

REVIEW

Diamonds are forever: the cortisone legacy

Stephen G Hillier

The Queen's Medical Research Institute, Centre for Reproductive Biology, The University of Edinburgh, 47 Little France Crescent, Edinburgh EH16 4TJ, UK
(Requests for offprints should be addressed to S G Hillier; Email: s.hillier@ed.ac.uk)

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Abstract

The year 1946 was not only the year that the Society for Endocrinology was founded, but also the year that Edward Kendall's compound E (cortisone) was first synthesised by Louis Sarett. By 1948, sufficient quantities of compound E were available for the rheumatologist Philip Hench to test it successfully for the first time in a patient with rheumatoid arthritis. It was immediately hailed as a 'wonder drug' and was shown to be effective in a number of inflammation-associated conditions, most notably rheumatoid arthritis. The subsequent development of endocrinology as a discipline is inextricably linked to the chemistry, biology and medicine of anti-inflammatory glucocorticoids. Sixty years after the first chemical synthesis of cortisone, corticosteroids remain among the top ten most commonly used prescription and over the counter drugs. Basic and clinical studies of glucocorticoid biosynthesis, metabolism and action have trail-blazed

developments in endocrinology ever since. This article surveys the extraordinary cortisone timeline, from first synthesis until now. The concluding scientific message is that intracrine metabolism of cortisone to cortisol via 11 β hydroxysteroid dehydrogenase type 1 likely sustains local amplification of glucocorticoid action at sites of inflammation throughout the body. The broader message is that the discovery of compound E by Kendall (basic scientist), its large-scale synthesis by Sarett (industrial chemist) and its therapeutic application by Hench (rheumatologist) serves as a paradigm for modern translational medicine. It is concluded that endocrinology will remain a force in health and disease if it continues to evolve *sans frontières* at the basic/applied/clinical science interface. A challenge for the Society for Endocrinology is to ensure this happens.

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Introduction

The Society for Endocrinology was founded in 1946 'to promote the advance of endocrinology by observational or clinical studies'. The year 1946 was also the year that Lewis Hastings Sarett, an organic chemist at Merck Research Labs in the USA, published the first synthesis of a recently discovered adrenal steroid hormone named 'compound E' (Sarett 1946). Compound E had been crystallised from bovine adrenal glands 10 years earlier by Edward Calvin Kendall (Mason *et al.* 1936). Kendall's compound E would eventually be known as 'cortisone' (Kendall 1953) and become one of the wonder drugs of the 20th century. Hence, 2006 was the diamond jubilee year of both the UK Society of Endocrinology and the first synthesis of compound E. This brief review traces the impact of cortisone on the development of steroid endocrinology from then until now. The concept is advanced that its intracrine activation to cortisol at sites of inflammation supports both natural and therapeutic anti-inflammatory effects of cortisone. More broadly, cortisone's discovery,

synthesis and therapeutic applications are celebrated as a paradigm for modern translational medicine.

The steroid rush

The bedrock of the Society for Endocrinology is steroid chemistry, which entered its heyday during the 1930s. Landmark developments around that time included elucidation of the signature perhydrocyclo-pentanophenanthrene steroid structure by Otto Rosenheim and Harold King in 1932 (Feiser & Feiser 1959) and introduction of the general name 'steroid' in 1936 to cover all compounds with a sterol-like skeleton (Klyne 1957). The sex steroids oestradiol, testosterone and progesterone were discovered between 1929 and 1935, followed by the adrenocortical hormones, cortisone and cortisol, in 1935–1938. By 1937, most of the classic steroid hormones had been isolated and their structures determined (Feiser & Feiser 1959). Following a hiatus during WWII, the field was massively boosted in 1948 by the

announcement of the dramatic therapeutic effects of cortisone (see below) and the race to synthesise more and more steroid analogues with beneficial therapeutic effects. By 1956, 10 years after the Society was founded, the number of novel steroidal substances synthesised had risen to over 7000 (Klyne 1957). During this period, the mineralocorticoid aldosterone was also discovered (Simpson *et al.* 1953). The first Society for Endocrinology Medal was awarded to the co-discoverer of aldosterone, James F Tait, in 1968. Significantly, the obverse prominently displays the perhydrocyclo-pentanophenanthrene steroid nucleus.

Kendall's compounds

Compound E was first isolated in 1935 from bovine adrenal glands along with a series of structurally related steroids (including cortisol, then named compound F) capable of improving muscular strength when administered to adrenalectomised rats or dogs (Mason *et al.* 1936, Reichstein 1936). Individual steroid yields were only between 85 and 500 mg cortisone per 100 lb adrenal glands (Feiser & Feiser 1959). Therefore it was initially agreed that their use should be confined to small animals and none should be employed for clinical medicine (Hench 1964). The impetus to develop synthetic methods for adrenocorticosteroids came from the US entry into WWII in 1941, initially fuelled by a rumour that Luftwaffe pilots were taking adrenal extracts to increase their resistance to oxygen deprivation at high altitudes. Although this rumour was unfounded, it is said to have kick-started the all-out quest for a large-scale synthetic route to the active adrenal hormone, which at the time was given higher strategic priority than penicillin and anti-malarials (Quirke 2005). Of the six biologically active steroids that had been isolated from adrenal glands, Kendall's compound A (11-dehydrocorticosterone) was initially targeted for synthesis because it possessed the simplest structure (Kendall 1964). Although synthetic 'A' proved to be active in animals, it had no beneficial effects in patients with Addison's disease. Therefore, attention turned to the closely related 'E' (cortisone), eventually leading to the historic 37-step synthesis from desoxycholic acid published by Sarett (1946). By summer 1948, sufficient compound E was available for Kendall's long-time collaborator at the Mayo Clinic, Philip Showalter Hench, to test clinically. A pilot trial of compound E on a patient with Addison's disease was 'encouraging' (Kendall 1964). Then, on 21 September 1948, the first i.m. injection of an aqueous suspension of compound E (100 mg) was given to a woman crippled with rheumatoid arthritis. Her spectacular improvement warranted reduction of the daily dose to 25 mg within 3 days, and within a week '...she walked out of the hospital in a gay mood and went on a shopping trip...' (Kendall 1953). Similar successes were achieved in 30 more patients over the following 7 months and essentially the same clinical results were obtained by injecting pituitary adrenocorticotrophic hormone (ACTH; Hench *et al.* 1949).

By January 1950, Kendall & Hench had named compound E as cortisone to avoid its confusion with vitamin E (Kendall 1964). In the same year, Kendall & Hench shared the Nobel Prize for Physiology or Medicine 'for research on the structure and biological effects of adrenal cortex hormones' with Tadeus Reichstein who had independently discovered cortisone at around the same time as Kendall and named it substance Fa (Reichstein 1936).

Diamond decades

Ever since it was 'launched' as a pharmaceutical in 1950 (Kendall 1964), cortisone and a succession of closely related synthetic analogues have remained among the most widely prescribed medications in the world. At the same time, the science of endocrinology – particularly steroid endocrinology – has advanced beyond recognition. Understanding how cortisone is formed, metabolised and acts in health and disease has been integral to this progress, as is now considered.

1950s: steroid chemistry

Kendall (1964) initially believed it, '...highly improbable that any product will ever be found which can be used in place of cortisone and the closely related compound F'. Compound F (hydrocortisone; cortisol) quickly became the first topically applied corticosteroid effective in a variety of inflammatory skin disorders (Sulzberger & Witten 1952, Ravis & Eaglstein 2007). Meanwhile, cortisone was being hailed as a panacea for treating various diseases of unknown cause but with an inflammatory basis. However, with high dosage and long-term usage, the remarkable therapeutic effects of cortisone were countered by undesirable side effects, such as excessive salt and water retention, increased gastric acidity and psychosis. Considerable effort was therefore directed at chemical and microbiological syntheses of new cortisone derivatives with lessened toxicity and improved efficacy (Feiser & Feiser 1959). Progress was aided by the arrival of conformational analysis, which allowed molecular structures and stereochemical confirmations to be assigned on the basis of quantitative physicochemical parameters (Barton & Cookson 1956). Milestones included the discovery that whereas 9 α -fluorination increased anti-inflammatory potency, it also caused excessive protein loss, potassium loss, sodium retention and oedema. On the other hand, introduction of a 1,2 double bond in the A ring (to create prednisone from cortisone and prednisolone from cortisol) created derivatives with improved anti-inflammatory properties and reduced undesirable side effects. 16 α -Hydroxylated compounds retained glucocorticoid activity without concomitant salt and fluid retention while 16 α -methylation further increased anti-inflammatory activity. Combining 9 α -fluorination, 1-dehydrogenation and 16 α -methylation yielded dexamethasone, which was the most potent non-salt retaining anti-inflammatory of its time (Feiser & Feiser

1959). Generic formulations of prednisone, prednisolone and dexamethasone have remained in widespread use to this day.

1960s: steroid biochemistry

Steroid hormone biosynthesis involves formation of cholesterol from acetate and onward metabolism of cholesterol via C21 (pregnenolone or progesterone) intermediates. This much was known by the beginning of the 1960s. Downstream pathways of steroid metabolism were subsequently shown to depend upon the pattern and cellular distribution of steroidogenic enzyme systems characteristic of each steroid-secreting gland (Ryan 1972). In the case of the adrenal gland, cortisol, corticosterone and aldosterone were the most important steroidal secretions. ACTH was shown to regulate conversion of cholesterol to pregnenolone and progesterone in the adrenal, and at least part of this action was mediated by second messenger cyclic AMP (Grahame-Smith *et al.* 1967). The sequence of metabolic steps in glucocorticoid biosynthesis involved hydroxylations at C17, C21 and C11 in the zonae fasciculata and reticularis (yielding cortisol and corticosterone; Dixon *et al.* 1967). C18-hydroxylation and onward metabolism to aldosterone occurred principally in the zona glomerulosa (Coghlan & Blair-West 1967). These seminal advances in steroid biochemistry had been made possible by the advent of ¹⁴C- and ³H-labelled substrates and intermediates for use as metabolic tracers *in vitro* (Heard *et al.* 1954) and *in vivo* (Gallagher *et al.* 1954). Solvent extraction, chromatographic separation and group-specific chemical (colorimetric or fluorimetric) tests had founded the first generation of quantitative glucocorticoid assays, sufficient to document normal plasma and urinary levels of groups of structurally related glucocorticoids (Peron 1962). The introduction of double-isotope (dilution) derivative assays provided reference methods for individual steroids (Landon *et al.* 1965), complemented by quicker and simpler competitive protein-binding assays based on saturation analysis using corticosterone-binding globulin (Murphy & Pattee 1964), presaging steroid immunoassay (see below). Four decades on, steroid biochemistry converged with contemporary molecular analysis to deliver steroidomics (Sjövall 2004).

1970s: RIA and recombinant gene technology

The 1970s endocrinology was dominated by RIA and saw the introduction of recombinant DNA technology. Berson and Yalow published the first RIA for plasma insulin in 1959. However, it took another 10 years before the first steroid RIA (oestradiol) was described (Abraham 1969) and three more years for a cortisol RIA (Ruder *et al.* 1972). The technique opened up new areas of investigation and revolutionised steroid endocrinology because of its increased sensitivity and specificity over previous analytical methods. This need was less urgent for cortisol because of its relatively high concentration in plasma when compared with other steroids

and more ready quantification by other methods. However, the improved sensitivity and specificity of RIA allowed advantages, such as direct measurement of biologically active ('free') cortisol in plasma or saliva. The latter avoided the stress-induced increases in glucocorticoid secretion associated with venepuncture and had particular benefit to paediatric endocrinology and dynamic testing of adrenal-pituitary function (Holder 2006). Adrenal endocrinology was mainstream clinical endocrinology. The hypothalamo-pituitary-adrenal axis, new biological actions and clinical uses of corticosteroids, new tests of adrenal function, diagnosis and treatment of adrenocortical insufficiency and hyperactivity, congenital hyperplasia; all were laid bare as the decade progressed (Bondy 1985).

The 1970s had also seen the application of tissue culture techniques combined with RIA to study steroid formation, metabolism and action at the cellular level (Channing & Ledwitz-Rigby 1975). The concept of paracrine (cell-to-cell) communication gained sway (Van Noorden & Polak 1979). With the application of recombinant DNA technology to the first cloning of a human gene (insulin; Bell *et al.* 1980), the scene was set to explore steroid endocrinology at the molecular level.

1980s: molecular endocrinology

Gene cloning studies established steroid hormone receptors as a superfamily of nuclear transcription factors that bind and transduce steroid action in target tissues (Weinberger *et al.* 1987). The rat glucocorticoid receptor (GR) was the first steroid hormone receptor to be cloned (Hollenberg *et al.* 1985) followed by mineralocorticoid receptor (MR) 2 years later, i.e. 1987 (Arriza *et al.* 1987). All the major steroid nuclear receptors – oestrogen receptors α and β (ER α and ER β), progesterone receptor, androgen receptor, GR and MR – had been cloned by the end of the century. Genome mapping and phylogenetic analysis revealed that they had been created by a series of duplications from a common ancestral ER gene, with MR and GR arriving after the lamprey-gnathostome divergence, as controls over osmosis and stress (Thornton 2001). As discussed below, the cloning of GR and MR not only illuminated the pathophysiology of adrenal steroid hormone action, but also highlighted the importance of pre-receptor (intracrine) steroid metabolism in determining the anti-inflammatory properties of cortisone.

1990s: pre-receptor metabolism

The molecular biology of steroid biosynthesis and metabolism had also become frontline research with the introduction of cloning and sequencing techniques (Miller 1988, Labrie 1991). The puzzling observation that, 'Patients given large doses of cortisone by mouth have very little cortisone in the plasma but a high plasma level of cortisol' (Bush 1956) was finally clarified. Paradoxically, Kendall's compound E is an inactive molecule that requires metabolism to cortisol in order

to exert anti-inflammatory action via GR (Cato & Wade 1996). Systemic conversion of cortisone to cortisol is principally via hepatic 11 β hydroxysteroid dehydrogenase type 1 (11 β HSD1) enzymic activity, which 11-*oxo*-reduces cortisone to cortisol. 11 β HSD2, which back converts cortisol to cortisone, is mainly expressed in tissues that depend on MR activation by mineralocorticoids, most notably kidney. Since aldosterone and cortisol are both potent MR agonists, 11 β HSD2 activity is required at such sites to deactivate cortisol and prevent it from occupying MR. Hence, the 'cortisone–cortisol shuttle' (Edwards & Stewart 1991) and 'guardian enzyme' (Williams 1992) hypotheses that explain the apparent specificity of GR and MR signalling in glucocorticoid and mineralocorticoid target tissues (Seckl & Walker 2004, Draper & Stewart 2005).

2000 and beyond

During his 1950 Nobel lecture, Hench (1964) remarked, 'Little is known about the metabolism of cortisone, about how much is utilized normally by the cells of the body, or how much is (normally) altered or destroyed in the body before it has had an effect'. We now know that the 'alteration' of cortisone to cortisol is crucial to its anti-inflammatory action. Beyond pre-receptor metabolism, glucocorticoid action involves both positive and negative regulation of gene expression with extensive crosstalk between GR and membrane-associated receptors for pro-inflammatory cytokines, such as interleukin-1 (IL-1) and tumour necrosis factor α (Rhen & Cidlowski 2005). Crucially, GR signalling leads to repression of pro-inflammatory transcription factors, such as nuclear factor κ B and activating protein-1 that mediate cytokine-induced inflammatory gene expression (Rosen & Miner 2005).

Finally, the cortisol–cortisone 'shuttle' principle extends to inflammation control (Tetsuka *et al.* 1999a, Chapman *et al.* 2006). Ovulation is a natural inflammatory process comprising haemodynamic, vascular and biochemical changes leading to proteolytic breakdown of the follicle wall and release of an oocyte for fertilisation (Hillier & Tetsuka 1998). Although ovary cannot biosynthesise glucocorticoids *de novo*, granulosa cells collected from follicles on the verge of ovulation selectively express 11 β HSD1 over 11 β HSD2 mRNA (Tetsuka *et al.* 1997, 1999b). Such cells predominantly undertake 11-*oxo*reduction of cortisone to cortisol *in vitro* and pre-ovulatory follicular fluid contains markedly raised levels of free cortisol (Yong *et al.* 2000, Andersen 2002). Treatment *in vitro* with inflammatory cytokines, such as IL-1 also raises 11 β HSD1 gene expression and increases 11-*oxo*-reductase-enzyme activity in granulosa cells (Tetsuka *et al.* 1999a) and ovarian surface epithelial cells (Yong *et al.* 2002, Rae *et al.* 2004). Many other cell types respond to inflammatory cytokines with increased 11 β HSD1 and/or reduced 11 β HSD2 gene expression *in vitro*, including kidney (Escher *et al.* 1997), lung (Feinstein & Schleimer 1999), fat (Tomlinson *et al.* 2001), bone (Cooper *et al.* 2001), blood vessels (Cai *et al.* 2001) and macrophages (Gilmour *et al.*

2006). Thus, intracrine activation by 11 β HSD1 could support anti-inflammatory glucocorticoid action at sites of inflammation throughout the body (Fig. 1).

Endocrine futures

Sixty years after Sarett's synthesis of cortisone, glucocorticoids remain blockbuster anti-inflammatories: drugs to beat (Barnes 2006). To this day, generic glucocorticoid preparations like fluticasone nasal spray for the management of chronic asthma or hay fever (Abdullah & Kahn 2007) remain among the most highly prescribed and over-the-counter drugs used in the USA (Mitchell *et al.* 2005). Kendall (1964) foresaw, '...cortisone will be unique, for it is new only in the sense that it has been made available. From the time, ages ago, when cortisone was first made in the adrenal cortex it has continued to serve as a powerful agent in health and disease'. The triumvirate of Kendall (basic scientist), Sarett (industrial chemist), and Hench (rheumatologist) created a paradigm for translational endocrinology, the essence of which remains valid to this day. Endocrinology, as an agent in health and disease, will continue to be most influential if it evolves along the same lines, *sans frontières*, at the basic–industrial–clinical

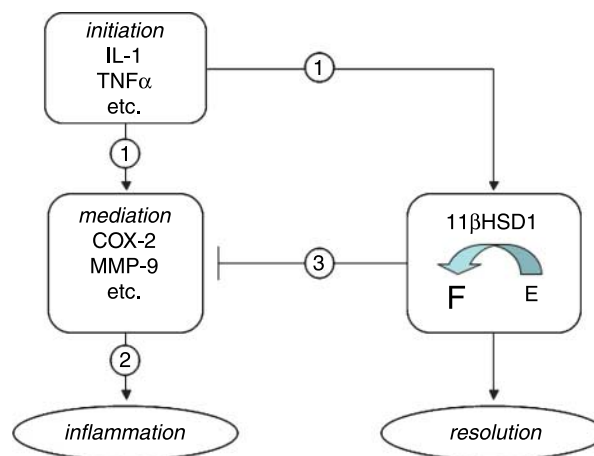


Figure 1 Proposed intracrine amplification of anti-inflammatory glucocorticoid action by 11 β hydroxysteroid dehydrogenase type 1 (11 β HSD1). (1) Pro-inflammatory cytokines, such as interleukin-1 (IL-1) and tumour necrosis factor α (TNF α) bind membrane-associated receptors on target cells to increase the expression of inflammation-associated gene products, such as cyclo-oxygenase-2 (COX-2) and matrix metalloproteinase-9 (MMP-9). The inflammatory response includes an associated increase in 11 β HSD1 (and/or reduced 11 β HSD2) mRNA and encoded 11-*oxo*reductase enzymic activity. (2) Cytokine-induced inflammatory mediators bring about haemodynamic, vascular and biochemical changes associated with inflammation. (3) Cortisol (F) formation from cortisone (E) is locally increased due to cytokine enhanced 11-*oxo*reductase activity. Increased binding of F to glucocorticoid receptor (GR) activates GR-mediated post-receptor anti-inflammatory signalling leading to resolution of inflammation. (Schematic interpretation based on Tetsuka *et al.* 1999a,b, Yong *et al.* 2002, Rae *et al.* 2004).

interface. It remains a challenge for the Society for Endocrinology to ensure that this happens. Meanwhile cortisone endures and inspires.

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