



Journalist Handbook

Special focus on Cushing's disease

Provided by Novartis Oncology



Cushing's disease: A Rare Endocrine Disorder

As we begin our overview of Cushing's disease – which is a rare endocrine disorder – it is important to provide a brief summary of the endocrine system³. The endocrine system

Hormone levels that are too high or too low may be caused by an endocrine disorder.

includes eight major glands throughout the body that produce hormones, which travel through the bloodstream to tissues or organs, affecting body processes from head to toe, such as growth and development, metabolism, sexual function, reproduction and mood. The endocrine system plays a critical role in many bodily functions and regulation of these processes contributes to a person's overall health⁴.

Endocrine disorders occur when hormone levels are imbalanced. Hormone levels that are too high or too low may be caused by an endocrine disorder. An endocrine disorder may also occur if the body does not respond to hormones the way it is supposed to⁴.

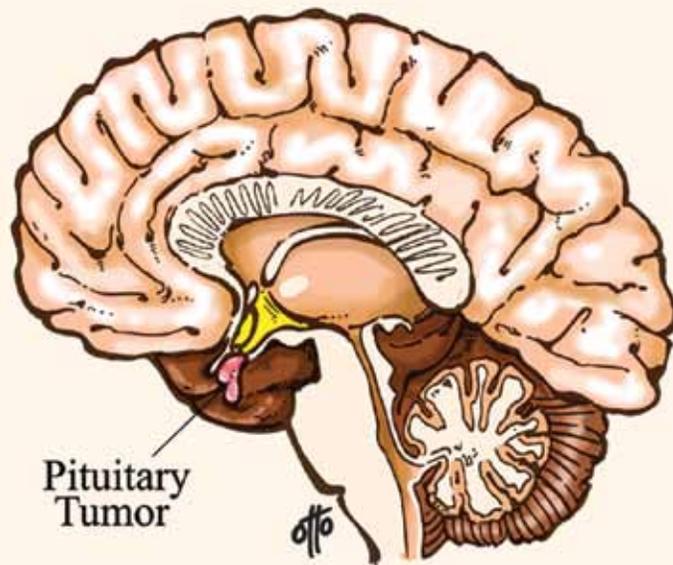
There are many different endocrine disorders that impact various parts of the body⁴. Diabetes, the most common endocrine disorder, affects more than 25 million people aged 20 and older in the United States and is associated with long-term complications that affect almost every part of the body^{5,6}. **Cushing's disease**, a less well-known disorder of the endocrine system, affects a much smaller portion of the US population but can also have enduring effects on the body^{2,7}.

Cushing's disease is caused by a tumor on the pituitary gland, an endocrine gland positioned at the base of the brain⁸. Because this disease affects only a small portion of the global population and presents with a constellation of symptoms easily mistaken for other diseases when looked at individually and not taken as a whole, it can be difficult to recognize and often takes years for patients to receive a correct diagnosis^{8,9}.

What is Cushing's disease?

Before defining Cushing's disease, it is first necessary to understand a disease called Cushing's syndrome. Cushing's syndrome is an endocrine disorder caused by excessive cortisol (hypercortisolism), a vital hormone that regulates metabolism, maintains cardiovascular function and helps the body respond to stress³. Some people have Cushing's syndrome because they are regularly exposed to medicine(s) that continually add too much

Cushing's disease is an endocrine disorder caused by excess cortisol in the body due to the presence of a non-cancerous pituitary tumor^{3,8}.



cortisol to the body (referred to as an exogenous – outside the body – cause)¹⁰. Others have Cushing's syndrome due to an internal trigger that causes the adrenal glands to overproduce cortisol – (referred to as an endogenous – inside the body – cause)¹¹.

Cushing's disease is the most common form of endogenous Cushing's syndrome, accounting for about 70% of all cases^{8,10}. It is caused when excessive cortisol production is triggered by a non-cancerous adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma (tumor)⁸.

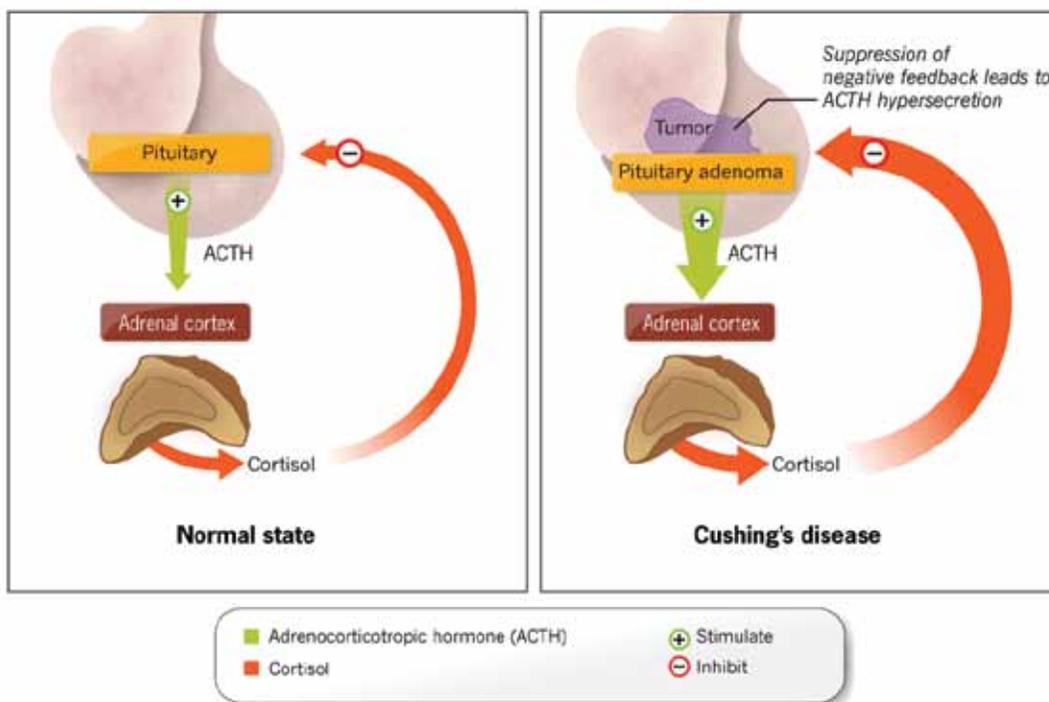
Mechanism of Disease

In a body not affected by Cushing's disease, the adrenal gland secretes the hormone cortisol, commonly known to prompt the "fight or flight" reaction, in response to stimulation by ACTH, which is produced by the pituitary gland^{14,15}. ACTH is secreted in response to two other hormones, corticotropin releasing hormone (CRH) and vasopressin, both of which are secreted from the hypothalamus (a part of the forebrain). This mechanism is controlled by a negative feedback loop, with cortisol driving the cycle by influencing both CRH and vasopressin in the hypothalamus, and ACTH in the pituitary¹⁵.

In healthy individuals, cortisol is secreted in a circadian rhythm. Levels are highest in the morning (7:00-9:00 AM) and gradually decline throughout the day, beginning to rise again at approximately 3:00 AM^{11,17}. The presence

of ACTH-secreting pituitary tumors results in the loss of the negative feedback of cortisol to both the hypothalamus and pituitary. This finally results in continuous cortisol secretion by the adrenal gland and subsequent loss of circadian rhythm^{18,19}. This condition is clinically referred to as Cushing's disease⁸.

The presence of ACTH-secreting pituitary tumors results in the loss of the negative feedback of cortisol to both the hypothalamus and pituitary.



The hypothalamus sends CRH to the pituitary, which responds by secreting ACTH. ACTH then causes the adrenals to release cortisol into the bloodstream^{3,15,16}.

Clinical Manifestations

The clinical manifestations of Cushing's disease caused by hypercortisolism are broad and diverse but can be grouped into three main categories that include, but are not limited to:

Physical

- Weight gain³
- Central obesity (abdomen that sticks out with thin arms and legs)³
- Moon face (round, red and full)⁸
- Purple striae (stretch marks) on the abdomen, thighs and breasts³
- Buffalo hump (collection of fat on the back of the neck)³
- Acne or skin infections⁸
- Easy bruising⁸
- Hirsutism (excessive and unusual hair growth in females)³
- Muscle weakness³
- Headache⁸

Hormonal

- Depression, anxiety, irritability³
- Impotence³
- Osteoporosis²⁰
- Irregular or absent menstruation³

Metabolic/Cardiovascular

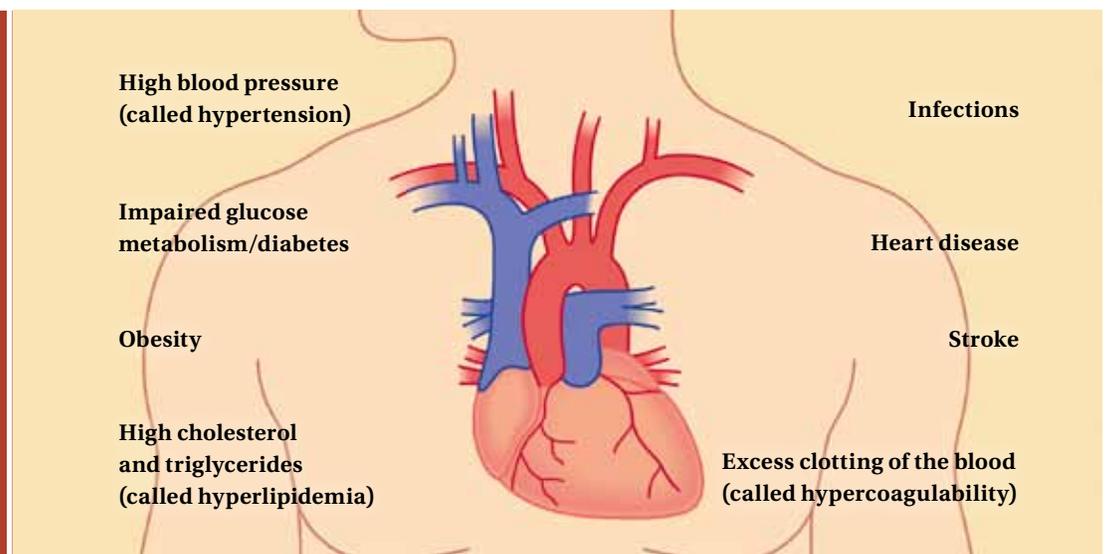
- Cardiovascular disease¹²
- Severe fatigue³
- Metabolic disturbance³
- Hypertension (high blood pressure)³
- Increased thirst and urination³

Additional clinical manifestations include backaches, swelling, feeling irritable, appetite changes, memory problems, sleeping problems, repeated infections, hair loss and wounds healing too slowly. Many of the signs and symptoms of Cushing's disease can be caused by more common health conditions, so it is important for patients to accurately convey symptoms they are experiencing to a healthcare professional¹¹.

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Complications

There are many serious health complications associated with Cushing's disease, including: osteoporosis and subsequently fractures, diabetes, high blood pressure (hypertension), lipid disorders, infections, kidney stones and blood clotting disorders^{8,15,20}. Cushing's disease may also reduce thyroid function (hypothyroidism) and cause infertility^{6,20}.



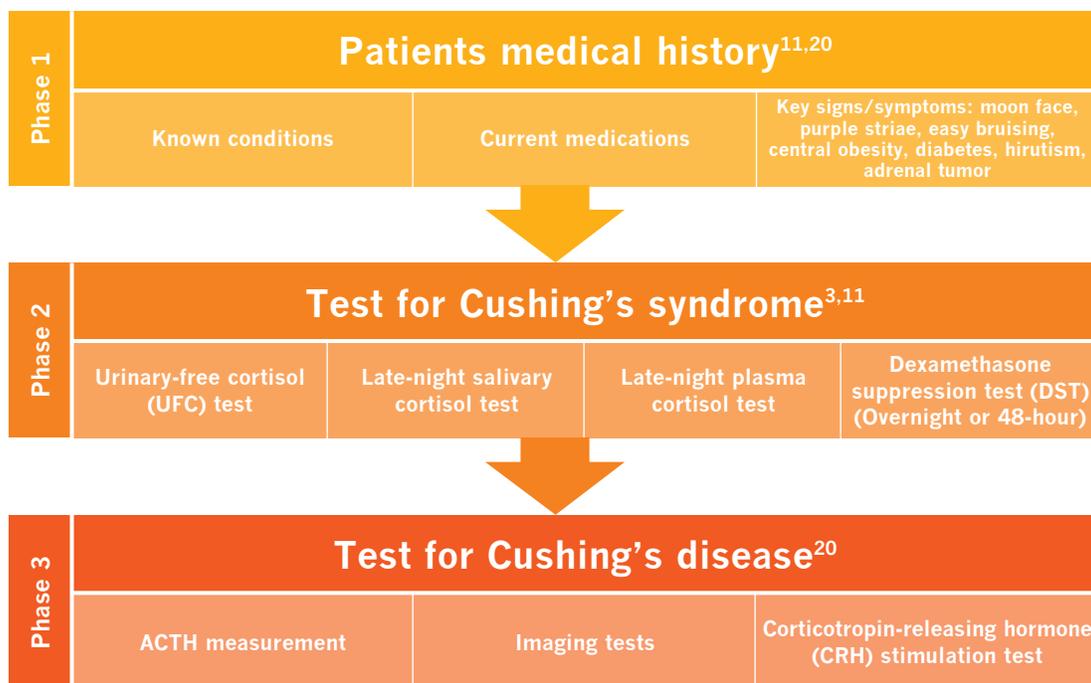
Diagnosing Cushing's Disease

Diagnosing Cushing's disease is challenging for several reasons. The most difficult step is recognizing Cushing's syndrome, which must be done first. Once Cushing's syndrome has been identified, doctors can run a number of tests to confirm the cause of excess cortisol, which will determine if the patient has Cushing's syndrome or Cushing's disease¹¹.

disease can be six years from the time they notice symptoms. To accurately confirm a suspected diagnosis of Cushing's disease, there are a variety of tests a doctor will employ⁹.

Diagnosis generally happens in three phases, with patients often visiting several medical specialists.

Phase 1: The first step to diagnose Cushing's syndrome is for a patient to provide the doctor with a complete medical history, including any known conditions and current medica-



As noted earlier, many of the signs and symptoms of Cushing's disease are indistinguishable from other health conditions when looked at individually. Because of this, healthcare professionals may delay testing for Cushing's disease in order to eliminate more common conditions such as depression or other psychiatric disorders, alcoholism, weight problems caused by improper diet and/or exercise, diabetes or polycystic ovarian syndrome¹¹. Additionally, clinical manifestations of the disease do not present the same way in all people affected – people may have all or some of the symptoms at any given time⁸.

As a result, the process for diagnosing Cushing's disease is often lengthy. The time to diagnosis for a patient with Cushing's

tions¹¹. Many medicines used for allergies, respiratory problems and skin problems contain glucocorticoid medicines, which may cause similar signs and symptoms associated with exogenous Cushing's syndrome^{43,10,20}.

After evaluating this information, doctors may test for hypercortisolism if any of the following characteristics and/or symptoms develop:

- Moon face⁸
- Purple striae³
- Easy bruising⁸
- Central obesity³
- Diabetes³
- Adrenal tumor found during an ultrasound or similar procedure¹¹

To confirm a diagnosis of Cushing’s syndrome, a doctor can employ several types of tests to measure the level of cortisol in the body.

Phase 2: To confirm a diagnosis of Cushing’s syndrome, a doctor can employ several types of tests to measure the level of cortisol in the body. These tests should only be done when exogenous hypercortisolism is ruled out¹¹.

Specifically, there are four tests that are used to identify Cushing’s syndrome. These tests measure the amount of cortisol in samples of urine, blood, or saliva to determine how much cortisol is circulating in the body. If the tests show that the level of cortisol is too high, a diagnosis of Cushing’s syndrome can be confirmed¹¹.

Tests for Cushing’s Syndrome

Urine-free cortisol (UFC) test	
What it measures:	Cortisol in urine ²⁰
Why it’s used:	Almost all people with Cushing’s syndrome have high urine cortisol levels. This test only measures the type of cortisol that causes Cushing’s syndrome, called, “circulating, free cortisol ¹¹ ”
How it’s done:	Urine samples are collected at every opportunity throughout a 24-hour period and provided to a lab for testing ¹¹
Late-night salivary cortisol test	
What it measures:	Cortisol in saliva ²⁰
Why it’s used:	Cushing’s syndrome will cause elevated levels of cortisol in saliva at night, when levels are usually lowest ¹¹
How it’s done:	A saliva sample is obtained between 11:00 PM and 12:00 AM on two different nights and provided to a lab for testing. The timing of the collection should be adjusted to the time of sleeping if your bedtime is usually long after midnight ²¹
Late-night plasma cortisol test	
What it measures:	Cortisol in the blood ²⁰
Why it’s used:	Cushing’s syndrome will cause elevated levels of cortisol in the blood at night, when levels are usually lowest ²⁰
How it’s done:	A blood sample is obtained at night while the patient is sleeping in a hospital and provided to a lab for testing ²⁰
Dexamethasone suppression test (DST)	
What it measures:	Cortisol in the blood ²⁰
Why it’s used:	Normally, low doses of the corticosteroid dexamethasone will reduce cortisol levels but in a person with Cushing’s syndrome, these doses will not have an effect ¹⁰
How it’s done:	There are two DST test options; overnight and 48-hour. Once a sample is collected, a lab test is done to determine if cortisol levels were reduced ¹⁰ <i>Overnight DST (short test):</i> A 1-mg dose of dexamethasone is taken between 11:00 PM and 12:00 AM. The next morning a blood sample is taken between 8:00 AM and 9:00 AM ^{10,20} <i>48-hour DST (long test):</i> A 0.5-mg dose of dexamethasone is taken every 6 hours for 48 hours. Six hours following the last dose, a blood sample is taken at the doctor’s office ^{10,20}

Tests for Cushing's disease

ACTH measurement	
What it measures:	ACTH in the blood ²⁰
Why it's used:	To determine tumor location Normal to high ACTH levels may be indicative of a tumor in the pituitary gland and would confirm a diagnosis of Cushing's disease ^{8,20}
How it's done:	A blood sample is collected and provided to a lab for testing ²⁰
Imaging tests	
What it measures:	Location/presence of a tumor ²⁰
How it's done:	If ACTH levels are high, a magnetic resonance imaging (MRI) or computerized tomography (CT) test will be conducted to confirm the location and presence of a tumor in the pituitary gland ²⁰
Corticotropin-releasing hormone (CRH) stimulation test	
What it measures:	How CRH changes ACTH and cortisol levels ²⁰
Why it's used:	To confirm the presence of a pituitary tumor if ACTH measurement or imaging tests are inconclusive ³
How it's done:	Blood tests are used to measure ACTH and cortisol levels, then a CRH intravenous injection is given, after which blood tests are repeated several times to recheck ACTH levels. If these levels have increased, this helps to confirm the presence of a pituitary tumor and therefore a diagnosis of Cushing's disease ²⁰
Inferior petrosal sinus sampling	
What it measures:	ACTH in the blood from the inferior petrosal sinuses ²²
Why it's used:	To confirm the presence of a pituitary tumor if ACTH measurement or imaging tests are inconclusive ²²
How it's done:	Tests are used to measure ACTH levels in blood taken from the inferior petrosal sinus, which collects venous drainage from the pituitary gland ²²

Phase 3: If a diagnosis of Cushing's syndrome is confirmed, additional tests will be conducted to determine why the patient's body is producing too much cortisol and confirm if it's due to a pituitary tumor (Cushing's disease) or a different form of Cushing's syndrome¹⁰.

If surgery is not appropriate or effective, other management options include radiation to the pituitary gland, stereotactic radiosurgery or gamma knife radiation, and in extreme cases full removal of the adrenal glands, called an adrenalectomy³.

Disease Management Guidelines

The first line and most common management approach for Cushing's disease is surgical removal of the tumor, known as selective adenomectomy, usually performed via trans-sphenoidal route³. Using a microscope and small instruments, a surgeon approaches the pituitary gland through a nostril or an opening made below the upper lip.

Selected Resources

This section provides an overview on where to obtain credible information regarding Cushing's disease.

Professional Medical Organizations

- Addison & Cushing International Federation: <http://www.nvacp.nl/>
- American Association of Clinical Endocrinologists: <https://www.aace.com/>
- European Neuroendocrine Association: <http://www.eneassoc.org/>
- European Organisation for Rare Diseases: <http://www.eurordis.org/>
- European Register on Cushing's Syndrome: <http://www.lohmann-birkner.de/ercusyn/>
- European Society for Immunodeficiencies: <http://www.esid.org/>
- European Society of Endocrinology: <http://www.euro-endo.org/>
- Instituto de Investigación de Enfermedades Raras: <http://iier.isciii.es/er/>
- The Endocrine Society: <http://www.endo-society.org/>

Patient and Disease-Related Organizations

- Canadian Organization for Rare Disorders (CA): <http://raredisorders.ca/>
- Cushing's Help and Support (USA): <http://www.cushings-help.com/>
- Cushing's Support and Research Foundation (USA): <http://www.csrff.net/>
- Cushing's Understanding Support & Help Organization (USA): <http://www.cush.org/>
- The Hormone Foundation (USA): <http://www.hormone.org/>
- The Pituitary Foundation (UK): <http://www.pituitary.org.uk/>
- National Organization for Rare Disorders (USA): <http://www.rarediseases.org/>
- Netzwerk Hypophysen- und Nebennierenerkrankungen e.V. (German Pituitary and Adrenal Network) (DE): <http://www.glandula-online.de/>
- Pituitary Network Association (USA): <http://www.pituitary.org/>

Peer-Reviewed Medical Journals

Novartis does not endorse and is not responsible for the content of any of the listed resources. Please note that this is not an exhaustive list of resources.

American Journal of Physiology:

Endocrinology and Metabolism:

Publishes original, mechanistic studies on the physiology of endocrine and metabolic systems. (<http://ajpendo.physiology.org/>)

Clinical Endocrinology:

Official clinical journal of the Society for Endocrinology. Publishes papers and reviews, which focus on the clinical aspects of endocrinology, including the clinical application of molecular endocrinology. (<http://www.wiley.com/bw/journal.asp?ref=0300-0664/>)

Endocrine Practice:

Official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. Published to enhance the healthcare of patients with endocrine diseases through continuing education of practicing endocrinologists. (<http://aace.metapress.com/home/main.mpx/>)

Endocrine Reviews: Publishes comprehensive, authoritative and timely review articles balancing both experimental and clinical endocrinology themes and crystallizing the most significant clinical experience and current research in endocrinology and related areas. (<http://edrv.endojournals.org/>)

Endocrinology: Publishes biomedical research ranging from subcellular mechanisms to whole animal physiology. Topics include bone and mineral, growth factors, reproductive/steroids, neuroendocrinology/signal transduction, thyroid and physiology. (<http://endo.endojournals.org/>)

Growth Hormone & IGF Research: Publishes research on the regulation of growth and metabolism in humans, animals, tissues and cells. (<http://www.sciencedirect.com/science/journal/aip/10966374/>)

Journal of Clinical Endocrinology &

Metabolism: Publishes endocrine clinical research and clinical practice reviews to provide in-depth coverage of new developments of the diagnosis and treatment of endocrine

and metabolic disorders. Regular features of special interest include clinical trials, clinical reviews, clinical practice guidelines, case seminars and controversies in clinical endocrinology, as well as original reports of endocrine and metabolic research.

(<http://jcem.endojournals.org/>)

Molecular and Cellular Endocrinology:

Publishes full-length original research papers, invited reviews and book reviews related to biochemical and molecular aspects of endocrine research and cell regulation.

(<http://www.elsevier.com/locate/mce>)

Glossary

Key terms for use in interpreting information and developing stories on Cushing's disease.

Adenoma: a non-cancerous tumor of a glandular structure or of glandular origin²³.

Adenomectomy: is the surgical removal of the tumor by a surgeon who approaches the pituitary gland through a nostril or an opening made below the upper lip. This process is the first line and most common disease management approach for Cushing's disease³.

Adrenalectomy: is the surgical removal of the adrenal glands, which may occur if surgery or other disease management options are not appropriate or effective. It is also known as a bilateral adrenalectomy³.

Adrenal glands: either of a pair of complex endocrine organs near the anterior medial border of the kidney consisting of a mesodermal cortex that produces glucocorticoid, mineralocorticoid and androgenic hormones, and an ectodermal medulla that produces epinephrine and norepinephrine²³.

Adrenocorticotropic hormone (ACTH): a protein hormone of the anterior lobe of the pituitary gland that stimulates the adrenal cortex²³.

Cardiovascular: of, relating to, or involving the heart and blood vessels²³.

Cholesterol: a steroid alcohol present in animal cells and body fluids that regulates membrane fluidity, functions as a precursor molecule in various metabolic pathways; as a constituent of LDL, it may cause arteriosclerosis²³.

Corticotropin-releasing hormone (CRH): a substance secreted by the median eminence of the hypothalamus that regulates the release of ACTH by the anterior lobe of the pituitary gland²³.

Cortisol: a glucocorticoid produced by the adrenal cortex upon stimulation by ACTH that mediates various metabolic processes (such as gluconeogenesis), has anti-inflammatory and immunosuppressive properties, and whose levels in the blood may become elevated in response to physical or psychological stress²³.

CT (CAT) scan: a sectional view of the body constructed by computed tomography²³.

Cushing's disease: Cushing's syndrome caused by excessive cortisol production triggered by a non-cancerous ACTH-secreting pituitary tumor²³.

Cushing syndrome: is an endocrine disorder caused by excessive cortisol, a vital hormone that regulates metabolism, maintains cardiovascular function and helps the body respond to stress⁴.

Dexamethasone: a synthetic glucocorticoid also used in the form of an acetate or sodium phosphate, especially as an anti-inflammatory and antiallergic agent²³.

Diabetes: A chronic, progressive disease in which the body does not produce or properly use insulin⁵.

Ectopic: occurring in an abnormal position²³.

Endocrinologist: a medical professional who studies the glands and hormones of the body and their related disorders²³.

Endogenous: caused by factors within the body or mind or arising from internal structural or functional causes. Cushing's disease is an endogenous disease caused by a tumor on the pituitary gland²³.

Exogenous: caused by factors (such as food or a traumatic factor) or an agent (such as a disease-producing organism) from outside the organism or system²³.

Glucocorticoid: any of a group of corticosteroids (such as cortisol or dexamethasone) that are involved in carbohydrate, protein and fat metabolism; that tend to increase liver glycogen and blood sugar by increasing gluconeogenesis; and that are used widely in medicine (such as in the alleviation of the symptoms of rheumatoid arthritis)²³.

High Blood Pressure: High blood pressure means that the body's blood flow is causing too much pressure against artery walls²³.

Hirsutism: excessive growth of facial/body hair of normal or abnormal distribution²³.

Hormone: product of living cells that circulates in body fluids (such as blood) or sap and produces a specific, often stimulatory, effect on the activity of cells usually remote from a hormone's point of origin²³.

Hypercortisolism: a state of overproduction of cortisol in the body, often a result of tumor(s) in the adrenal or pituitary glands²³.

Hypothyroidism: deficient activity of the thyroid gland; also, a resultant bodily condition characterized by lowered metabolic rate and general loss of vigor²³.

Infertility: not fertile; incapable of or unsuccessful in achieving pregnancy over a considerable period of time (such as a year) in spite of determined attempts by heterosexual intercourse without contraception²³.

Magnetic resonance imaging (MRI): a non-invasive diagnostic technique that produces computerized images of internal body tissues and is based on nuclear magnetic resonance of atoms within the body induced by the application of radio waves²³.

Malignant: tending to produce death or deterioration; especially tending to infiltrate, metastasize, and terminate fatally²³.

Metabolic disturbance: A combination of problems that includes excess weight around the waist, high blood pressure, abnormal levels of cholesterol and triglycerides in the blood and insulin resistance³.

Obesity: A high body mass index (that is, the amount of fat in the body). Central obesity is when high BMI occurs in the middle part of the body (around the abdominal area), while arms and legs remain thin²⁰.

Osteoporosis: a condition that especially affects older women and is characterized by decrease in bone mass with decreased density and enlargement of bone spaces, producing porosity and brittleness²³.

Pituitary gland: a small, vascular endocrine organ that is attached to the brainstem. The pituitary gland has several parts associated with various hormones that directly or indirectly affect most basic bodily functions and include substances that exert a controlling and regulating influence on other endocrine organs by controlling growth and development or modifying the contraction of smooth muscle, renal function and reproduction²³.

Steroid hormone: any of numerous hormones (such as estrogen, testosterone, cortisone and aldosterone) having the characteristic ring structure of steroids and formed in the body from cholesterol²³.

Triglycerides: any of a group of fats that are formed from one molecule of glycerol and three molecules of one or more fatty acids; they are widespread in fat tissue²³.

Tumor: an abnormal non-cancerous or malignant new growth of tissue that possesses no physiologic function and arises from uncontrolled usually rapid cellular proliferation²³.

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