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From anatomy to therapy: the historical journey to cortisone

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Abstract

Objective. To comprehensively trace the historical journey of adrenal gland research from the first anatomical descriptions in the 16th century to the development and clinical application of cortisone in the mid-20th century.
Methods. This review examines key phases in adrenal gland research, including anatomical discoveries, microscopic studies, experimental physiology, biochemical advancements, and clinical applications. We analyzed primary historical sources, scientific papers, and medical records to construct a chronological narrative of adrenal gland understanding and cortisone development.
Results. The review highlights significant milestones, beginning with Bartolomeo Eustachio's 1564 discovery of the adrenal glands. It details the crucial microscopic phase, initiated by Moritz Nagel's 1836 study, which revealed the cortex-medulla distinction. Julius Arnold's 1866 description of the three-zone cortical structure and the identification of chromaffin cells are also discussed. The experimental physiology phase, featuring groundbreaking work by Thomas Addison and Charles-Édouard Brown-Séquard, established the vital role of the adrenal cortex. The biochemical phase, marked by the isolation and synthesis of cortisone, is examined in depth, with particular focus on the contributions of Edward Calvin Kendall, Tadeus Reichstein, and others. Finally, the clinical phase is detailed, emphasizing Philip Showalter Hench's revolutionary application of cortisone in rheumatoid arthritis treatment in 1948.
Conclusions. This historical journey demonstrates how advancements in anatomy, histology, physiology, and biochemistry synergistically contributed to our understanding of the adrenal glands. The development of cortisone, culminating with this collective knowledge, revolutionized the treatment of inflammatory diseases, marking a significant milestone in medical history and setting the stage for modern endocrinology and rheumatology.

Key words: adrenal gland research, history of medicine, rheumatology, cortisone.

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Introduction

The 1950 Nobel Prize in Physiology or Medicine, awarded to Tadeus Reichstein (1897-1996), Edward Calvin Kendall (1886-1972), and Philip Showalter Hench (1896-1965), marked a pivotal moment in medical history. The introduction of cortisone revolutionized the treatment of rheumatoid arthritis (RA), providing highly effective symptomatic therapy where none had previously existed (1). While it is now well established that cortisone does not cure RA, this was not immediately evident at the time of its discovery, when early reports spoke of "reversibility" and raised hopes for a definitive solution (2). The discovery of cortisone and its clinical application represented a significant advancement in rheumatology, leading to the development of more potent anti-inflammatory steroids with fewer side effects. These drugs are now used to treat various autoimmune, inflammatory, and allergic diseases and can be a life-saving medication in various medical emergencies, such as severe asthma attacks. The persistence of side effects and the emergence of steroid resistance remain major challenges in clinical practice. Epidemiological data suggest that at least 1% of the population is actually using chronic glucocorticoid therapy (3). While these adverse effects are often outweighed by the potent anti-inflammatory efficacy of glucocorticoids (including their life-saving role in hospitalized COVID-19 patients), they must not be overlooked. However, this medical milestone was built upon four centuries of adrenal gland research, spanning anatomy, histology, physiology, and clinical medicine, each discovery providing crucial groundwork for future breakthroughs. Understanding this historical progression is vital for modern medical research and practice. It illustrates how advances in seemingly unrelated fields, *e.g.*, microscopy, can drive progress in medical understanding and treatment. Moreover, it underscores the importance of basic anatomical and physiological research in paving the way for clinical breakthroughs. This review aims to trace the historical journey from Eustachio's first anatomical description of the adrenal glands in 1564 to the first clinical application of cortisone in 1948. By exploring this interdisciplinary path, we gain insight into the complex process of medical discovery and the foundations upon which modern treatments are built.

Possible earlier clues to adrenals in ancient primary sources

Previous studies have suggested potential early references to adrenal glands in ancient texts, including Leviticus, Homer's Iliad, and Galen's anatomical works (4-7). Italian anatomist Tommaso Petrucci (1648-1711) cited Leviticus (the third book of the Hebrew

Bible and the Christian Old Testament) to support the existence of adrenal glands (8, 9) (*Supplementary Table 1*). He used a Latin standard version (Douay-Rheims Bible) containing the term *renunculum* and equating it with *renes subcenturiatos*. This contrasts with the Authorized Version (1611), mentioning only "the two kidneys and the fat" (10) in several passages of the Pentateuch (the first five books of the Bible) (*Supplementary Table 1*). Most reviews, however, consider this biblical reference to the adrenals questionable (4-7).

Homer's Iliad (Book 21, lines 200-4) contains the word ἐπινεφρίδιος, meaning "upon the kidneys" (11) (*Supplementary Table 1*). Some interpret it as a reference to adrenal glands (12), while others suggest it only refers to perinephric fat (7).

Galen's Ἀνατομικὰς ἐγχειρήσεις, preserved partially in Arabic (13, 14), and translated in German and in English (15, 16), mentions "loose flesh" near the left kidney (15) (*Supplementary Table 1*). Max Simon interpreted "namely adrenal gland" (*Supplementary Table 1*) (15), which led Stephen W. Carmichael to claim Galen as the first to describe it (5). Miller and White are more cautious, suggesting Galen may have been the first to mention the adrenal (7).

These early references, while intriguing, remain subject to interpretation and debate in the context of adrenal gland history. The varying translations and interpretations of ancient texts highlight the challenges in definitively identifying early descriptions of the adrenal glands.

The early anatomical phase

Intriguing sketches by Leonardo da Vinci (1452-1519) might suggest that he depicted supra-renal structures (7). However, the first documented anatomical description of adrenal glands was provided in 1564 by Bartolomeo Eustachi (1500-1574), better known as Eustachio (17), in Opuscula Anatomica (18). Eustachio called them *glandulam reni incumbentem* (glands that lean on the kidney). This book did not contain illustrations of the newly discovered glands. The separate set of anatomical plates engraved in 1552, which Eustachio intended to print, was never published during his lifetime due to poor health and financial difficulties. *Tabula Prima* and *Tabula Secunda,* illustrating the adrenals, were only published posthumously in 1714 by Giovanni Maria Lancisi (1654-1720) (19) (Figure 1). The publication date of Eustachio's Opuscula Anatomica has been debated. Lancisi reported 1564 (19), accepted by Miller and White (5). Earlier authors indicated 1563 (4, 6, 20). The correct date is 1564, but a typographical error in Roman numerals on some copies' title pages led to confusion. A contemporary historical report uses 1563/64 to acknowledge this discrepancy (17).

The delay in the publication of plates contributed to the slow recognition of Eustachio's discovery of the adrenal glands. Archangelo Piccolomini (1525-1586) in Anatomicae Prelectiones mentioned the glands without crediting Eustachio (21). Moreover, André du Laurens (1558-1609) acknowledged him in Historia Anatomica Humani Corporis (22), noting the glands' inconsistent presence.

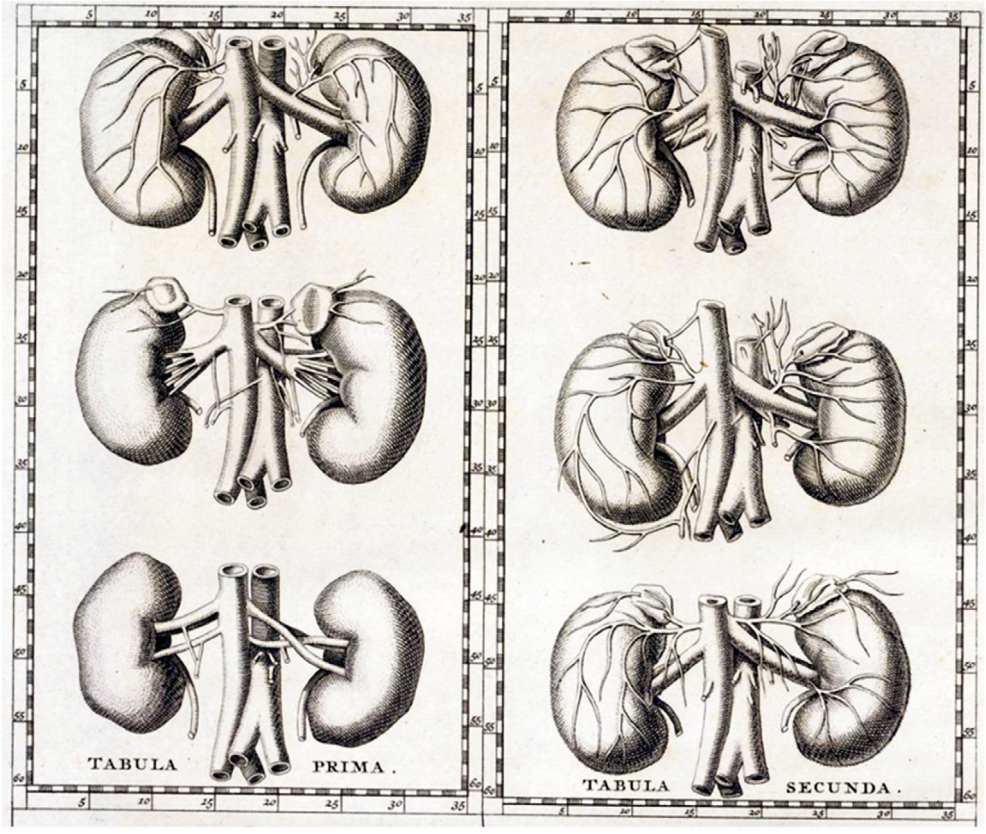

Figure 1. Bartolomeo Eustachio's discovery of the adrenal glands (17). Eustachio's *Tabula Prima* and *Secunda* showing *glandula incumbens reni*, according to Giovanni Maria Lancisi's Tabulae Anatomicae (17).

Following Eustachio's discovery, in 1611, Caspar Bartholin the Elder (1585-1629) named them *capsulas atrabilarias* (black bile-containing capsules) (23). Interestingly, Bartholin also mentioned the term *renes succenturiatos*, attributing it to Giulio Cesare Casseri (1545-1616). This early use of the term, before Casseri's own publication in 1627, is explained by Bartholin's personal acquaintance with Casseri during his studies in Padua. Casseri later provided the first published illustration of the glands, officially calling them *corpuscula reni incumbentia sive renes succenturiati* (24) (Figure 2A).

In Ouvres Anatomiques (1629), Jean Riolan the Elder (1539-1605) posthumously credited Eustachio for discovering a large gland above the kidney (25). This was likely added by translator Pierre Constant, as Riolan's earlier Latin edition only described the gland without mentioning Eustachio (26).

Jean Riolan the Younger (1580-1657) first reported in 1618 that the adrenal gland was more prominent in mature foetuses than in adults (27). He later reaffirmed this observation in 1649 (28). This surprising finding was further elaborated by Isbrand van Diemerbroeck (1609-1674) in 1679, who observed that in fetuses and children up to 6 months, the glands were close in size to the kidneys, but thereafter did not grow proportionally with the rest of the body (29). Neither of them illustrated their observations.

The first illustration of newborns' adrenal glands was published by Godefridus Bidloo (1649-1713) in 1685 (30) (Figure 3). Here, Bidloo indicated that the *renales glandulae* "appear larger than expected". Bidloo's image was reprinted by Jean-Jacques Manget (1652-1742) (31), who referred to neonatal adrenal glands as "very large". A debate on the adrenal glands' internal structure emerged in the 17th century. Thomas Bartolin (1616-1680), besides including in his anatomical textbook some anatomically detailed plates on adrenal glands (Figure 2B and C), suggested they were hollow, a statement he affirmed definitively in 1651 (32). This claim was contested by Riolan the Younger (26). Thomas Wharton (1614-1673) supported Bartholin's view in 1656 (33). Giovanni Battista Morgagni (1682-1771) later reported no excretory duct found in these glands (34). This led to classifying the adrenals as "ductless glands" alongside the spleen, thymus, and thyroid (35).

Wharton noted glands' rich innervation without illustration; it was later precisely depicted in the 19th century, respectively in 1839 and in 1891 (36, 37) (*Supplementary Figure 1*).

By the late 17th century, the glands were known by three names: *Renes succenturiati*, *Capsulae atrabilariae*, and *Glandulae ad nerveum plexum sitae*. In 1732, Jacob Benignus Winslow (1669-1760) proposed "Supra-renal Glands", which became widely adopted (38). The actual term "adrenal" was introduced by Richard Owen (1804-1892) in 1863 (39).

Adrenal function remained mysterious despite anatomical progress. In a *Discours sur l'usage des glandes rénales* pronounced on 25 August 1718 as Secretary of the Académie des Sciences de Bordeaux, Montesquieu (1689-1755) withheld prizes for a study on adrenal gland function, citing lack of evidence (40). A century later, Jean Vincent François Vaidy (1776-1830) still deemed functional hypotheses groundless (41).

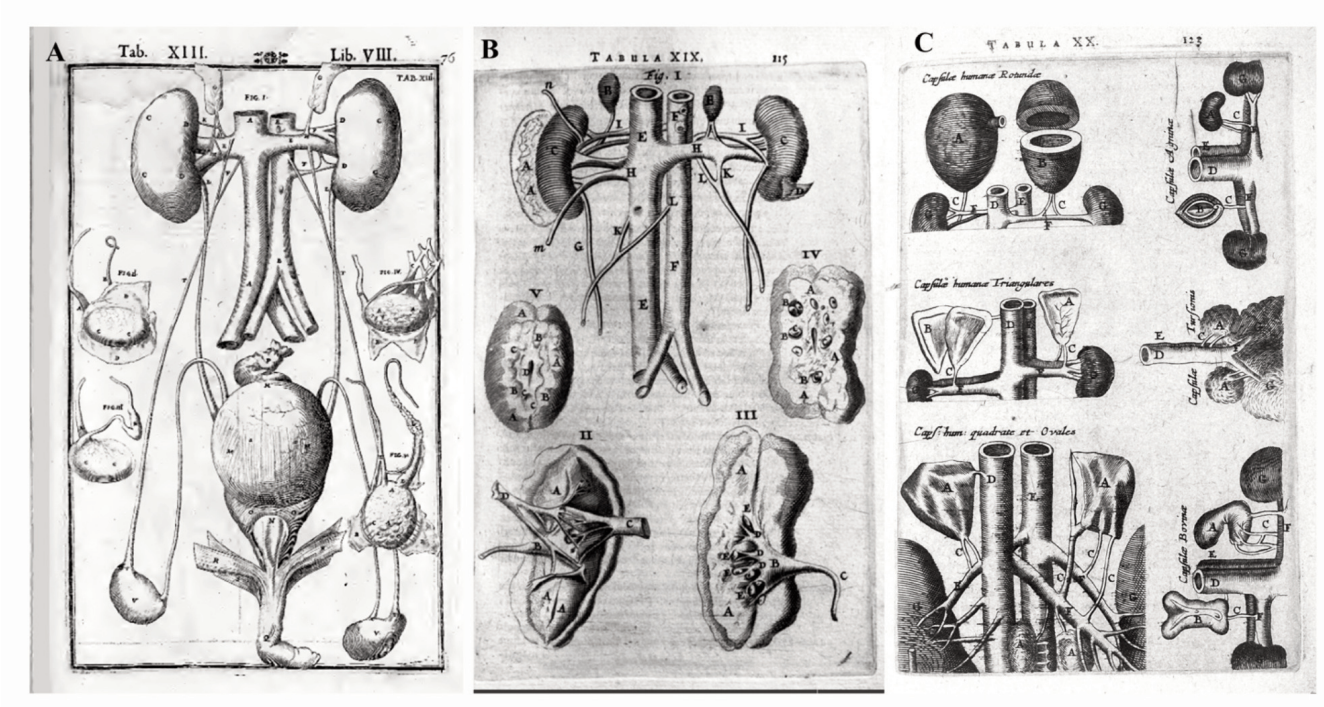

Figure 2. Anatomical plates of adrenal glands (22,3 0). **A**) Plate by Casseri GC (22), from T*abulae anatomicae. Corpuscula reni incumbentia sive Renes succenturiati* visible, labeled "B"; **B**) Tabula XIX by Bartholin T (30), from *Anatomia Reformata*. Caption: "*Tabula proponit renes… BB. Capsula atrabilaria, seu renes succenturiati*". Similar to Casseri's one; **C**) Tabula XX by Bartholin T (30). Caption: *"FIGURARUM EXPLICATIO. Capsulae atrabiliaris hominis, et aliorum animalium exhibentur. A. Capsula integra representat. B. Eadem dissectas, ut in conspectum veniant cavitates interiors diversa forma varias".*

The microscopic phase

Modern medicine was revolutionized by the introduction of the achromatic microscope in 1830 (42). Utilizing a Lister microscope borrowed from his teacher Johannes Peter Müller (1801-1858), Moritz Nagel (1801-1871) published the first microscopy study of a sheep adrenal in 1836, delineating the *Rindensubstanz* (cortical substance) and *Marksubstantz* (medullary substance) (43, 44). This discovery, anticipated in 1832 and guided by Müller (45), merits joint attribution (44).

Claims attributing the first cortex-medulla distinction to George Cuvier (1769-1832) or initial cortex-medulla terminology to Emil Huschke (1797-1858) need revision (6, 46). Morgagni had previously documented this distinction in 1740, employing the terms *cortex* and *nucleum* (34). Johann Christoph Heino Schmidt (1761-1787) also noted this in 1785 (47). Cuvier's 1805 descriptions echoed these earlier observations (48). The terms *Rindensubstanz* and *Marksubstanz* were also utilized by Müller and Nagel prior to Huschke's work (49).

Nagel disproved the adrenal cavity myth, attributing it to a misinterpreted adrenal vein ostium. Karl Eberth (1835-1926) additionally explained that *post-mortem* adrenomedullary autolysis created a cavity-like structure, misleading early anatomists in unpreserved cadavers (50).

In 1846, Alexander Ecker (1816-1887) first characterized the cortex as composed of closed glandular tubes (*Drüsenschläuchen*) arranged in parallel rows (Figure 4A), while the medulla contained fine-grained cells (*Plasma mit Kernen*) surrounded by connective tissue (51) (Figure 4B). The cortical columnar arrangement was confirmed by Arthur Hill Hassall (1817-1894) in 1849 (52) (Figure 4C), Albert von Kölliker (1817-1905) in 1852, who termed them *Rindencylindern* (53), and George Harley (1829-1896) in 1858 (54) (Figure 4D). Kölliker subsequently illustrated the arched pattern in horse adrenal glomerulosa (Figure 4E).

After a preliminary report by Gregor Philipp Joesten (1840-?) (55), Jakob Henle (1809-1885) in 1865 discovered that potassium bichromate turned adrenal medulla dark brown within 12-24 hours, leaving cortex unchanged (56), a phenomenon now known as the "chromaffin reaction". Later, Henle reiterated this observation (57).

Some authors attribute this discovery to Bertholdus Werner in 1864 (5, 7, 58). However, Werner's dissertation merely mentioned using chromic acid to harden organs and replicated experiments by Alfred Vulpian (1826-1896) on color reactions of adrenal extracts (59).

Henle did not name the reaction or the cells involved. Heinrich Stilling (1853-1911) proposed "chromophile cells" in 1890 for the stained medullary cells (60). Alfred Kohn (1867-1959) introduced "chromaffin cells" in 1898 to emphasize their affinity to chromium (61, 62). Subsequently, "phaeochrome Zellen" was coined (63), leading to the term "phäochromocytome" by Ludwig Pick (1868-1944) for adrenal medulla tumors (64).

Kölliker first linked medullary cells to innervation, associating the cortex with secretion and the medulla with the nervous system (65). Franz von Leydig (1821-1908) described medullary cells as "multipolar gangliar cells" (66). Carl Jacobj (1857-1955) demonstrated adrenal-sympathetic connections and the glands' inhibitory role on the vagus nerve, suggesting an unknown secretory product (37).

In 1866, Julius Arnold (1835-1915) introduced the fundamental subdivision of the adrenal cortex into three zones: zona glomerulosa, fasciculata, and reticularis, based on vascular arrangement (67) (Figure 5A). The subzonation derived from the vascular organization Arnold observed: glomerulosa from Latin *glomus* (ball of yarn) due to vessel formations resembling small balls, fasciculata from *fasciculus* (small bundle) as vascular tubes emerged from glomeruli with a radial arrangement, and reticularis from *reticulum* because of a dense vascular network of wide capillaries.

Hassall had already described this vascular pattern in 1849 (52), providing a detailed image of cortical vascularization (Figure 5B), superior to Arnold's one. Arnold's subdivision gained wide acceptance (50) and became standard by the late 19th century. Moreover, in 1872, Eberth first used Owen's term "adrenals" in a histology textbook (50).

Late 19th-century optical microscopy advances, such as the condenser and immersion lens, along with improved microtomy, sample processing, and aniline dyes, enabled high-quality imaging of adrenal structures and postnatal reorganization studies.

A significant discovery was the identification of the adrenal cortex "fetal zone". Olaf Scheel (1875-1942) had observed that newborns' adrenal glands were heavier than adults' and decreased in weight during the first year, slowly increasing again at 1-2 years (68). Erwin Thomas (1881-1969) attributed the absence of adrenal weight gain during the first year to a compensatory organ destruction that offset the expected physiological growth (69).

In 1910, Stella Starkel (1885-1969) and Leslaw Węgrzynowski (1885-1956) conducted the first histological study of human adrenal glands in fetuses and children from 6 months to

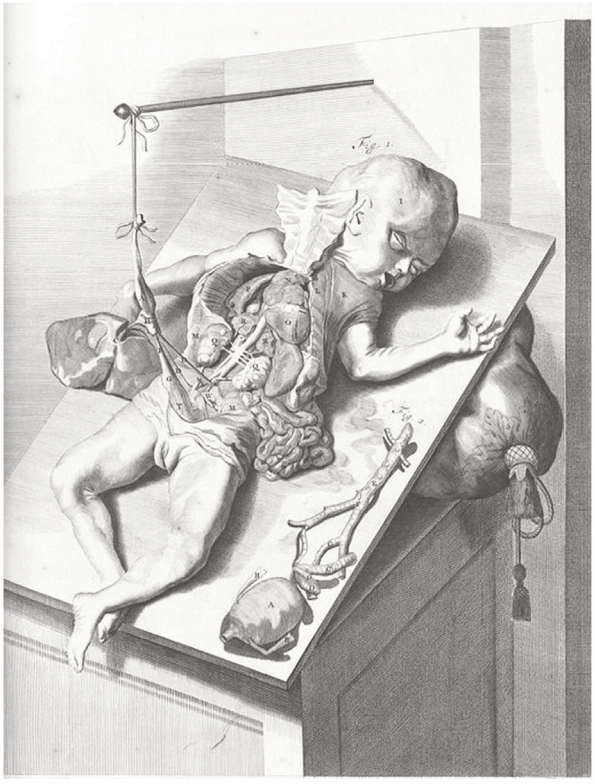

Figure 3. Anatomy of neonatal adrenal glands (28). A) Plate LXIII, Figure 1, from *Godefridus Bidloo's Anatomia Humani Corporis. Adrenal glands indicated by letter "R". Original caption: "Renales Glandulae R. ultra expectationem magnae apparent"* (The renal glands R. appear larger than expected) (28).

5 years (70, 71) (*Supplementary Figure 2A*). They found incompletely developed cortical layers in newborns. By the third week, three layers emerged: cortical substance, a "medullary zone" (80% of cortex), and medullary substance. The "medullary zone" regressed as the medullary substance developed, with traces sometimes found in 5-year-olds. They concluded Arnold's three-zone structure was not fully established until late childhood.

This unique human process was corroborated by Thomas (69, 72) and others (71). In fact, in 1926, Albert Dietrich (1873-1961) and Siegmund Herbert (1892-1954) summarized in detail, with a list of references, the process of remodeling of the infant adrenal gland, illustrating it with much better color drawings (73). In 1938, Karl Georg Peter (1870-1955) described in much detail the unique process occurring in the adrenal glands of newborn humans, where the central parts of the cortex degenerate and are then regenerated (74) (*Supplementary Figure 2B*). This process, which began shortly after birth, involved hyperemia, cell degeneration, and eventual replacement of the degenerated zone with connective tissue. The remodeling was thought to be related to the child's need to establish a new hormonal equilibrium after birth. The process was gradual, lasting through the first year of life and potentially up to puberty, and is not observed in the same way in other mammals (74). Of note, Wolfgang Rotter (1910-2000) graphically represented an adrenal cortex's life curve in 1949 (75) (*Supplementary Figure 2C*).

Recent studies show these structural changes align with hormonal shifts, including decreased post-birth dehydroepiandrosterone production and hypothalamic-pituitary-adrenal axis maturation. Advanced techniques have clarified these postnatal changes, offering valuable insights for pediatric care.

The experimental physiology phase

The study of adrenal gland physiology began with the monograph by Thomas Addison (1795-1860) describing Addison's disease (76). Although Nicolas Le Pois (1527-1590) may have described similar symptoms in 1580 in his *De ictero nigro* (77), Addison first linked these symptoms to adrenal pathology. His work gained immediate recognition, with Armand Trousseau (1801-1867) proposing the name *maladie d'Addison* (78). This led to the first experiments involving adrenal gland removal, which had not been previously attempted. Between 1856 and 1857, Charles-Édouard Brown-Séquard (1817-1894) published articles demonstrating the adrenals' essential role in life (79-81). His

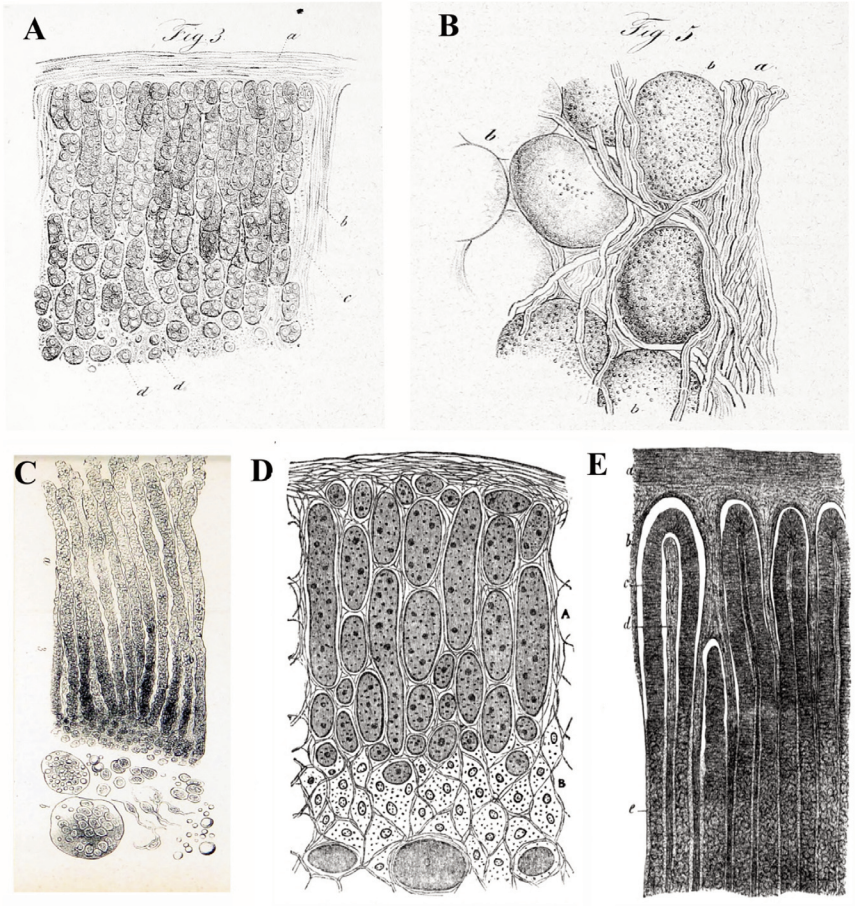

Figure 4. Histology of the adrenal gland (49-52). **A,B**) From Ecker A (49), A: Plate I, Figure 3. Vertical section of human adrenal cortex; **B**) Plate I, Figure 5. Section of horse adrenal medulla; **C**) From Hassall AH (50), Plate LXII, Figure 3. Tubes of supra-renal capsule; **D**) from Harley G (52), Figure 2. Transverse section of human adrenal, showing cortical and medullary substances; **E**) from Kölliker von A (51), Figure 370. Vertical section of horse adrenal cortex, showing the arched pattern.

experiments were controversial, with various researchers repeating them on different animals, often yielding conflicting results. Jean-Baptiste Bouillaud (1798-1881) dismissed Brown-Séquard's work as *physiologie amusante* (82).

Stilling's significant contribution was elucidating the inconsistent outcomes of adrenal extirpation experiments, demonstrating that cortical cells underwent proliferation. Therefore, extirpation of one suprarenal gland had no discernible consequences. Moreover, cortical cells left *in situ* due to incomplete surgical excision, or any existing cortical cells in accessory suprarenal glands, equally underwent proliferation. This phenomenon of compensatory hypertrophy explained the frequent absence of observable effects following single gland removal in experimental animals (60, 83).

The Italian physician Nicola Pende (1880-1970) demonstrated the adrenal cortex's vital role in the early 1900s. His 1903 thesis showed that adrenal denervation caused selective medulla atrophy (84). In 1909, Pende conducted a three-phase experiment on a cat (85). He first removed the right adrenal gland without consequences. Two months later, he denervated the left gland, causing medullary atrophy. Finally, 3 months after the second operation, he removed the remaining left adrenal, resulting in the cat's death. This experiment conclusively proved the cortex's essential role in survival. These significant findings, published in Italian, had limited international reach due to language barriers, despite being reported in German by Carmelo Ciaccio (1877-1956) (86).

Hungarian pathologist and endocrinologist Arthur Biedl (1869-1933) drew a definitive conclusion from these experiments. In his 1913 publication, he asserted that the evidence unequivocally demonstrated the adrenal cortex's indispensable role in sustaining animal life (87). As reviewed by Miller (88), the historical development of the hypothalamic–pituitary–adrenal axis – from its anatomical identification to the elucidation of its hormonal components and regulatory mechanisms – reflects a progressive convergence of endocrinology, biochemistry, and modern physiological knowledge.

Adrenal removal experiments were supplemented by replacement therapy trials using adrenal extracts or organ transplantation. By the late 1920s, adrenal extracts were shown to successfully treat adrenalectomized dogs (89) as well as Addison's disease patients (90).

The biochemical and organic chemical phase

Early adrenal replacement therapy faced multiple challenges: subcutaneous extract caused local irritation and abscesses, had mineralocorticoid effects, contained catecholamines, causing hypertension, and was scarce. These issues necessitated the purification of "cortin", the adrenal cortex hormone named in 1927 (91).

Leonard G. Rowntree (1883-1959), who had demonstrated the Pfiffner-Swingle extract's efficacy on Addison's disease patients (90), involved Mayo Clinic biochemist Edward Calvin Kendall in cortin purification. As reported by Dwight Joyce Ingle (1907-1978), Kendall, successful in thyroid endocrinology, briefly hosted Albert Szent-Györgyi (1893-1996) in 1929, inheriting his adrenal extract preparation setup (92). An agreement with Parke-Davis provided Kendall access to 1,000 pounds of bovine adrenal glands

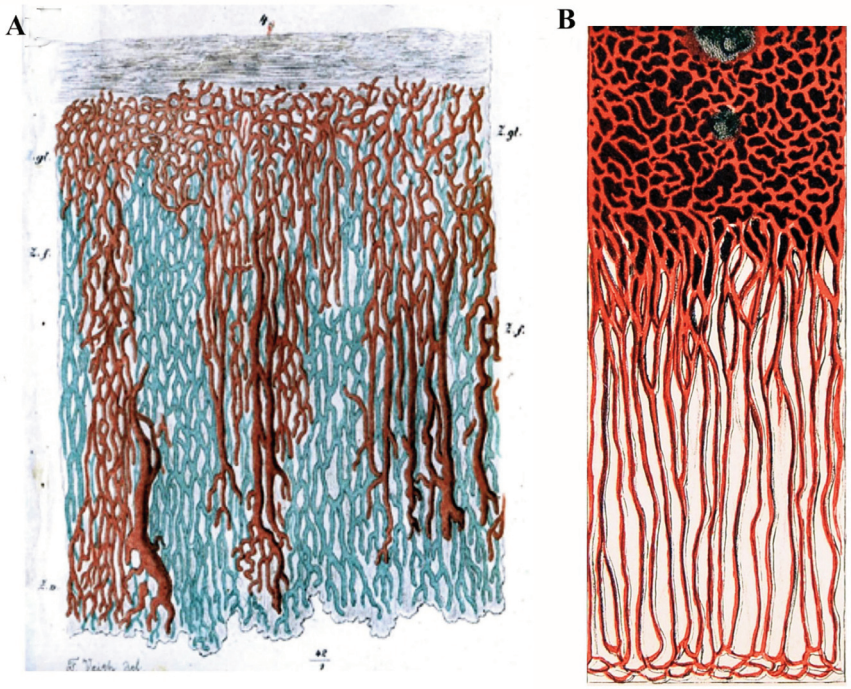

Figure 5. Zonation of adrenal cortex based on vascular arrangement (50, 65). **A**) From Arnold J (65). Microcirculation in adrenal cortex, showing zona glomerulosa (Z. gl.), zona fasciculata (Z. f.), and zona reticularis (Z. r.). Arteries in red, veins in blue; **B**) from Hassall AH (50), Plate LXII, Figure 5. Vessels of supra-renal capsule, showing surface plexus, intertubular vessels, and central plexus.

weekly for 5 years (92).

In the early 1930s, three groups independently worked on isolating cortin: Oskar Paul Wintersteiner (1898-1966) and Joseph J. Pfiffner (1903-1975) at Columbia University, Kendall at Mayo Clinic, and Tadeusz Reichstein in Switzerland (93). By 1936, all groups had isolated crystalline compounds from the adrenal cortex (94-97). Eventually, 28 compounds were isolated, six being biologically active (93, 98). Cortisone was named differently by each group: *Compound E* by Kendall, *Substance Fa* by Reichstein, and *Substance F* by Wintersteiner and Pfiffner, but Reichstein proved their identity in 1936 (96). In 1937, Reichstein achieved partial synthesis (that is, by modification of other naturally abundant steroids) of desoxy-corticosterone (99), which was successfully used to treat Addison's disease by 1939 (100). By 1952, substitution therapy with desoxy-corticosterone and cortisone enabled adrenal gland removal in cases like Cushing's disease (101). Research on adrenal cortical hormones for Addison's disease slowed due to decreased incidence from improved hygiene reducing tuberculosis, prohibitively expensive commercial treatments, and the discovery of an effective low-cost dietary approach using high sodium and low potassium for patients at Mayo Clinic (92, 102). World War II, starting September 1st, 1939, significantly delayed adrenal hormone research. Rumors of German efforts to isolate adrenal hormones for Luftwaffe pilots, though unfounded, were not baseless, given their use of methamphetamine (103, 104). In October 1941, the U.S. National Research Council established a consortium of laboratories, including Kendall's and Reichstein's groups and Merck & Co. In 1944, Merck & Co. chemist Lewis Hastings Sarett (1917-1999) achieved the partial synthesis of cortisone (Kendall's Compound E) from bile-derived deoxycholate. Due to wartime restrictions, Sarett's work was not published until 1946 (105).

The clinical phase

Scientific interest shifted from Addison's disease to RA, led by Philip Showalter Hench, Director of Mayo Clinic's rheumatology section since 1926. Hench observed spontaneous remission of RA in patients with jaundice and during pregnancy (2, 106). He hypothesized the existence of an "antirheumatic substance X" (107), normally inactivated by the liver. The pregnancy-related remission may be linked to fetal adrenal development and increased steroid synthesis (108). Notably, Pende had earlier reported cortical cell modifications in pregnant animals, suggesting increased adrenal function (84).

Hench's attempts to study jaundice-induced joint changes in rats led to his collaboration with Kendall (92). Hench reported infrequent discussions with Kendall about "substance X" before 1938, but their collaboration intensified thereafter (2). Kendall noted that in January 1941, they decided to use Compound E (cortisone) to treat RA (93). This account was corroborated by both Hench and Ingle (2, 92).

The choice of Compound E (cortisone) for treating RA was largely intuitive. Ingle suggested that Kendall and Hench were "playing a hunch without much evidence" (92). Kendall himself noted in 1952 that previous results with adrenal cortex extracts showed no significant effect on conditions like RA (101). However, Valy Menkin (1901-1960) at Harvard University Medical School had reported in 1940 that adrenal cortical extract suppressed inflammation-induced capillary permeability (109). In 1942, Menkin observed the same effect with Kendall's Compound E (110), providing the first experimental evidence of cortisone's anti-inflammatory properties.

On September 4th, 1948, Hench requested Compound E from Merck & Co. to treat RA patients. On September 21st, 1948, at Mayo Clinic, Charles Henry Slocumb (1905-1996), who would become head of the Division of Rheumatology and Internal Medicine in 1953 at the same Institution, began treating Mrs. G. with 100 mg daily injections of Compound E, resulting in marked improvement within three days (107). Similar results were achieved with ACTH. Oral administration of cortisone acetate proved equally effective. Preliminary results were presented on April 20th, 1949, at Mayo Clinic (106), and quickly confirmed by others (111, 112). In 1950, Hench, Kendall, and Reichstein were awarded the Nobel Prize in Physiology or Medicine for their discoveries on adrenal cortex hormones (113).

The challenge of supplying cortisone for widespread therapy

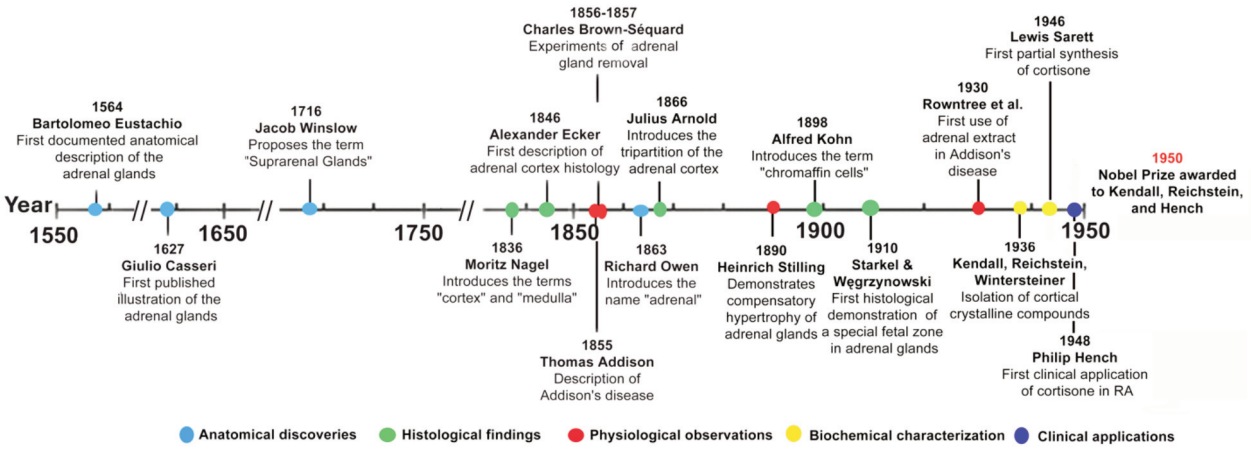

Figure 6. Chronological overview of key milestones in adrenal gland research (1564-1951).

was addressed when Woodward *et al*. achieved its total synthesis (*i.e*., the complete laboratory creation of cortisone from simple starting materials) in 1951 (114). Sarett *et al.* reported stereospecific cortisone synthesis in 1952 (115). Although these synthesized compounds were not immediately commercialized (116), Upjohn began marketing cortisone in 1952 and hydrocortisone in 1953 (117). In 1953, it was discovered that cortisol, derived from the *in vivo* conversion of cortisone, was the active hormone form (118).

Following Menkin's findings, it became increasingly evident that cortisone and ACTH reduced inflammatory responses to various stimuli (119). This was supported by microscopic examination of synovial specimens from a patient treated by Hench's group with Compound E, showing significantly reduced inflammation (106). Modern understanding of glucocorticoid action reveals a complex interplay of mechanisms (120). While the classical pathway involves inhibition of arachidonic acid release through modulation of phospholipase A2 activity, recent studies have uncovered more nuanced effects. Glucocorticoids now appear to function as transcriptional regulators, reshaping immune cell metabolism with cell-specific effects mediated by distinct receptor isoforms (121, 122). Furthermore, they reprogram macrophage mitochondrial metabolism, increasing the production of anti-inflammatory itaconate and accelerating the tricarboxylic acid (TCA) cycle (123). Stifel *et al.* (2022) have shown that glucocorticoids repress glycolysis in inflammatory myeloid cells while promoting TCA cycle flux, which enhances succinate metabolism and prevents intracellular succinate accumulation (124). They also identified HIF1α as a key regulator of glucocorticoid responsiveness during inflammatory challenge, linking metabolism to gene regulation by glucocorticoids in macrophages. These discoveries not only deepen our comprehension of glucocorticoids' anti-inflammatory properties but also pave the way for developing innovative anti-inflammatory therapies targeting cellular metabolism (123, 124).

Soon after clinical use began, cortisone's serious side effects became apparent alongside its anti-inflammatory benefits. It was soon observed that cortisone, in addition to its anti-inflammatory (glucocorticoid) action, also exerted mineralocorticoid effects, leading to fluid retention. This manifested clinically as peripheral edema and arterial hypertension – phenomena particularly evident in the first patients treated and thoroughly documented in the historical account by Pasero and Marson (125). Beginning in the 1950s, the availability of semisynthetic cortisone analogs lacking mineralocorticoid activity – prednisone and prednisolone (126), betamethasone (127), and dexamethasone in 1958 (128) – helped overcome this issue, improving both therapeutic profile and clinical tolerability. Nevertheless, side effects related to glucocorticoid activity, such as alterations in glucose and bone metabolism, remained an unresolved challenge, especially in long-term treatments (129). Despite these side effects, cortisone continues to be used today, as no true alternative has yet been found to fully replace its clinical efficacy.

As previously described (125), early cortisone use faced significant challenges in dosing and administration. Excessive doses led to iatrogenic hypercorticism, while problematic administration methods contradicted natural cortisol rhythms. Long-acting corticosteroids further complicated hormonal axis suppression. After ineffective early mitigation attempts, single morning dosing and alternate-day regimens gradually emerged as improvements. Intermediate-acting steroids were eventually preferred for balancing efficacy and side effects. This period of trial and error underscored the complexities in optimizing steroid therapy.

These cumulative discoveries, spanning nearly four centuries, are summarized in Figure 6, which provides a chronological overview of the key milestones in adrenal gland research and cortisone development.

This overview marks the end of cortisone's complex journey from early anatomical studies to optimized clinical use. While this historical account ends here, research on corticosteroids continues, constantly refining their application in modern medicine.

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Online supplementary material:
Supplementary Figure 1. Anatomy of adrenal gland innervation.
Supplementary Figure 2. Fetal and postnatal development of the adrenal gland.
Supplementary Table 1. Putative early references to the adrenal glands in ancient sources

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