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Discovery of the Wonder Drug: From Cows to Cortisone

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Featured Article: Hench PS, Kendall EC, Slocumb CH, Polley HF. The effects of the adrenal cortical hormone 17-hydroxy-11-dehydrocorticosterone (Compound E) on the acute phase of rheumatic fever; preliminary report. Mayo Clin Proc 1949;24:277–97.[2]

A passage in the *New Testament* describes a paralyzed man miraculously regaining the ability to stand and walk. In a small town in southeast Minnesota on the morning of September 21, 1948, a similar miracle began to unfold. A 29-year-old woman was hospitalized at the Mayo Clinic (Rochester, MN) for severe rheumatoid arthritis that caused debilitating joint immobility. She was injected with a small amount of an experimental new drug, at the time named Compound E, which was discovered and investigated in tandem by Edward C. Kendall and Philip S. Hench. Two days and 2 more injections later the patient could walk and left the hospital to enjoy a 3-hour shopping spree. Just 2 short years later Kendall and Hench shared the Nobel Prize in Physiology or Medicine with Tadeus Reichstein, a Swiss scientist who independently isolated hormones of the adrenal cortex *(1)*. The famous Compound E is known today as cortisone.

The independent physiologic and biochemical discovery of cortisone began in 1929 at the Mayo Clinic with Hench, a rheumatologist, and Kendall, a biochemist. On April 1, 1929, Hench treated a patient with rheumatoid arthritis whose symptoms mysteriously disappeared upon an acute affliction with jaundice. Hench further observed an improvement in patients' rheumatic symptoms during pregnancy or following a recent surgery, leading him to hypothesize that certain medical conditions induced release of an antirheumatic substance. That same year Kendall committed his scientific efforts to isolating the chemical moieties associated with the adrenal glands, and regular shipments of adrenal tissues from Chicago slaughterhouses began arriving in his laboratory. In the 1930s Kendall succeeded in isolating 6 hormones from bovine adrenal glands, and identified each by a letter A through F. Four of the compounds had physiologic activity (A, B, E, and F). Compound A (11-dehydrocorticosterone) and Compound E (cortisone) were chosen for the initial studies owing to their structural simplicity.

In 1941, as American involvement in World War II evolved, rampant rumors emerged that German scientists had produced extracts of the adrenocorticosteroids that allowed Luftwaffe pilots to fly at high altitudes without becoming hypoxic. Research surrounding Compounds A and E was generously funded and studies were given the highest priority, taking precedence over drug development for penicillin and antimalarial medication. In 1942 a chemist from Merck and Company, Lewis Sarett, worked for 3 months in Kendall's laboratory and then returned to Merck with the goal of developing large-scale synthetic methods for Compounds A and E. Yields of the individual steroids were low, with only between 85 and 500 mg of cortisone isolated per 100 lb of adrenal glands *(2)*. Therefore, it was initially agreed that the use of steroids should be confined to studies with small animals and none should be used in the realm of clinical medicine *(3)*. Although synthetic Compound A demonstrated physiologic activity in animals, there were no beneficial effects in patients with Addison disease. As a result, attention was quickly diverted to the closely related Compound E, eventually leading to the historic 37-step synthesis from desoxycholic acid published by Sarett in 1946 *(4)*.

After the commencement of World War II, federal funding of adrenal steroid research quickly waned but Merck continued their collaboration with Kendall and Hench. In 1948 the first "miracle" patient was given Compound E and miraculous similar results were observed in 30 patients seen at the Mayo Clinic over the next 7 months. In 1949 Hench gave Compound E the generic name "cortisone," as an acronym for **corti**co**ster**o**ne**, to avoid confusion with vitamin E *(5)*.

Methods for quantifying glucocorticoids have evolved substantially since the first-generation cortisol assays, which involved solvent extraction, chromatographic separation, and group-specific chemical (colorimetric or fluorometric) detection methods. Cortisol RIAs rapidly gained popularity in the 1970s, almost 13 years after Berson and Yallow developed the first insu-

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[2] This paper has been cited 1048 times since publication.
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lin RIA *(6)*. Further developments arose with measurement of free cortisol in plasma, urine, and saliva along with analytically sensitive and specific quantification of glucocorticoids by using liquid chromatography–tandem mass spectrometry.

Sixty years after Kendall, Hench, and Reichstein were awarded the Nobel Prize for their groundbreaking research of adrenal steroids, cortisone and other structurally related synthetic analogs remain among the most widely prescribed medications, and steroid endocrinology remains an active area of research. The "triple-threat" combination of a basic scientist (Kendall), industrial/pharmaceutical chemist (Sarett), and physician (Hench) created the ultimate paradigm that continues to lead to rapid integration and implementation of tests and procedures successfully into clinical practice.

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