

## **Adrenal Gland Disorders**

Adrenal gland disorders are characterized by adrenal insufficiencies, where there are deficiencies in the availability of steroids that are produced by the adrenal glands. Adrenal gland disorders are challenging to diagnose, but if left untreated, they are life threatening. There are two parts of the adrenal glands, the adrenal cortex and the adrenal medulla. The adrenal cortex produces cortisol, a hormone that regulates nearly every type of organ and tissue within the body. The adrenal cortex also produces aldosterone. It helps to maintain appropriate proportions of water and salts within the body. When the proportions are disrupted, it results in low blood pressure. Most patients with adrenal insufficiency may experience fatigue, poor appetites, dizziness, weight loss, and nausea.

The body has two adrenal glands, one near the top of each kidney. The inner part (medulla) of the adrenal glands secretes hormones, such as epinephrine and nor-epinephrine (adrenaline), that help control blood pressure, heart rate, sweating, and other activities also regulated by the sympathetic nervous system. The outer part (cortex) secretes different hormones, including corticosteroids (cortisone-like hormones, such as cortisol) and mineralocorticoids (particularly aldosterone, which control blood pressure and the levels of salt and potassium in the body). The adrenal glands also play a role in stimulating the production of androgens (testosterone and similar hormones).

The adrenal glands are controlled in part by the brain. The hypothalamus, a small gland in the brain involved in hormonal regulation, produces corticotrophin-releasing hormone and vasopressin. These two hormones trigger the pituitary gland to secrete corticotrophin (also known as adrenocorticotrophic hormone or ACTH), which stimulates the adrenal glands produce corticosteroids. The rennin-angiotensin-aldosterone system, regulated mostly by the kidneys, causes the adrenal glands to produce more or less aldosterone.

The body controls the levels of corticosteroids according to need. The levels tend to be much higher in the early morning than later in the day. When the body is stressed from illness or otherwise, the levels of corticosteroids increase dramatically.

### **Addison's Disease**

*In Addison's disease, the adrenal glands are underactive, resulting in a deficiency of all adrenal hormones.*

Addison's disease can start at any age and affects males and females equally. In 70% of people with Addison's disease, the cause is not precisely known, but the adrenal glands are affected by an autoimmune reaction in which the body's immune system attacks and destroys the adrenal cortex. In the other 30%, the adrenal glands are destroyed by cancer, an infection such as tuberculosis, or another identifiable disease. In infants and children, Addison's disease may be due to a genetic abnormality of the adrenal glands.

Secondary adrenal insufficiency is a term given to a disorder that resembles Addison's

disease. In this disorder, the adrenal glands are underactive because the pituitary gland is not stimulating them, not because the adrenal glands have been destroyed or have otherwise directly failed.

When the adrenal glands become underactive, they tend to produce inadequate amounts of all of the adrenal hormones. Thus, Addison's disease affects the balance of water, sodium, and potassium in the body, as well as the body's ability to control blood pressure and react to stress. In addition, loss of androgen, such as dehydroepiandrosterone (DHEA), may cause a loss of body hair in women. In men, testosterone from the testes more than makes up for this loss. DHEA has additional effects that do not relate to androgens. When the adrenal glands are destroyed by infection or cancer, the adrenal medulla and, thus, the source of epinephrine is lost. However, this loss does not cause symptoms.

A deficiency of aldosterone, in particular, causes the body to excrete large amounts of sodium and retain potassium, leading to low levels of sodium and high levels of potassium in the blood. The kidneys are not able to concentrate urine, so when a person with Addison's disease drinks too much water or loses too much sodium, the level of sodium in the blood falls. Inability to concentrate urine ultimately causes the person to urinate excessively and become dehydrated. Severe dehydration and a low sodium level reduce blood volume and can culminate in shock.

Corticosteroid deficiency leads to an extreme sensitivity to insulin so that the level of sugar in the blood may fall dangerously low. The deficiency prevents the body from manufacturing carbohydrates from protein, fighting infections, and healing wounds very well. Muscles weaken, and even the heart can become weak and unable to pump blood adequately. In addition, the blood pressure may become dangerously low.

People with Addison's disease are not able to produce additional corticosteroids when they are stressed. They, therefore, are susceptible to serious symptoms and complications when confronted with illness, extreme fatigue, severe injury, surgery, or, possibly, severe psychological stress. In Addison's disease, the pituitary gland produces more corticotrophin in an attempt to stimulate the adrenal glands. Corticotrophin also stimulates melanin production, so dark pigmentation of the skin and the lining of the mouth often develop.

### **Symptoms**

Soon after developing Addison's disease, a person feels weak, tired, and dizzy when standing up after sitting or lying down. These problems may develop gradually and insidiously. People with Addison's disease develop patches of dark skin; this darkness may seem like tanning, but it appears on areas not even exposed to the sun. Even people with dark skin can develop excessive pigmentation, although this change may be harder to recognize. Black freckles may

develop over the forehead, face, and shoulders; a bluish black discoloration may develop around the nipples, lips, mouth, rectum, scrotum, or vagina.

Most people lose weight, become dehydrated, have no appetite, and develop muscle aches, nausea, vomiting, and diarrhea. Many become unable to tolerate cold. Unless the disease is severe, symptoms tend to become apparent only during times of stress. Periods of hypoglycemia, with nervousness and extreme hunger, can occur, particularly in children.

If Addison's disease is not treated, severe abdominal pains, profound weakness, extremely low blood pressure, kidney failure, and shock may occur (adrenal crisis). An adrenal crisis often occurs if the body is subjected to stress, such as an accident, injury, surgery, or severe infection. Death may quickly follow.

### **Diagnosis**

Because the symptoms may start slowly and subtly, and because no single laboratory test is definitive in the early stages, doctors often do not suspect Addison's disease at the outset. Sometimes a major stress makes the symptoms more obvious and precipitates a crisis.

Blood tests may show low sodium and high potassium levels and usually indicate that the kidneys are not working well. A doctor who suspects Addison's disease measures cortisol levels, which may be low, and corticotrophin levels, which may be high. However, a doctor usually confirms the diagnosis by measuring cortisol levels after they have been stimulated with corticotrophin. If cortisol levels are low, further tests are needed to determine if the problem is Addison's disease or secondary adrenal insufficiency.

### **Treatment**

Regardless of the cause, Addison's disease can be life threatening and must be treated with corticosteroids. Usually treatment can be started with hydrocortisone or prednisone (a synthetic corticosteroid) taken by mouth. However, people who are severely ill may be given cortisol intravenously or intramuscularly at first and then hydrocortisone tablets. Because the body normally produces most cortisol in the morning, replacement hydrocortisone should also be taken in divided doses, with the largest dose in the morning. Hydrocortisone will need to be taken every day for the rest of the person's life. Larger doses of hydrocortisone may be needed when the body is stressed, especially from an illness, and may need to be given by injection if the person has severe diarrhea or vomiting.

Most people also need to take fludrocortisone tablets every day to help restore the body's normal excretion of sodium and potassium. Supplemental testosterone is not usually needed,

although there is some evidence that replacement with DHEA improves the quality of life. Although treatment must be continued for life, the outlook is excellent.

### **Suppression of Adrenal Function by Corticosteroids**

In people who take large doses of corticosteroids, such as prednisone, the function of the adrenal glands can become suppressed. This suppression occurs because large doses of corticosteroids prevent the hypothalamus and pituitary glands from producing the hormones that normally stimulate adrenal function. If the person abruptly stops taking corticosteroids, the body cannot restore adrenal function quickly enough, and temporary adrenal insufficiency (a condition similar to Addison's disease) results. Also, when stress occurs, the body is not able to stimulate the additional production of corticosteroids that are needed.

Therefore, doctors never discontinue the use of corticosteroids abruptly if they have been taken for more than 2 or 3 weeks. Instead, they taper the dose over weeks and sometimes months. Also, the dose may need to be increased in people who become ill or otherwise severely stressed while taking corticosteroids. Corticosteroid use may need to be resumed in a person who becomes ill or otherwise severely stressed within weeks of having the corticosteroid tapered or discontinued.

### **Cushing's Syndrome**

*In Cushing's Syndrome, the level of corticosteroids is excessive, usually from overproduction by the adrenal glands.*

The adrenal glands may overproduce corticosteroids because of a problem in the adrenal glands or because of too much stimulation from the pituitary gland. An abnormality in the pituitary gland, such as a tumor, can cause the pituitary gland to produce large amounts of corticotrophin, the hormone that controls the production of corticosteroids from the adrenal glands. Tumors outside the pituitary gland, such as small-cell lung cancer, can produce corticotrophin as well (a condition called ectopic corticotrophin syndrome). Corticotrophin may also be produced by a tumor called a carcinoid, which may occur almost anywhere in the body.

Sometimes a noncancerous tumor (adenoma) develops in the adrenal glands, which causes them to overproduce corticosteroids. Adrenal adenomas are extremely common; half of all people have them by the age of 70. Only a small fraction of adenomas produce excess hormones, however. Cancerous tumors of the adrenal glands are very rare.

Cushing's syndrome can also develop in people who must take large doses of corticosteroids

because of a serious medical condition. Those who must take large doses have the same symptoms as those who produce too much of the hormone. The symptoms can occasionally occur even if the corticosteroids are inhaled, as for asthma, or are used topically for a skin condition.

### **Symptoms**

Corticosteroids alter the amount and distribution of body fat. Excessive fat develops throughout the torso and may be particularly noticeable at the top of the back. A person with Cushing's syndrome usually has a large, round face (moon face). The arms and legs are usually slender in proportion to the thickened trunk. Muscles lose their bulk, leading to weakness. The skin becomes thin, bruises easily, and heals poorly when bruised or cut. Purple streaks that look like stretch marks may develop over the abdomen. People with Cushing's Syndrome tend to tire easily.

High corticosteroid levels over time raise the blood pressure, weaken bones (osteoporosis), and diminish resistance to infections. The risk of developing kidney stones and diabetes is increased, and mental disturbances, including depression and hallucinations, may occur. Women usually have an irregular menstrual cycle. Children with Cushing's Syndrome grow slowly and remain short. In some people, adrenal glands also produce large amounts of androgens (testosterone and similar hormones), leading to increased facial and body hair in women, balding, and an increased sex drive.

### **Diagnosis**

When doctors suspect Cushing's Syndrome, they measure the level of cortisol, the main corticosteroid hormone, in the blood. Normally, cortisol levels are high in the morning and lower late in the day. In people who have Cushing's syndrome, cortisol levels are very high throughout the day.

If the cortisol levels are high, the doctor may recommend a dexamethasone suppression test. Dexamethasone suppresses the pituitary gland and should lead to suppression of cortisol secretion by the adrenal glands. If Cushing's syndrome is caused by too much pituitary stimulation, the level of cortisol will fall to some extent, although not as much as in people who do not have Cushing's syndrome. If Cushing's syndrome has another cause, the level of cortisol will remain high. A high corticotrophin level further suggests overstimulation of the adrenal gland.

Other laboratory tests may be needed to determine the exact cause, including a computed tomography (CT) or magnetic resonance imaging (MRI) scan of the pituitary or adrenal glands

and a chest x-ray or CT scan of the lungs; however, these tests often fail to find the tumor. When the overproduction of corticotrophin is thought to be the cause, blood samples are taken from different parts of the body to determine the source.

### **Treatment**

Treatment depends on whether the problem is in the adrenal glands, the pituitary gland, or elsewhere. Surgery or radiation therapy may be needed to remove or destroy a pituitary tumor. Tumors of the adrenal gland (usually adenomas) can often be removed surgically. Both adrenal glands may have to be removed if these treatments are not effective or if no tumor is present. People who have both adrenal glands removed and many people who have part of their adrenal glands removed must take corticosteroids for life. Tumors outside the pituitary and adrenal glands that secrete excess hormones are usually surgically removed. Certain drugs can lower cortisol levels and can be used while awaiting more definitive treatment such as surgery.

### **What is Nelson's Syndrome?**

People who have both their adrenal glands removed for Cushing's disease may develop Nelson's syndrome. In this disorder, a pituitary tumor develops, producing large amounts of corticotrophin and other hormones that stimulate melanocytes, leading to darkening of the skin. The enlarging pituitary tumor may compress nearby structures in the brain, producing headaches and defects in vision. Some experts believe that this may be prevented, at least in some people, by radiation therapy to the pituitary gland. If necessary, Nelson's syndrome can be treated with radiation or surgical removal of the pituitary gland.

### **Virilization**

*Virilization is the development of exaggerated masculine characteristics, usually in women, often as a result of the adrenal glands overproducing androgens (testosterone and similar hormones).*

The most common cause of virilization is an enlargement of the hormone-producing portions of the adrenal cortex (adrenal hyperplasia). Sometimes the cause is a small hormone-producing tumor (adenoma or cancer) in the gland. Occasionally, virilization occurs when a cancer outside the adrenal gland produces androgens. Athletes who take large amounts of androgens (anabolic steroids) to increase their muscle bulk may develop symptoms of virilization. Cystic enlargement of the ovaries may cause virilization, but such cases are almost always mild. Sometimes an abnormality in an enzyme (a protein) in the adrenal glands can also produce virilization.

## **Symptoms and Diagnosis**

Symptoms of virilization include excess facial and body hair (hirsutism), baldness, acne, deepening of the voice, increased muscularity, and an increased sex drive. In women, the uterus shrinks, the clitoris enlarges, the breasts become smaller, and normal menstruation stops.

The combination of body changes makes virilization relatively easy for a doctor to recognize. A test can determine the level of androgens in the blood. If the level is very high, a dexamethasone suppression test can help determine if the problem is coming from the adrenal glands and whether the problem is an adenoma or adrenal hyperplasia. If the problem is an adenoma or cancer, dexamethasone reduces androgen production only partially or not at all.

The doctor may also order a computed tomography (CT) or magnetic resonance imaging (MRI) scan to obtain a view of the adrenal glands. In women with cystic ovaries, the testosterone level may appear to be normal, but its binding protein is low so that the free (unbound) fraction is relatively high.

## **Treatment**

Androgen-producing adenomas and adrenal cancers are usually treated by surgically removing the adrenal gland that contains the tumor. For adrenal hyperplasia, small amounts of corticosteroids, such as dexamethasone, generally reduce the production of androgens. The mild virilization caused by cystic ovaries may need no treatment. It can be treated with drugs that lower the free testosterone levels, such as oral contraceptives, or that block the effects of testosterone.

## **Hyperaldosteronism**

*In Hyperaldosteronism, overproduction of aldosterone leads to fluid retention and increased blood pressure, weakness, and, rarely, periods of paralysis.*

Aldosterone, a hormone produced and secreted by the adrenal glands, signals the kidneys to excrete less sodium and more potassium. Aldosterone production is regulated by corticotrophin (secreted by the pituitary gland) and partly through the renin-angiotensin-aldosterone system. Renin, an enzyme produced in the kidneys, controls the activation of the hormone angiotensin, which stimulates the adrenal glands to produce aldosterone.

Hyperaldosteronism can be caused by a tumor (usually a noncancerous adenoma) in the

adrenal gland (a condition called Conn's syndrome), although sometimes both glands are involved and are overactive. Sometimes Hyperaldosteronism is a response to certain diseases, such as very high blood pressure (hypertension) or narrowing of one of the arteries to the kidneys.

### **Symptoms and Diagnosis**

High aldosterone levels can lead to low potassium levels. Low potassium levels often produce no symptoms but may lead to weakness, tingling, muscle spasms, and periods of temporary paralysis. Some people become extremely thirsty and urinate frequently.

A doctor who suspects Hyperaldosteronism first tests the levels of sodium and potassium in the blood. The doctor may also measure aldosterone levels. If they are high, spironolactone, a drug that blocks the action of aldosterone, may be given to see if the levels of sodium and potassium return to normal. In Conn's syndrome, the levels of renin are also very low.

When too much aldosterone is being produced, doctors examine the adrenal glands for a noncancerous tumor (adenoma). Computed tomography (CT) or magnetic resonance imaging (MRI) can be helpful, but sometimes blood samples from different parts of the body must be tested to localize the source of the hormone.

### **Treatment**

If a tumor is found, it can usually be surgically removed. When the tumor is removed, blood pressure returns to normal, and other symptoms disappear about 70% of the time. If no tumor is found and both glands are overactive, partial removal of the adrenal glands may not control high blood pressure, and complete removal will produce Addison's disease, requiring treatment for life. However, spironolactone can usually control the symptoms, and drugs for high blood pressure are readily available. Rarely do both adrenal glands have to be removed.

### **Pheochromocytoma**

A pheochromocytoma is a tumor that usually originates from the adrenal glands' chromaffin cells, causing overproduction of catecholamines, powerful hormones that induce high blood pressure and other symptoms.

Pheochromocytomas may grow within the adrenal glands or in chromaffin cells outside the adrenal glands. Only 5% of pheochromocytomas that grow within the adrenal glands are cancerous, but this percentage is higher for those outside the adrenal glands.

Pheochromocytomas may occur in men or women at any age, but they are most common in people between the ages of 30 to 60.

The tumor is named for its colorful reaction in fixatives containing chromic acid salts. In modern-day language, these tumors are often referred to as "pheos." Most pheos secrete a number of hormones, including norepinephrine, epinephrine, dopamine, vanilylmandelic acid, and metanephrines. Pheochromocytomas are usually benign (non-cancerous), but can cause dangerously high blood pressure and other symptoms, including pounding headaches, heart palpitations, flushing of the face, nausea, and vomiting. Pheochromocytoma symptoms usually include paroxysms of extreme hypertension, accompanied by sweating, headache, and other autonomic disturbances, probably resulting from physical compression and/or ischemia of the "pheo." Doctors and patients often refer to these bouts as "episodes."

Some people who develop pheochromocytomas have a rare inherited condition called multiple endocrine neoplasia that makes them prone to tumors in the thyroid, parathyroid, and adrenal glands. Pheochromocytomas may also develop in people who have von Hippel-Lindau disease and in those who have neurofibromatosis (von Recklinghausen's disease).

## **Symptoms**

Pheochromocytomas are usually very small. However, even a small pheochromocytoma can produce large amounts of potent catecholamines. Catecholamines are hormones such as *adrenaline (epinephrine), norepinephrine, and dopamine, which tend to greatly increase blood pressure, heart rate, and other symptoms usually associated with life-threatening situations.*

The most prominent symptom of a pheochromocytoma is high blood pressure, which may be very severe. Other symptoms include a fast and pounding heart rate, excessive sweating, lightheadedness when standing, rapid breathing, cold and clammy skin, severe headaches, chest and stomach pain, nausea, vomiting, visual disturbances, tingling fingers, constipation, and an odd sense of impending doom. When these symptoms appear suddenly and forcefully, they can feel like a panic attack. In half of the people, symptoms come and go, sometimes triggered by pressure on the tumor, massage, drugs (especially anesthesia and beta-blocking drugs), emotional trauma, and, on rare occasions, the simply act of urination.

However, many people may have these symptoms as manifestations of an anxiety state, not a glandular disorder.

## **Diagnosis**

A doctor may not suspect a pheochromocytoma because almost half of the people have no

symptoms other than persistent high blood pressure. However, when high blood pressure occurs in a young person, comes and goes, or accompanies other symptoms of pheochromocytoma, the doctor may request certain laboratory tests. For example, the level of certain catecholamines may be measured blood or urine samples. Because of high blood pressure and other symptoms, a doctor may prescribe a beta-blocker before knowing that the cause is a pheochromocytoma. Beta-blockers can make high blood pressure worse in people with pheochromocytoma. This paradoxical reaction often makes the diagnosis of pheochromocytoma clear.

If the level of catecholamines is high, a computed tomography (CT) or magnetic resonance imaging (MRI) scan can help locate the pheochromocytoma. A test using injected radioactive chemicals that tend to accumulate in pheochromocytomas is also useful. A scan is then performed to see where the radioactive chemicals are.

### **Treatment**

Usually the best treatment is to remove the pheochromocytoma. Surgery is often delayed, however, until a doctor can bring the tumor's secretion of catecholamines under control with drugs, because having high levels of catecholamines can be dangerous during surgery. Phenoxybenzamine is generally given to stop hormone secretion. Once this step is accomplished, a beta-blocker can safely be given to further control symptoms.

If the pheochromocytoma is cancerous and has spread, chemotherapy with cyclophosphamide, vincristine, and dacarbazine may help slow the tumor's growth. Treatment with a radioisotope known as MIBG that targets the tumor tissue can also be highly effective. The dangerous effects of the excess catecholamines secreted by the tumor can almost always be blocked by continuing to take Phenoxybenzamine or a similar drug and beta-blockers.