

CORTISONE

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1. Core Definition and Classification

Cortisone is a naturally occurring or synthetically manufactured corticosteroid hormone, belonging to the broader class of glucocorticoids. Chemically, it is known as 17-hydroxy-11-dehydrocorticosterone. Its physiological role is inextricably linked to the functioning of the adrenal cortex, where it is produced as part of the body's essential regulatory systems. Unlike many hormones that exhibit immediate biological activity upon secretion, Cortisone is notable because it is physiologically inactive in its native state. This means that while it circulates throughout the body, it must undergo a crucial metabolic transformation, primarily within the liver and other specific peripheral tissues, before it can exert its characteristic hormonal effects. This status as a prodrug is a defining feature of Cortisone, distinguishing it from its highly active derivative, **cortisol** (hydrocortisone).

The classification of Cortisone within the glucocorticoid family highlights its primary function: regulating metabolism and managing the body's inflammatory response. Glucocorticoids are critical for maintaining homeostasis, influencing processes such as glucose metabolism, protein catabolism, and lipolysis. Therapeutically, synthetic Cortisone is categorized as a short-acting glucocorticoid, often employed in replacement therapy for patients suffering from adrenal insufficiency. Its structure is closely related to cortisol, differing only by the presence of a ketone group at the C-11 position instead of a hydroxyl group. This subtle chemical difference dictates its inactivity until enzymatic conversion takes place, which provides the body with a complex mechanism for localized hormonal control and activation.

The initial identification and isolation of Cortisone were groundbreaking moments in endocrinology and pharmacology, setting the stage for the development of an entire class of anti-inflammatory drugs. While often overshadowed in modern clinical practice by more potent or longer-acting synthetic glucocorticoids (like prednisone or dexamethasone), Cortisone maintains historical and biochemical importance. Its existence as an intermediate metabolic compound emphasizes the complexity of adrenal steroidogenesis and the intricate enzymatic pathways necessary to produce the final, biologically potent hormones required for survival and stress response.

2. Biosynthesis and Metabolic Activation

The natural synthesis of **Cortisone** begins in the adrenal cortex, specifically within the zona fasciculata. This process is tightly regulated by the Hypothalamic-Pituitary-Adrenal (HPA) axis, where the release of adrenocorticotrophic hormone (ACTH) from the pituitary gland stimulates the

adrenal glands to produce corticosteroids. Within the adrenal glands, Cortisone is an important, though less active, precursor and metabolite generated alongside cortisol. However, the true significance of Cortisone lies in its role as a reservoir for the active hormone. It is fundamentally a storage form that can be quickly mobilized and converted into cortisol when and where the body requires glucocorticoid activity.

The transformation of inactive Cortisone into active **cortisol** is catalyzed by the enzyme 11-beta-hydroxysteroid dehydrogenase type 1 (11 β -HSD1). This enzyme is expressed in key metabolic tissues, including the liver, adipose tissue, lung, and central nervous system. The reaction involves the reduction of the ketone group at the C-11 position, turning the molecule into cortisol. The liver is particularly efficient at this conversion, acting as the primary site for activating administered Cortisone into its therapeutically useful form. Conversely, the related enzyme, 11-beta-hydroxysteroid dehydrogenase type 2 (11 β -HSD2), performs the opposite function, converting active cortisol back into inactive cortisone, particularly in mineralocorticoid target tissues (like the kidney) to protect the mineralocorticoid receptor from cortisol binding.

This complex enzymatic interplay of 11 β -HSD1 and 11 β -HSD2 represents a vital prereceptor regulatory mechanism. It allows the body to control the local availability of active glucocorticoids, protecting sensitive tissues from excessive exposure while ensuring adequate levels in others. For example, when Cortisone is administered as a drug, its efficacy relies entirely on the successful function of 11 β -HSD1 in the target organs. If an individual has impaired liver function or enzyme deficiency, the conversion process--and thus the therapeutic effect--may be significantly diminished. This reliance on metabolic activation means that Cortisone is effectively a prodrug for cortisol, necessitating its initial passage through the liver to become biologically functional.

3. Therapeutic Applications and Indications

Historically and clinically, **Cortisone** has played a crucial role in treating a variety of conditions, primarily those involving inflammation, immune dysfunction, and adrenal insufficiency. The initial therapeutic breakthrough, for which it gained worldwide recognition, was its profound efficacy in treating severe inflammatory disorders, most notably **rheumatoid arthritis**. By suppressing the immune response and inhibiting the production of inflammatory mediators (such as prostaglandins and leukotrienes), Cortisone--once converted to cortisol--can dramatically reduce pain, swelling, and joint damage associated with chronic inflammatory diseases.

A primary indication for the use of Cortisone and its derivatives is in corticosteroid replacement therapy. Patients suffering from conditions that lead to inadequate natural production of glucocorticoids, such as **Addison's disease** (primary adrenal insufficiency) or secondary adrenal insufficiency due to pituitary dysfunction, require exogenous corticosteroid administration. The source content notes that Cortisone is utilized remedially to regulate illnesses in which there is a

lack of corticosteroid. While cortisol (hydrocortisone) is often the preferred agent due to its immediate activity, oral Cortisone acetate can be used as a replacement drug, leveraging its slow and steady conversion in the liver to provide sustained physiological levels of cortisol throughout the day.

Furthermore, Cortisone is used to treat localized inflammatory processes, often administered via injection. The source material specifically mentions that Cortisone is sometimes injected into the skin to lessen the appearance of pimples. This highlights its potent anti-inflammatory properties utilized in dermatology. Local injections are employed across various medical fields to manage conditions like bursitis, tenosynovitis, and certain types of joint pain, delivering a high concentration of the glucocorticoid directly to the site of inflammation while minimizing systemic side effects. The mechanism of action involves stabilizing lysosomal membranes, decreasing capillary permeability, and inhibiting leukocyte migration to the inflamed area.

4. Historical Significance and Discovery

The history of **Cortisone** is intrinsically linked to one of the most significant pharmacological discoveries of the 20th century. Its isolation and subsequent clinical application led to the 1950 Nobel Prize in Physiology or Medicine, awarded jointly to Edward Calvin Kendall, Tadeus Reichstein, and Philip Showalter Hench. Kendall and Reichstein were pivotal in isolating and identifying various compounds from the adrenal cortex, collectively known as steroids E, F, A, B, and S, during the 1930s and 1940s. Compound E, which was later named Cortisone, proved to be particularly challenging to synthesize in large quantities, a bottleneck eventually overcome through chemical synthesis from bile acids.

The breakthrough in clinical use came through the work of Philip S. Hench, a rheumatologist at the Mayo Clinic. In 1948, Hench successfully used Cortisone to treat patients suffering from debilitating rheumatoid arthritis. The results were dramatic; patients who had been severely incapacitated experienced rapid, sometimes seemingly miraculous, relief from pain and stiffness. This demonstration of Cortisone's powerful anti-inflammatory effects revolutionized the treatment of chronic diseases and established the profound therapeutic potential of glucocorticoids.

The initial enthusiasm for Cortisone was immense, signaling a new era in medicine where severe inflammatory and autoimmune diseases could finally be managed effectively. Although initial supplies were extremely limited and expensive, the subsequent development of synthetic pathways ensured wider availability. The discovery spurred massive research efforts globally, leading not only to structural modifications of Cortisone to create drugs with improved potency and half-lives (e.g., prednisone, prednisolone) but also to a deeper understanding of the entire class of steroid hormones and their interaction with the human endocrine system.

5. Pharmacokinetics and Administration

When administered orally, **Cortisone** is typically supplied as **Cortisone acetate**. This preparation is readily absorbed through the gastrointestinal tract. However, owing to its nature as a prodrug, it lacks significant activity until it undergoes first-pass metabolism in the liver. This hepatic conversion process, mediated by the 11β -HSD1 enzyme, transforms Cortisone into its active form, cortisol. The rate and extent of this conversion are critical factors determining the drug's therapeutic efficacy and require careful dosage adjustment, especially in patients with compromised liver function.

The half-life of Cortisone is relatively short, usually placing it within the category of short-acting glucocorticoids, similar to cortisol itself. Following conversion, the active cortisol circulates bound to plasma proteins, primarily corticosteroid-binding globulin (CBG) and albumin. Only the unbound fraction is biologically active, capable of diffusing into target cells and binding to intracellular glucocorticoid receptors (GRs). This binding modulates gene transcription, leading to the synthesis or repression of specific proteins that mediate the drug's anti-inflammatory and metabolic effects.

Routes of administration vary based on the clinical goal. For systemic replacement therapy or generalized immunosuppression, oral administration is standard. For localized inflammation, such as musculoskeletal conditions or dermatological issues, Cortisone is often delivered via intramuscular or intra-articular injection (e.g., injection into a joint space). Localized injection bypasses systemic circulation for a concentrated effect at the injury site, reducing the likelihood of widespread side effects, though the risk of local tissue damage remains a consideration. The metabolism of both Cortisone and cortisol culminates in their inactivation in the liver, followed by conjugation with sulfates or glucuronides, rendering them water-soluble for renal excretion.

6. Adverse Effects and Management

While therapeutically indispensable, long-term or high-dose systemic administration of **Cortisone**, like all glucocorticoids, is associated with a wide spectrum of significant adverse effects due to its widespread influence on metabolic and immune processes. These effects stem from the sustained hypercortisolism mimicking endogenous Cushing's syndrome. Common side effects include metabolic disturbances such as hyperglycemia (steroid-induced diabetes), increased appetite leading to weight gain, and redistribution of fat deposits resulting in characteristic central obesity and "moon face."

Furthermore, Cortisone use profoundly affects the musculoskeletal system, contributing to muscle wasting (myopathy) and osteoporosis, particularly affecting the axial skeleton, due to inhibited calcium absorption and increased bone resorption. Immunologically, chronic use leads to immunosuppression, increasing susceptibility to infections and masking their clinical signs. In the skin, glucocorticoids can cause thinning, easy bruising, and impaired wound healing.

Neuropsychiatric effects are also common, ranging from mood swings and insomnia to severe psychosis in susceptible individuals.

Perhaps the most critical risk associated with prolonged Cortisone therapy is the suppression of the natural HPA axis. Exogenous glucocorticoids signal the pituitary gland to reduce ACTH production, leading to atrophy of the adrenal cortex and the inability to produce endogenous cortisol. Abrupt cessation of the drug can therefore precipitate a life-threatening acute adrenal crisis, necessitating a mandatory, carefully managed tapering schedule to allow the HPA axis to gradually recover endogenous function.

7. Comparison with Cortisol and Prednisone

Understanding **Cortisone** requires differentiation from its chemically and clinically related counterparts, **cortisol** (hydrocortisone) and **prednisone**. The distinction between Cortisone and cortisol is primarily one of activity: cortisol is the biologically active molecule, whereas Cortisone is the inactive pro-drug that requires conversion via 11 β -HSD1. Clinically, hydrocortisone is often preferred for rapid-onset replacement therapy or intravenous administration in acute stress, whereas Cortisone acetate is generally used for maintenance therapy due to its gradual activation profile.

The comparison with prednisone highlights the evolution of steroid pharmacology. Prednisone is a synthetic glucocorticoid structurally modified from cortisone. Like cortisone, prednisone is also a pro-drug, requiring conversion in the liver (to prednisolone) to become active. However, prednisone possesses significantly greater anti-inflammatory potency (approximately four to five times that of cortisone/cortisol) and less mineralocorticoid activity, meaning it causes less salt and water retention. This improved potency and selectivity often make prednisone and prednisolone the preferred choices for managing severe inflammatory and autoimmune diseases in contemporary medicine.

In essence, Cortisone represents the foundational compound, demonstrating moderate anti-inflammatory power but relying entirely on endogenous enzymatic action. Cortisol is the natural end-product, balancing glucocorticoid and mineralocorticoid effects. Prednisone, and subsequent generations of steroids, represent pharmacological optimization, offering enhanced potency and reduced side-effect profiles in specific therapeutic contexts, thereby demonstrating the direct lineage of drug development initiated by the discovery and application of Cortisone.

Further Reading

[Corticosteroid - Wikipedia](#)

[Cortisol - Wikipedia](#)

[Hypothalamic-Pituitary-Adrenal \(HPA\) Axis - NCBI Bookshelf](#)

Cushing's Syndrome - National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
The Nobel Prize in Physiology or Medicine 1950 (Kendall, Reichstein, Hench)

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