues.

The inflammation of sarcoidosis can occur in almost any organ and always affects more than one. Most often, the inflammation starts in either the lungs or the lymph nodes (small bean-shaped organs of the immune system). Once in a while, the inflammation occurs suddenly and symptoms appear quickly, but usually it develops gradually and only later produces symptoms.

Sarcoidosis usually is a mild condition and does not result in lasting harm to tissues. In most patients, the inflammation that causes the granulomas gets better with or without treatment and the lumps go away. In others, however, the lumps do not heal or disappear, and the tissues remain inflamed. If untreated, these tissues can become scarred. The tissue is then called "fibrotic." But even those who need treatment can usually lead a normal life.

The cause of sarcoidosis is not yet known—there may be several. For instance, an abnormal response from the immune system may be involved. (The immune system normally attacks and eliminates foreign substances, such as bacteria, that enter the body.)

Once thought rare, sarcoidosis is now known to be common and affects persons worldwide. In fact, sarcoidosis is the most common chronic fibrotic interstitial lung disorder. (Chronic illnesses are those that last for some time or recur often; interstitial lung diseases affect the tissue that surrounds the air sacs, blood vessels, and air passageways.)

This fact sheet gives an overview of sarcoidosis. It tells who gets sarcoidosis, the disease's symptoms, diagnosis, and treatment, and reviews some of the studies underway to learn more about the illness. In addition, it provides references to articles and support groups to contact for more information. The fact sheet also has special sections on diagnostic tests, the disease's effects on various organs, and commonly asked questions. The fact sheet closes with a glossary.

What Is the History of Sarcoidosis?

Sarcoidosis was first identified more than a century ago. In 1869, Jonathan Hutchinson, an English doctor, saw a 58-year-old man who had "multiple, raised, dusty-red patches on his feet, fingers, and arm." Hutchinson later reported on more patients with patches or lumps on the skin, eyes, or other organs. These patients had only one affected organ and only later was the disease known to involve the whole body.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Heart, Lung, and Blood Institute

The name "sarcoidosis" was coined by Dr. Caesar Boeck of Norway, who thought the skin lesions looked like benign (not life-threatening) sarcomas (tumors). The words "sark" and "oid" come from Greek and refer to the disease's flesh-like tumors.

Today, it is known that sarcoidosis can affect almost any part of the body—lungs, eyes, skin, bones, lymph nodes, spleen, liver, heart, and so on. It also is now known that sarcoidosis can cause hypercalcemia (in which there is too much calcium in the blood) and hypercalciuria (in which there is too much calcium in the urine), both of which can lead to kidney stones.

Knowledge has brought better tests to diagnose the disease and improved treatment. For example, in the 1970s, the use of a flexible bronchoscopic biopsy was initiated to help diagnose sarcoidosis in the lungs. In this procedure, doctors take a sample of lung tissue with a bronchoscope, a long, thin, flexible tube, about the thickness of a pencil (see Box 1). The bronchoscope also lets a doctor look inside the lungs and, besides improving diagnosis, has added to scientists' understanding of how the immune system may be involved in the development of sarcoidosis.

Treatment too has steadily advanced: Cortisone (a steroid drug) was first used to treat the disease in 1951. In 1958, an x ray "staging" method that describes the lung x ray pattern was devised to aid diagnosis and treatment. In 1975, researchers found that the levels in the blood of a substance called angiotensin converting enzyme (ACE) could be used as a biochemical marker to help identify and treat those with sarcoidosis. ACE is made by cells in the granulomas. However, ACE levels are not always elevated in those with sarcoidosis and a high level alone does not mean someone has the disease. A high level also does not mean that treatment must be given. Still, the discovery has handed doctors another tool to help them make diagnosis and treatment decisions.

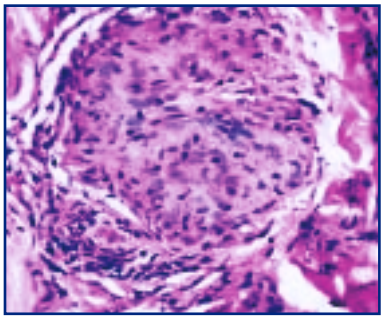
Who Gets Sarcoidosis?

Sarcoidosis occurs worldwide. It affects men and women of all ages and races. However, it occurs most commonly in adults between the ages of 20 and 40, and in those of African (especially women), Asian, German, Irish, Puerto Rican, or Scandinavian origin. In the United States, the disease occurs slightly more often and more severely among African Americans than whites.

Studies also have shown that the disease is more likely to affect certain organs in certain populations. For example, sarcoidosis of the heart and eye appears to be more common in Japan. Painful skin lumps on the legs (erythema nodosum) occur more often in people from Northern Europe.

Sarcoidosis may occur in families. In the United States, this happens more often among African Americans than whites.

Environmental factors also may affect the occurrence of sarcoidosis. For example, sarcoidosis occurs more often in nonsmokers than smokers. Several studies have noted higher rates of sarcoidosis among health care workers. Other environmental factors, such as beryllium metal (used in aircraft and weapons manufacture) and organic dust from birds or hay, may cause sarcoidosis-like reactions in the lungs. Thus, doctors need to know a person's history of occupational and environmental exposure in trying to diagnose sarcoidosis. Infectious agents have been suspected of causing sarcoidosis, but there is no proof of an infectious cause. More research is needed to better understand the effect of environmental factors on a person's risk of developing sarcoidosis.



Biopsy sample taken from a sarcoidosis skin lesion, multiplied 200 times. The granuloma is round and contains large cells.

What Are the Pathology and Course of the Disease?

A normal organ is made of an orderly arrangement of cells. Sarcoidosis upsets this arrangement, eventually causing lumps to form in organs. These lumps get larger and are called "granulomas" because they look like grains of sugar or sand. These "grains" are very small and can only be seen with a microscope.

Various other diseases can cause the formation of granulomas. For example, tuberculosis can cause granulomas. However, in other diseases, the granuloma forms around a particle, germ, or other foreign substance. In the case of tuberculosis, for instance, the granuloma forms around the invading organism, which is a mycobacterium. The immune system causes granulomas to form so that the

particles, germs, or other foreign substances can be isolated or eliminated.

In sarcoidosis, there is no such visible enclosed particle or germ. No cause for the granuloma can be seen under the microscope. The immune system appears to be responding to an unknown substance.

When thousands of these microscopic granulomas clump together, they result in a variety of small and large lumps. These lumps can appear on the lungs, skin, or other organs, such as the eyes, mouth, salivary glands, liver, spleen, or lymph nodes in the neck, armpits, and groin. Lymph nodes are small organs of the body's immune system.

The lumps can show up as shadows on x rays. If many large groups of granulomas form, they can affect the organ's function. This can cause symptoms that need to be treated.

The disease has active and nonactive stages. In the active stage, the immune system is fighting the disease and granulomas form or enlarge. In this stage, symptoms can develop and scar tissue can form. In the nonactive stage, the disease is easing, and the granulomas are stable, shrinking, or have become scars.

The course of the disease varies: In most persons, the sarcoidosis goes away over time. In others, the sarcoidosis does not get worse, but the disease remains and a person can feel well or continue to have symptoms. When treatment is given, it usually shrinks the granulomas, and they may even disappear. Such treatment may last for many months. In still other persons, scars can form in the granulomas. The scars often remain, even with treatment, and symptoms may never go away, and an affected organ may continue to function poorly.

What Are the Symptoms?

Most people with sarcoidosis have no symptoms. Some have only one symptom, while still others have many. Symptoms typically depend on which organs the disease affects. General symptoms caused by the disease include weight loss, fatigue, night sweats, fever, and an overall feeling of ill health.

Most often, the disease will affect the lungs. Thus, the most common symptoms of the disease are a cough that does not go away and shortness of breath, particularly with exertion.

Symptoms common in sarcoidosis include the following—for more on each organ and for some not listed below, see Box 2:

General Symptoms

- Uneasiness, feeling sick ("malaise")
- Tiredness, fatigue, weakness
- Loss of appetite or weight
- Fever
- Sweating at night during sleep

Lymph Node Symptoms

- Enlarged lymph nodes—most often those of the neck, but also may be those under the chin, in the arm pits, or in the groin

Skin Symptoms

- Skin rash—painful or hot red bumps on the legs or arms, or small brownish and painless bumps on the arms, legs, and/or back

Eye Symptoms

- Burning, itching, tearing, pain
- Red eye
- Sensitivity to light (photophobia)
- Dryness
- Seeing black spots (called floaters)
- Blurred vision

Lungs and Heart Symptoms

- Shortness of breath
- Wheeze
- Cough
- Chest pain
- Irregular heartbeat (palpitations)

Joint Symptoms

- Joint stiffness, swelling—most commonly of the ankles, feet, and hands

How Is Sarcoidosis Diagnosed?

The symptoms of sarcoidosis are like those of other diseases, some more harmful and even life-threatening. So it is important to properly diagnose the condition.

Someone who is thought to have the disease should see a doctor who specializes in sarcoidosis, usually a lung physician (pulmonologist). The specialist will work with patients and their regular physician to help diagnose the disease and to develop a schedule of treatment and follow-up care.

To make a diagnosis, a doctor will ask for a medical history and do a physical examination. The doctor also may need to take laboratory tests of the blood, a chest x ray, and breathing tests. Some of the tests and procedures used to help diagnose sarcoidosis are described in Box 1.

Only a biopsy gives a reliable diagnosis of sarcoidosis. In a biopsy, a sample of tissue is taken from an affected organ. The biopsy tissue can be taken from any affected organ. So the simplest and least uncomfortable tissue to biopsy is usually chosen. For example, if the skin and lungs are affected, the biopsy will be done on the skin. In many cases, a simple skin or a conjunctival (membrane lining the eyelid's inner surface) biopsy is done in a doctor's office under local anesthesia, and no hospital stay is needed.

The tissue is examined for the presence of granulomas. As noted, these granulomas will have no germs or particles within them.

A biopsy may not be needed in every case. For instance, erythema nodosum (painful red bumps, usually on the legs–see Box 2), may be diagnostic of sarcoidosis when accompanied by an abnormal chest x ray.

In 1941, a skin test was developed to help diagnose sarcoidosis, but it is not readily available in the United States. Called the Kveim-Siltzbach test, it involves injecting a standardized preparation of "sarcoidosis" tissue into the skin. The test is considered positive if a lump forms at the injection site and a biopsy of the lump shows granulomas. The result is not always positive, even if the person has sarcoidosis. It is rarely used in the United States because the U.S. Food and Drug Administration has not approved a test preparation for sale. However, some hospitals and clinics may have privately prepared a standardized test preparation.

Box 1: Key Tests for Diagnosis and Treatment

Various tests and procedures are used to help diagnose sarcoidosis. Some of these also help monitor the disease during and after treatment. Here are some of the key tests:

■ Physical Examination

The doctor will look for symptoms of the disease, such as red bumps on the skin, swollen lymph nodes, or redness in the eyes. The doctor also will check for other possible causes of any symptoms.

■ Chest X Ray

A chest x ray, which poses little risk to health, can detect sarcoidosis. About 90 percent of all persons with sarcoidosis will have an abnormal chest x ray.

X-ray beams cannot pass as easily through granulomatous or scarred tissue as through normal tissue. The x ray may show granulomas, which appear as a shadow, or enlarged lymph glands in the chest. Frequently, sarcoidosis is diagnosed because a chest x ray, taken routinely or for some other reason, shows an abnormality.

Chest x rays also may be taken to follow the course of the disease. However, the x rays typically are not done as often for this purpose as are the pulmonary function tests.

■ Blood Tests

Blood analyses evaluate the number and types of blood cells in the body. The tests also measure the blood levels of various proteins, such as ACE (see page 2), which are known to be involved in immunological activities, as well as increases in calcium levels. Additionally, they can show liver, kidney, and bone marrow abnormalities that can occur with sarcoidosis.

■ Pulmonary Function Tests

Pulmonary function tests are used to monitor the course of the disease in the lungs. These tests are safe and easy to do. The results are compared over time.

One pulmonary function test uses a "spirometer," a device that measures how much and how fast a person can blow air out of the lungs after taking a deep breath. This amount will be less than normal if there is significant inflammation and/or scarring in the lung.

Another test measures lung volume, which indicates how much air the lungs can hold. In some patients, the lungs may shrink or contract due to sarcoidosis, and the lung volumes will be smaller than normal.

Other tests check for diffusing capacity, or how well a gas moves into the bloodstream from the lungs. Sarcoidosis makes it harder for oxygen to move from the lungs into the bloodstream. In one test, a device called a pulse oximeter is placed on the finger to give the doctor a rough idea of the level (or saturation) of oxygen in the patient's blood. An arterial blood gas test is a more accurate way to check the level of oxygen in the bloodstream. Blood from an artery (usually in the wrist) is used because it has passed through the lungs and taken up oxygen. The blood is then analyzed for its oxygen and carbon dioxide

levels. The better the lungs are working, the more oxygen there will be in the arterial blood.

■ Fiberoptic Bronchoscopy

In this procedure, a long, narrow, flexible tube with a light at the end is inserted into an airway of the lung. This makes it possible for the doctor to look at the tissue lining the air passageways of the lungs. It is also possible to use the bronchoscope to obtain small samples of lung tissue and to obtain lung washings (that contain lung cells) from various parts of the lungs.

■ Fiberoptic Bronchoscopy Biopsy

In this procedure, a sample of lung tissue is removed. The procedure is usually done to make the diagnosis when pulmonary function tests or chest x rays are abnormal and characteristic of sarcoidosis. If performed, it is done at the time of a fiberoptic bronchoscopy. The test is done while the patient is awake but slightly sedated. The test is usually very safe and done on an outpatient basis.

■ Bronchoalveolar Lavage

Often, a procedure called a bronchoalveolar lavage (BAL) is done as part of a fiberoptic bronchoscopy. BAL involves injecting saline (salt water) into a region of the lung. The fiberoptic bronchoscope then uses suction to remove the fluid, which has washed out cells and other materials from the tiny air sacs (alveoli) of the lung. The pulmonary inflammation associated with sarcoidosis begins in the lung in these air sacs. The removed sample is then examined for signs of inflammation that reflect the disease's active stage.

■ CT Scan

A computed tomographic (CT) scan is a complicated kind of x ray that gives a better picture of the lungs than the ordinary chest x ray. A CT scan may be done to better assess how much of the lung is affected by sarcoidosis.

CT scans are not done routinely because they expose a person to more radiation than an ordinary chest x ray and are costly. Instead, they are done when specific factors call for their need. For example, a CT scan might be done to diagnose sarcoidosis in the brain, spinal cord, nerves—all of which are dangerous to biopsy. CT scan of the lungs is important if the patient is coughing up blood.

■ MR Scan

Magnetic resonance (also called nuclear magnetic resonance, NMR scanning, or magnetic resonance imaging, MRI) uses powerful magnets and radio waves to see inside the body. A computer generates images of the heart, brain, and other organs. The test is not invasive and has no known hazards. It can show if features typical of sarcoidosis are present in organs.

■ Thallium and Gallium Scans

These scans are used to help diagnose sarcoidosis and are often done to see if it is in the heart. Thallium and gallium are radioactive elements. The doctor injects one of these into a vein and the element collects at places in the body that have been affected by sarcoidosis or another inflammatory condition. At a specified time after the injection, the body is scanned for radioactivity. An increase in the activity at any site might indicate that inflammatory activity has developed there. The test gives an idea of which tissues in the body have been affected by the disease and by how much. Since any inflammation will cause an uptake of the radioactive element, the test does not give a definitive diagnosis of sarcoidosis.

■ Eye Test

All persons diagnosed with sarcoidosis should have an eye test done by an ophthalmologist (eye doctor). Even if there are no symptoms of the disease in the eyes, the results of the test can be used to help monitor the disease. If eye symptoms appear, the test will be repeated during treatment. It also should be repeated periodically for those treated for their sarcoidosis with a particular drug called chloroquine or hydroxycholoroquine (Plaquenil) that can sometimes cause side effects related to vision. Also, patients receiving corticosteroids need to be seen by an ophthalmologist to check for signs of cataract development. For the eye examination, the doctor looks into the eye for abnormalities and does tests to check for color blindness.

How Is Sarcoidosis Treated?

The treatment of sarcoidosis depends on a person's symptoms. Often, no treatment is needed—up to 60 percent of those with sarcoidosis receive no therapy. But, for some, intense treatment is required, especially if there is critical organ involvement, such as of the lungs, eyes, heart, or central nervous system.

Here are some key points about the use of treatment:

- *Treatment is done to control symptoms or to improve the function of organs affected by the disease.*
- *Treatment may or may not affect the long-term outcome of the disease.* One study found that 5-10 years after diagnosis, there was no difference in recovery between those who had received a short course of treatment and those who had not.
- Sarcoidosis granulomas result from a response of the immune system. *Thus, most medications used to treat sarcoidosis suppress the immune system.* This can leave a person more likely to get sick from an infection, and this risk must be considered in making treatment decisions.

Treatment for sarcoidosis involves the use of medications. A wide variety is available, but most are strong and can cause bad side effects. Different ones will work better for different persons, and sometimes more than one is used. Living with the symptoms of the disease must thus be weighed against the side effects produced by the drugs.

Drugs are either taken by mouth for "systemic" effects throughout the body or are applied locally to an affected area. Local therapy is the safest way to treat the disease, since only the affected area is exposed to the drug. Drugs can be applied locally by drop, inhaler, or cream. Drugs used in this way include corticosteroids.

However, to use drugs locally, the affected area must be easily reached. For instance, drops and creams help with some eye or skin problems, while inhalers are used to apply steroids to affected lung tissue, especially to ease coughing and wheezing. However, it does not appear that an inhaled drug can relieve such symptoms when the affected lung tissue is deep within the chest.

Here is a list of the main drugs used to treat sarcoidosis:

- *Prednisone*. Prednisone belongs to a group of medicines called corticosteroids or steroids. It is the most commonly used drug for sarcoidosis. Sometimes it is used in combination with one of the other drugs listed in this section. Sometimes other steroids are used.

Prednisone almost always relieves symptoms due to inflammation. If a symptom does not get better after a couple of months of treatment with prednisone, then there are two possibilities: either the symptom is not due to sarcoidosis, or it will not improve because sarcoidosis has already caused scarring. In the first case, the doctor may look for another cause of the symptom; in the second case, the symptom will not improve with further prednisone treatment—the drug may even cause more symptoms due to its side effects.

Prednisone treatment usually lasts for many months, but can go on for many years. If prednisone treatment is stopped after 3 months, the chance that symptoms will return is 80 percent. If treatment is stopped after 6 months, the chance that symptoms will return is 50 percent. But, if treatment is stopped after 1 year, the chance of a return is only 30 percent and, if treatment is stopped after 2 years, the chance of a return is only 25 percent.

However, prednisone can have bad side effects. These include weight gain, diabetes, high blood pressure, mood swings, difficulty sleeping at night, heartburn, acne, and, when prednisone is taken for long periods, thinning of the bones (osteoporosis) and skin, cataracts, and occasionally glaucoma. Side effects usually can be managed by the patient working with his or her doctor. Also, low doses of prednisone can frequently relieve symptoms without causing significant side effects.

- *Hydroxychloroquine*. The brand name of this drug is Plaquenil. Hydroxychloroquine is used to treat various diseases. It has long been used for malaria and is given for such other diseases as rheumatoid arthritis and lupus erythematosis (a disorder that causes inflammation of the skin and other parts of the body). With sarcoidosis, the drug is effective in about a third of persons. It is more likely to be effective if sarcoidosis has affected the skin and if there is a high level of calcium in the blood. Hydroxychloroquine has few side effects, but it can irritate the stomach and cause eye problems.

Anyone taking the drug should have his or her eyes examined every 6 months.

■ *Methotrexate*. This drug too has long been used to treat other diseases. With sarcoidosis, the drug works in 60 to 80 percent of persons. However, it takes up to 6 months to relieve symptoms.

The drug can have various side effects, including nausea and mouth sores. Methotrexate also can kill white blood cells, a type of blood cell used by the immune system to fight off infection. Thus, blood tests must be taken regularly to check the level of these cells. Rarely (less than 1 percent of the time) methotrexate causes an allergic reaction in the lungs. But this reaction goes away when treatment with the drug ends. The most serious possible side effect with methotrexate is liver damage. If methotrexate must be taken for more than 2 years, a liver biopsy may be done first to see if the organ has been damaged or if the drug can continue to be used. The drug also can harm an unborn baby and should not be taken if a woman is pregnant.

Side effects from methotrexate usually occur when the drug is taken at higher doses than those needed to treat sarcoidosis. The chance of having a bad side effect also can often be decreased by taking the vitamin folic acid.

■ *Azathioprine*. The brand name of this drug is Imuran. It also has long been used to treat various diseases and in organ transplantation. It works in about 50 percent of those with sarcoidosis. Treatment lasts for more than 6 months. It can lower the number of white blood cells and may cause nausea. The biggest concern is that it may increase the risk of developing cancer after treatment. However, this risk has been found only in transplant patients–and not in those taking the drug for other diseases. Azathioprine can harm an unborn baby and should not be taken by a pregnant woman.

■ *Cyclophosphamide*. The brand name of this drug is Cytoxan. Cyclophosphamide is a very strong drug. It is more likely to lower white blood cells and cause nausea than either methotrexate or azathioprine. Thus the level of white blood cells in the blood must be closely monitored during treatment. The drug also can irritate the bladder. Some of those on the drug for more than 2 years have developed bladder cancer. Because of these side effects, the drug is given only to those with severe forms of the disease, such as neurosarcoidosis. The drug can harm an unborn baby and should not be taken by a pregnant woman.

Cyclophosphamide can be given intravenously, which lessens some of its side effects but does not reduce the risk of cancer.

What Tests Are Done To Follow the Disease?

Those with sarcoidosis need to have their condition checked during and after treatment. Those who receive no treatment also need regular checkups, since symptoms can develop later.

The patient will work with his or her sarcoidosis specialist and regular physician to develop a schedule of periodic examinations and laboratory tests. The followup examination usually includes a review of symptoms, a physical examination, a chest x ray, breathing tests, and laboratory blood tests. How often these examinations and tests are done depends on the severity of the symptoms and the organs affected at diagnosis, the therapy used, and any complications that may develop during treatment.

Routine followup care usually lasts for 2-3 years. Whether the specialist or primary doctor oversees this care depends on symptoms during the first year of followup (see the first bullet below). Patients should tell their doctor about any new symptom that lasts for more than a week. They also should see the doctor if symptoms appear and do not go away before the next regularly scheduled followup visit. Changes in sarcoidosis occur slowly—usually over months. Except for disturbed heart rhythms, sarcoidosis does not cause sudden illness.

Box 1 gives an overview of followup care. Here are some recommendations for followup care, based on the condition at diagnosis or the treatment used:

■ *If at diagnosis, there are no symptoms, a normal breathing test, and an abnormal chest x ray, then the following is recommended:* A followup examination should be done every 6-12 months until the illness is stable or improving. The breathing test may be repeated, depending on a patient's symptoms and exercise capacity.

If new eye symptoms have appeared, then the eye test should be repeated. Eye symptoms are often severe.

If no new symptoms have developed, and the chest x ray is normal, then the patient can see his or her regular family physician for future followup care.

(Continued on page 12)

Box 2: Effects by Organ

Sarcoidosis is a "multiorgan" disease—it always involves more than one organ. An organ is affected when granulomas cause an abnormality that can be found during diagnosis or about which a patient complains. For example, a biopsy may show that bumps on the skin are made of granulomas. If no other cause for the granulomas is found and there is evidence of sarcoidosis in another organ, such as the lungs, the problem is diagnosed as sarcoidosis. Only one organ biopsy is necessary.

Some organs are affected more often than others. Sarcoidosis occurs most often in the lungs. It also commonly affects the skin, eyes, lymph nodes, and liver. Less commonly, it affects the spleen, brain, nerves, heart, tear glands, salivary glands, and bones and joints. Rarely, it affects other organs, such as the thyroid gland, breasts, kidneys, and male and female reproductive organs.

A doctor may not detect sarcoidosis in every organ affected by the disease. Often, the effects of sarcoidosis in an organ are so mild that there are no symptoms and the organ continues to function well. In such cases, identifying the disease in that organ is not necessary and would not change the treatment given. For more on diagnosis, see pages 4 and 5.

Here is a rundown of how sarcoidosis affects different organs, starting with the organ most frequently affected and going to the least affected.

■ Lungs

Sarcoidosis most commonly affects the lungs. It may affect the lung tissue itself and lymph nodes in the chest. Its effects can range from very mild (without symptoms) to severe. Symptoms caused by the disease occurring in the lungs include shortness of breath, coughing, wheezing, and, rarely, chest pain. If chest pain occurs, it often is felt in the middle of the chest and worsens with deep breathing or coughing.

The disease is usually seen on an x ray. A staging system is used to classify chest x rays taken to detect sarcoidosis. Stage 0 is a normal chest x ray. Stage 1 is a chest x ray with enlarged lymph nodes but otherwise clear lungs. Stage 2 is characterized by a chest x ray with enlarged lymph nodes plus infiltrates (shadows) in the lungs. In Stage 3, the infiltrates are present but the lymph nodes are no longer seen. In Stage 4, the chest x ray shows scars in the lung tissue. The x-ray stages do not tell the severity of the disease. However, in general the higher the stage of the x ray, the worse the person's symptoms and lung function (as measured by breathing tests). Persons with Stage 4 x rays usually have some permanent lung damage. But there is a lot of individual variation, and persons at Stages 0 through 3 may or may not have symptoms.

When no symptoms appear, treatment usually is not given, and persons recover with time. With or without treatment, persons with symptoms often improve, and their x-ray and breathing tests become normal.

■ Eyes

All those diagnosed with sarcoidosis should see an eye doctor. The doctor looks in the eyes and does simple tests. In a third of all those diagnosed with sarcoidosis, the eyes will be affected by the disease.

The disease can cause eyes to become red and painful, especially in bright light, and blur vision. Other common symptoms are burning and itching, discomfort, and, if tear ducts and glands are affected, dryness. Very rarely, permanent damage results, and blindness may occur.

Sarcoidosis of the eyes almost always responds well to treatment. Most often, the only treatment needed is eye drops.

■ Skin

Sarcoidosis of the skin can result in rashes or various types of skin lesions. About 10-35 percent of persons with sarcoidosis develop skin lesions. Other illnesses also can result in skin lesions, so a biopsy is frequently done to aid diagnosis.

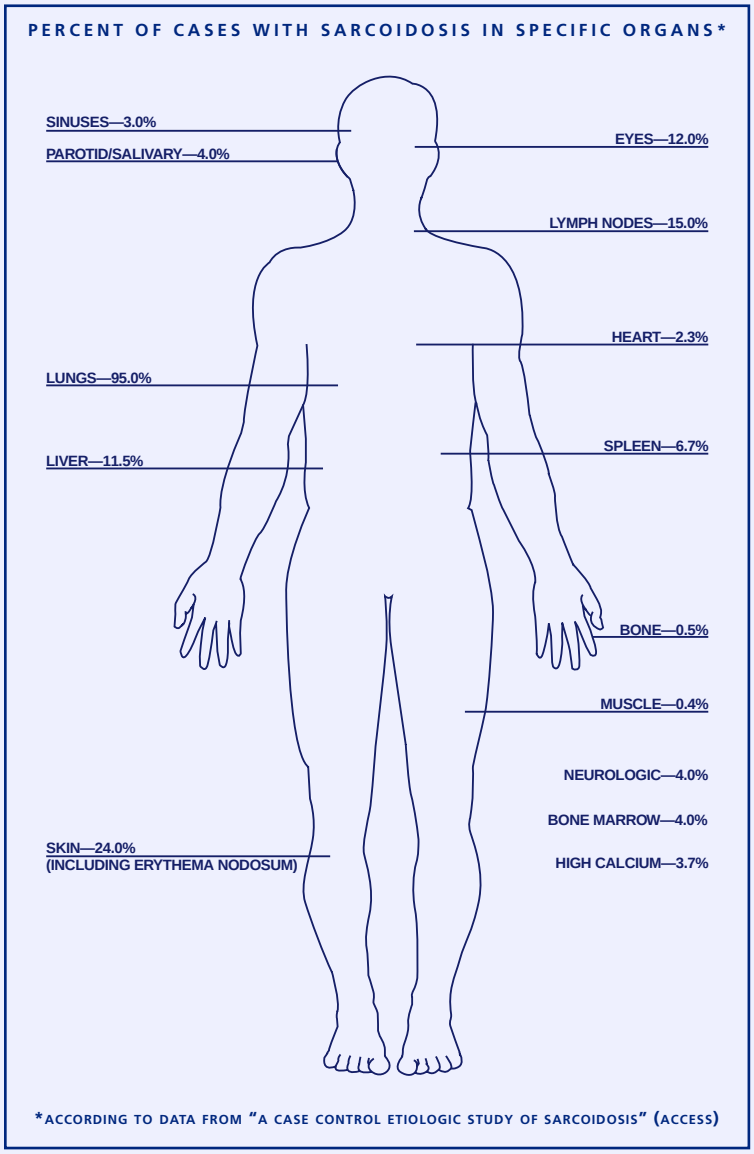
One type of lesion is called erythema nodosum. It produces painful bumps that can be warm, tender, and red or painful, purple-to-red, and slightly raised bumps. The bumps appear on the skin, commonly on the ankles and shins. The lesions may occur along with fever and swollen ankles.

These lesions do not contain granulomas (therefore are not biopsied) and they may occur in other diseases too. However, the lesions are usually an early sign of sarcoidosis.

Typically, erythema nodosum lesions go away in weeks to months with or without treatment. Because of this, treatment does not involve drugs ordinarily given for sarcoidosis. Persons receive either no drugs or, for those who are very uncomfortable, aspirin or ibuprofen (an over-the-counter anti-inflammatory medication).

Specific skin lesions are another type of problem, and these show granulomas when a biopsy is done. These lesions may appear as bumps, ulcers, or, rarely, flat areas of discolored skin. They occur most commonly near the nose, eyes, back, arms, legs, and scalp and last a long time. Typically, they are not painful but sometimes itch.

Another lesion is named lupus pernio. This type causes disfiguring lesions on the nose. Treatment is frequently needed. Also, the lesions tend to be chronic and often return after treatment is over.



■ Lymph Nodes

The body has lymph nodes (or glands) in various areas, including the neck, armpits, and groin. The nodes are part of the body's immune system. The nodes in these areas may be affected by sarcoidosis and appear as swollen lumps. Treatment may be given to reduce swelling.

■ Liver

Granulomas often form in the liver. However, the disease rarely causes significant liver damage.

Symptoms of the disease in the liver include fever, fatigue, itching, and pain in the upper right part of the abdomen (area of the body under the right ribs). The disease can cause the liver to enlarge.

Blood tests, a CT scan of the abdomen, or a biopsy may be done to detect sarcoidosis in the liver. The CT scan will show if the liver is enlarged and if there is a pattern suggesting granulomas in the organ. The biopsy is done less often and also shows the formation of granulomas.

Sarcoidosis of the liver almost never causes permanent damage to the organ and, therefore, is usually not treated unless it is causing significant symptoms. Followup care includes regular blood tests to monitor how well the liver is working.

If needed, drug treatment reduces granulomas. Rare cases in which the disease worsens have been treated successfully by liver transplantation.

Box 2: Effects by Organ (Continued from page 9)

■ Salivary Glands

These include the two parotid glands, which are below and in front of the ears. When sarcoidosis affects the parotid glands, it causes them to swell—making the cheeks look enlarged. Sarcoidosis in the salivary glands can cause the mouth and throat to be excessively dry. Treatment can be given to ease symptoms.

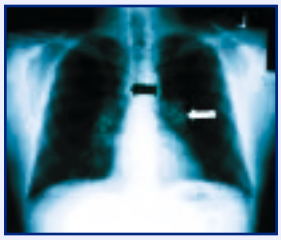
■ Blood, Urinary Tract, and Kidneys

Sarcoidosis can cause too much calcium in the blood and urine. This results from an enzyme made by the granulomas. Excess calcium in the urine can lead to painful kidney stones. A blood test for calcium should be done. If the calcium level is high, it probably will need treatment. Sarcoidosis patients with high calcium levels should not take vitamin and mineral supplements containing calcium or vitamin D.

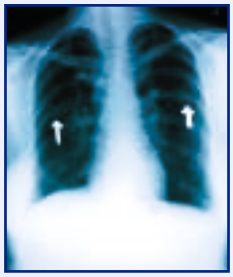
■ Nervous System

The nervous system includes the brain and all the body's nerves, and it may be affected by sarcoidosis. The disease can cause a mass of granulomas in the brain or meninges, which are the membranes that cover the brain. The disease also can affect one or more nerves anywhere in the body. Most often, it affects the nerves of the face.

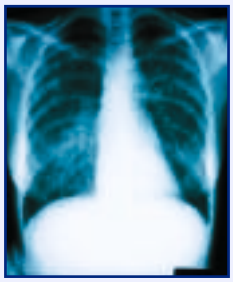
Symptoms of the disease in the nervous system vary. If there is a mass in the brain, symptoms can include headaches, visual problems, and weakness or numbness of an arm or leg. Coma also can occur, but does so rarely. Sarcoidosis can also can cause headaches.



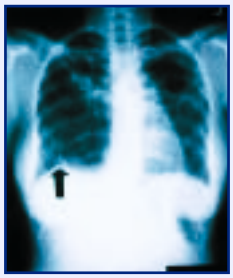
Chest x ray of Stage 1 sarcoidosis shows normal lungs with enlarged lymph nodes (see arrows) in the middle of the chest.



Chest x ray of Stage 2 sarcoidosis shows enlarged lymph nodes (see arrows) and streaks in the lungs.



Chest x ray of Stage 3 sarcoidosis shows streaks in lungs, but no enlarged lymph nodes.



Chest x ray of Stage 4 sarcoidosis shows small lungs with streaks and spots. Dark areas at the top of both lungs are caused by air cysts. The diaphram (see arrow) has peaks, which are evidence of scars in the lungs.

When sarcoidosis affects a facial nerve, it can cause one side of the face to droop. This may be the first symptom that someone has sarcoidosis. The droop often goes away or improves without therapy. When sarcoidosis affects the spinal cord, it can cause weakness or even paralysis of the arms or legs. When multiple nerves in more than one place are affected, the disease can cause weakness, pain, or a "stinging needles" sensation in those areas.

Sarcoidosis of the nervous system is often hard to diagnose. To be sure of the diagnosis, a biopsy may have to be done, but this is hard to do on the brain, nerves, or spinal cord. For the brain, if symptoms are typical of sarcoidosis and, especially, if the disease has affected other organs, a CT or MRI scan will be taken to check for any abnormalities (see Box 1).

Neurologic sarcoidosis usually needs treatment. Nerve tissue heals slowly, so treatment lasts a long time and may consist of multiple drugs at high doses.

■ Heart

Sarcoidosis sometimes affects the heart. This happens most often in Japanese persons living in Japan. The reason is unknown.

Sarcoidosis can cause the heart to pump weakly. This results in such symptoms as shortness of breath, swelling of the legs, wheezing,

and coughing. Sarcoidosis also can affect the heart's electrical pacing and transmission system, which tells it when to beat. This can make the heart beat too fast or very slowly, or skip beats. Symptoms of an electrical-system problem include palpitations (a fluttering sensation of rapid heartbeats), skipped beats, and, rarely, fluid buildup in the lungs or sudden loss of consciousness.

Sarcoidosis of the heart is often hard to diagnose. A biopsy can be taken and a diagnosis made if granulomas are seen. However, granulomas are often not seen because the tissue sample is small. Thallium or gallium scans also are used to detect inflammation in the heart (see Box 1). If a scan shows a particular abnormal pattern, then the diagnosis of sarcoidosis is made. The diagnosis is more likely if a biopsy has already proven that the disease exists in another organ.

Sarcoidosis in the heart is usually treated with steroids (see page 6). Additionally, heart drugs are given to improve the heart's pumping ability or to correct a disturbed heart rhythm. If a rhythm disturbance is severe, it may be restored to normal by use of a cardiac pacemaker (a small battery-operated device, often put under the skin, that regulates the heartbeat) or defibrillator (an implanted device that shocks a heart into a normal heartbeat or, if it has stopped, into beating). If the heart is severely affected and does not respond to therapy, a transplant may be done. But this is rarely needed.

■ Musculoskeletal

Sarcoidosis may affect the musculoskeletal system. This includes the muscles ("musculo"), joints, and bones ("skeletal").

In muscles—Sarcoidosis of the muscles may cause severe muscle pain, a mass in the muscle, or muscle weakness.

In joints—Persons with the skin lesions of erythema nodosum also may develop arthritis in the ankles.

This form of arthritis usually clears up in several weeks. Sarcoidosis also can cause a granulomatous form of arthritis. Although less common, this condition is chronic and can last for months or even years. Granulomatous arthritis requires treatment.

In bones—Sarcoidosis can cause painless holes in bones and painless swelling, most commonly in the fingers. Sarcoidosis also can affect the bone marrow (soft, organic material that fills bone cavities), which produces blood cells. This can result in anemia, in which there are too few red blood cells, or a lowered number of white blood cells. Red blood cells are needed to deliver oxygen to the body; white blood cells help fight infections. Treatment is usually given to counter these effects.

■ Other

Sarcoidosis can affect almost any organ, but rarely strikes the thyroid gland, the breasts, female and male reproductive systems, or the intestines. Other areas affected more commonly by the disease include the following:

Sinuses—These are cavities in the skull, and they can be affected by sarcoidosis and result in frequent bouts of sinusitis (inflammation of the sinus cavities). Treatment is given to reduce inflammation.

Spleen—When sarcoidosis affects the spleen, it can reduce the numbers of red or white blood cells, or platelets (important in helping blood to clot). The spleen also may enlarge. The person may feel pain in the upper left part of the abdomen. Treatment is usually given to increase cell counts and ease pain. Rarely, the spleen may need to be removed.

(Continued from page 7)

- *If at diagnosis, there are symptoms and an abnormal chest x ray, but no treatment is needed, then the following is recommended:* A followup examination should be done in 3-6 months. If the sarcoidosis has worsened by then–causing symptoms, or another abnormal x-ray and abnormal laboratory tests–treatment may be needed. If treatment is started, further followup tests may need to be done more often.
- *If after diagnosis, treatment is begun with prednisone, then the following is recommended:* Followup tests will be done to monitor for the side effects of elevated blood pressure, too much weight gain, diabetes, and arthritis of one or both hips.
- *If after diagnosis, treatment is begun with hydroxychloroquine, then the following is recommended:* The patient needs to have an eye examination every 6 months while the drug is being taken.
- *If after diagnosis, treatment is begun with methotrexate, then the following is recommended:* Monthly blood tests will be done to avoid anemia (in which the blood lacks enough red blood cells), low white blood cell and platelet levels, and inflammation of the liver.

What Is the Prognosis?

Sarcoidosis affects the body in many ways and the outcome can vary from person to person. But the chance of recovering from the disease is good. Most often, the disease goes away within a few years. About 75 percent of all patients have only the acute form of sarcoidosis and, for about half of them, the disease leaves no significant problems.

However, sarcoidosis sometimes stays for years and can cause organ damage and significantly reduce physical activity. About 25 percent of all patients have the chronic form of the disease. In these patients, the disease usually leaves scar tissue in the lungs, skin, eyes, or other organ. However, chronic cases can be improved with treatment.

Sarcoidosis–whether acute or chronic–rarely results in death.

What Does the Future Hold?

Scientists in the United States and around the world are trying to learn more about sarcoidosis and improve its diagnosis and treatment. Much of this research is being supported by the National Institutes of Health (NIH), located in Bethesda, MD.

One NIH study is called ACCESS, which stands for "A Case Control Etiologic Study of Sarcoidosis." It followed the varied course of the disease in a large group of persons and resulted in new standards for the diagnosis and management of sarcoidosis.

Other studies now underway are trying to find the agent or substances that cause sarcoidosis. That knowledge would lead to much-improved diagnostic tests for the disease, along with treatments able to target its cause and, perhaps, a prevention.

Research also is aimed at finding out why sarcoidosis appears to behave differently in different races and why it clusters in some families. For instance, scientists are comparing sarcoidosis symptoms in African Americans with those in whites. Other researchers are seeking clues about how genes, passed from one generation to another, may make some members of a family more likely than others to develop sarcoidosis.

Still other researchers are examining how sarcoidosis progresses at the cellular and biochemical levels. They want to know what happens after the agent or substance causing the disease has invaded the body—how cells behave and communicate with each other to result in sarcoidosis. Some of these studies already have led to possible new treatments, which in turn are under investigation.

Scientists also are testing new drug treatments for sarcoidosis. These drugs include medicines used for other diseases, such as thalidomide, pentoxifylline, and infliximab.

Box 3: Commonly Asked Questions

1. Is sarcoidosis a form of cancer?

Sarcoidosis is not a form of cancer. Also, having sarcoidosis does not appear to increase a person's risk of developing cancer. In cancer, cells multiply out of control and lack order; in sarcoidosis, cells act as if they are growing around an unseen "invader," forming granulomas or lumps.

However, persons who have sarcoidosis may be at a slightly elevated risk for developing some types of cancer–for example, lymphomas, and liver, lung, and skin cancers. The increased risk may be related to the chronic inflammation in the organ. The overall risk is similar to what is seen in other chronic conditions, such as diabetes, inflammatory bowl disease, and rheumatoid arthritis.

Some drugs used to treat sarcoidosis have been shown to increase the risk of cancer, but only when used in high doses for other conditions.

2. Is sarcoidosis contagious?

Sarcoidosis is not considered contagious. One person cannot "catch" it from another person.

3. Is sarcoidosis a genetic disease?

A genetic disease is one passed from parent to child. Sarcoidosis has not been found to be passed from parents to children. However, for reasons as yet unknown, it can occur in families. If one family member has the disease, others may be at an increased risk of developing it. But that risk is still relatively low.

4. How did I get sarcoidosis?

The cause of sarcoidosis is not known. Thus, it is impossible to say how anyone got the illness. Once the cause is found, it will lead to improved ways to diagnose and treat the disease. To help find the answer, the NIH supports research in the United States and worldwide.

5. Why is it so difficult to make the diagnosis of sarcoidosis?

Since its cause is unknown, sarcoidosis cannot be diagnosed directly. Instead, it must be diagnosed by a number of factors, including symptoms, results of a medical examination, laboratory tests, and a biopsy. The process is like putting together the pieces of a jigsaw puzzle. The pieces allow the doctor to say, "The diagnosis is sarcoidosis." The process gives a correct diagnosis more than 95 percent of the time.

6. What can I do to avoid sarcoidosis or to make it go away?

Since the cause of sarcoidosis is still a mystery, there is no known way to prevent the disease. Most experts do not believe that making environmental or lifestyle changes will affect the course of sarcoidosis. However, those with sarcoidosis can help protect themselves by staying healthy: Do not smoke. Keep away from substances, such as dusts and chemicals, which can harm the lungs. Talk with the doctor about whether or not to use drugs to help stop the inflammation caused by sarcoidosis. Most patients will get better without treatment.

7. Can doctors tell if the disease will get worse or go away?

No. But the types and severity of symptoms are clues about how the disease will progress. For instance, those who have shortness of breath that grows worse usually develop a chronic and more severe case of sarcoidosis. Also, those who have sarcoidosis of the skin sometimes develop a chronic and more severe case of the disease, while those with erythema nodosum almost always get better.

8. Can I become pregnant and have children?

Severe sarcoidosis can reduce the chance of becoming pregnant, particularly for older women. Nevertheless, many women have given birth to healthy babies while being treated for sarcoidosis. In turn, a pregnancy has little effect on the course of sarcoidosis, and treatment usually continues without interruption. Occasionally, the disease worsens in women after delivery of a new baby. Women planning to have a baby should discuss the matter with their doctor.

It is especially important for women with sarcoidosis to have medical checkups throughout and after pregnancy.

9. Does sarcoidosis affect African Americans more than others?

African Americans have a higher risk for sarcoidosis than do other Americans. However, the illness occurs in every race in the United States—and throughout the world.

For More Information

Various groups offer information about sarcoidosis. Call or write to them or, where applicable, visit their Web site.

For the names of U.S. scientists studying sarcoidosis, contact the following:

- **National Heart, Lung, and Blood Institute (NHLBI), NIH**
  Division of Lung Diseases
  2 Rockledge Center
  6701 Rockledge Drive
  MSC 7952
  Suite 10018
  Bethesda, MD 20892-7952

To find out about participating in a clinical study of sarcoidosis at the NHLBI, a patient should have his or her doctor write to:

- **National Heart, Lung, and Blood Institute (NHLBI), NIH**
  Pulmonary Branch
  9000 Rockville Pike
  Building 10, Room 6D06
  Bethesda, MD 20892

For general information about other lung diseases, contact the following:

- **National Heart, Lung, and Blood Institute Health Information Center**
  P.O. Box 30105
  Bethesda, MD 20824-0105
  Phone: (301) 592-8573
  TTY: (240) 629-3255
  Fax: (301) 592-8563
  Web site:
  www.nhlbi.nih.gov

The site includes a list of clinical trials at the NHLBI.

- **National Institute of Allergy and Infectious Diseases (NIAID), NIH**
  NIAID Office of Commuication and Public Liaison
  Building 31, Room 7A50
  31 Center Drive, MSC 2520
  Bethesda, MD 20892-2520
  Web site:
  www.niaid.nih.gov

To find a local support group for those with sarcoidosis, check your telephone directory or contact the following—many also provide general information on the disease:

- **American Lung Association**
  1740 Broadway
  New York, NY 10019
  Phone: (212) 315-8700
  Web site:
  www.lungusa.org
- **National Sarcoidosis Resources Center**
  P.O. Box 1593
  Piscataway, NJ 08855-1593
  Phone: (732) 699-0733
  Web site:
  www.nsrc-global.net
- **Sarcoidosis Networking**
  13925 80th Street East
  Puyallup, WA 98372
  Phone: (253) 845-3108
  Website:
  www.sarcoidosis_network@prodigy.com
- **Sarcoidosis Research Institute**
  3475 Central Avenue
  Memphis, TN 38111
  Phone: (901) 327-5454
  Web site:
  www.sarcoidosisresearch.org
- **The Sarcoidosis Awareness Network**
  10313 Farrar Avenue
  Cheltenham, MD 20623
  Phone: (301) 372-2885
  Web site:
  www.sarcoidosisawareness.org

Glossary

Abdomen—Area of the trunk below the heart, lungs, and diaphram (partition that separates the chest and abdomen) and above the pelvis; the area holds the stomach, intestines, liver, and other organs

Active stage—Of sarcoidosis, when it is producing new granulomas; this may pose a risk for scar formation in the future; see also nonactive stage

Acute—Of sarcoidosis, when it occurs once and goes away; acute forms of the disease include swollen lymph nodes and erythema nodosum

Alveoli—Tiny sac-like air spaces in the lung where carbon dioxide and oxygen are exchanged

Anemia—Condition in which there are too few red blood cells

Benign—Not life-threatening; not cancerous

Bone marrow—Soft, organic material that fills the cavities of bones

Cancer—A tumor or mass of cells that are multiplying out of control

Cardiac—Refers to the heart

Cardiac pacemaker— A small, battery-operated device that regulates the heartbeat; permanent ones are put under the skin

CT scan—Computed tomographic (CT) scan; x ray that gives a better picture of the lungs than the ordinary chest x ray; sometimes also called CAT scan, for computed axial tomographic scan

Chronic—Of long duration or frequent recurrence

Conjunctiva—Delicate membrane that lines the inside of the eyelid and covers the surface of the white part of the eye.

Defibrillator—Also called an automated implantable defibrillator; it is a device that gives an electrical pulse to the heart to resume a normal heartbeat if it has become irregular or to shock it back into beating if it has stopped

Fiberoptic bronchoscope—A long, narrow, flexible tube with a light at the end that is used by the doctor for direct observation of the airways, as well as for biopsy of tissue and collection of cells and other materials from the lungs

Fibrotic tissue—Scar tissue

Folic acid—A vitamin important for health and the prevention of birth defects

Gene—The unit of heredity; a segment of DNA (deoxyribonucleic acid, a molecule carrying information for all functions of cells)

Genetic disease—A disease passed from parent to child

Glaucoma—A disease in which the normal fluid pressure inside the eyes slowly rises, leading to vision loss or blindness

Granuloma—Small mass or nodule of inflamed tissue

Granulomatous—Adjective for granuloma; has traits of granulomas

Hypercalcuria—Too much calcium in the urine

Immune system—A system of glands, tissues, and cells that helps the body fight off infection and tumors

Inflammation—A basic response of the body to injury, usually showing up as redness, warmth, swelling, and pain but not in granulomatous inflammation

Interstitial lung diseases—Cause inflammation to occur deep in the lungs; affect the air sacs (alveoli) of the lungs, where oxygen goes into the bloodstream, causing less oxygen to enter the blood

Lavage—To wash out a body organ

Local therapy—A therapy that is applied only to the area affected by the disease

Lymph nodes—Small, bean-shaped glands or organs of the immune system that are distributed throughout the body

Meningitis—An inflammation of the membrane that covers the brain and spinal cord

MR scan—Magnetic resonance scan; also called magnetic resonance imaging (MRI) or nuclear magnetic resonance (NMR); it uses powerful magnets and radio waves to make computer-generated images of the heart, brain, and other organs

Multiorgan disease—A condition that affects more than one organ

Musculoskeletal—Refers to muscles, joints, and bones

Nodule—Small lump of tissue

Nonactive stage—When sarcoidosis is not progressing and poses less risk of further scar formation or the granulomas have already changed to scars; see also active stage

Ophthalmologist—Eye doctor

Osteoporosis—A disease marked by severe thinning of the bones

Palpitations—Irregular heartbeats

Parotid glands—Salivary glands that occur below and in front of the ear

Prognosis—Probable outcome of a disease

Pulmonologist—A specialist in lung diseases; the doctor often seen by those with sarcoidosis

Saline—Salt water

Salivary glands—Glands that secrete saliva

Serum—Clear liquid portion of animal fluid, such as blood

Sinusitis—Inflammation of the sinus cavities

Spirometer—Device that measures how much and how fast a person can blow air out of the lungs after taking a deep breath

Systemic therapy—Affects the body as a whole

White blood cells—Type of cell in the blood that is used by the immune system to fight off infection

References

1. American Thoracic Society. Medical Section of the American Lung Association: statement on sarcoidosis. *Am J Respir Cri Care Med.* 1999;160:736-55.

2. Askling J, Grunewald J, Eklund A, et al. Increased risk for cancer following sarcoidosis. *Am J Respir Cri Care Med.* 1999;160(5 Pt 1:1668-72).

3. Baughman RP, Lower EE. Alternatives to corticosteroids in the treatment of sarcoidosis. *Sarcoidosis Vasc and Diffuse Lung Dis.* 1997;14:121-30.

4. Baughman RP, Winget DB, Lower EE. Methotrexate is steroid sparing in acute sarcoidosis: results of a double blind, randomized trial. *Sarcoidosis Vasc and Diffuse Lung Dis.* 2000;17:60-6.

5. Costable U. Sarcoidosis: clinical update. *Eur Respir J.* 2001;18(suppl32):56s-68s.

6. Hunninghake GW, Costable U, Ando M, et al. ATS/ERS/WASOG statement on sarcoidosis. *Sarcoidosis Vasc and Diffuse Lung Dis.* 1999;16:149-73.

7. McGrath DS, Goh N, Foley PJ, et al. Sarcoidosis: genes and microbes–soil or seed? *Sarcoidosis Vasc and Diffuse Lung Dis.* 2001;18:149-64.

8. Newman LS, Rose CS, Maier LA. Sarcoidosis. *NEngl J Med.* 1997;336(17):1224-34.

9. Paramothayan S, Jones PW. Corticosteroid therapy in pulmonary sarcoidosis: a systematic review. *JAMA.* 2002;287(10):1301-7.

10. Yee AM, Pochapin MB. Treatment of complicated sarcoidosis with infliximab anti-tumor necrosis factor-α therapy. *Ann Internal Med.* 2001;135(1):27-31.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Heart, Lung, and Blood Institute

NIH Publication No. 02-5060

April 2003