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Review article

SOME SOCIAL ASPECTS OF DISCOVERY, SYNTHESIS AND PRODUCTION OF CORTISONE IN THE 1930s–1950s

NEKI DRUŠTVENI ASPEKTI OTKRIĆA, SINTEZE I PRODUKCIJE KORTIZONA IZMEĐU 1930-IH I 1950-IH GODINA

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Summary

A discovery, synthesis and therapeutic application of cortisone present a paradigm for modern translational medicine (Hillier 2007, Saenger 2010), since they represented a joint achievement of discoveries by biochemists, Edward Calvin Kendall and Tadeus Reichstein; large scale synthesis by an industrial chemist, Lewis Hastings Sarett, and therapeutic application by a rheumatologist, Philip Showalter Hench. The goal of translational medicine is to speed up the process between basic research and clinical practice, and to integrate multiple disciplines in order to understand diverse outcomes (Zhang et al. 2014). In this paper conditions that made this basic/applied/clinical research interface possible will be presented: the rise of steroid chemistry, simultaneous individual accomplishments as well as continuous cooperation among scientists, military competitiveness, and cooperation among pharmaceutical companies.

Key words: *cortisone; translational medicine; Edward Kendall; Philip Hench; social aspects of pharmacology.*

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Introduction

Since their first medical use in 1948 cortisone and its synthetic analogues have remained among the most widely prescribed medications in the world (Hillier 2007). Cortisone belongs to the group of steroid hormones of the adrenal cortex, first isolated in the 1930s by biochemist Edward Calvin Kendall in the USA and independently by Tadeus Reichstein in Switzerland at about the same time. Discovery, synthesis and therapeutic application of cortisone present a paradigm for modern translational medicine (Hillier 2007, Saenger 2010), since they represented a joint achievement of discoveries by two biochemists; large scale synthesis by an industrial chemist, Lewis Hastings Sarett, and therapeutic application by a rheumatologist, Philip Showalter Hench.[1]

The goal of translational medicine is to speed up the process between basic research and clinical practice, and to integrate multiple disciplines in order to understand diverse outcomes (Zhang et al. 2014).[2] Translational research is the dominant new strategy across the field of drug discovery that sets changes in the relationships between academies, biotechnological companies, and pharmaceutical corporations (Fishburn 2013). Recently it has become one of the most important areas of biomedicine because it facilitates laboratory discovery and therapeutic application, especially in the prediction, prevention, diagnosis, and treatment of critical diseases (Zhang et al. 2014). The discovery of cortisone turned out to have a medical, scientific and industrial importance, and it led to further discoveries with wider implications for drug development, such as conformational analysis[3] (See Quirke 2005, Slater 2000).

Steroids are employed as research materials in a wide range of research contexts, both in academic and industrial laboratories, also in biology and in chemistry (Slater 2000). They are a group of compounds with a common structure based on the steroid nucleus, consisting of three six-membered carbon rings and one five-membered carbon ring, which occur in plants and animals (Slater 2000). The general name *steroid* was introduced in 1936 to cover all compounds with a steroid-like skeleton. The sex steroids oestradiol,

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1 Stephen G. Hillier emphasized the paradigm label celebrating the Diamond Jubilee of the Society for Endocrinology in 2006 in the Jubilee Medal Lecture dedicated to the cortisone legacy, later published as the article "Diamonds are forever", in the Journal of Endocrinology 195 (1).

2 Translational medicine, also known as translational science or translational research was introduced as "bench to bedside" by Dennis Choi in 1992, and first formally proposed in 1996 (Zhang et al. 2014).

3 Conformational analysis is a method for correlating steroid structures with the physical and chemical properties of the molecules. See Quirke 2005: 647, Slater 2000.

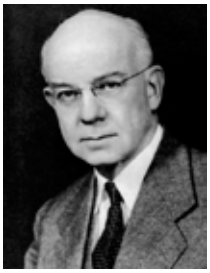
testosterone and progesterone were discovered between 1929 and 1935. What followed is the discovery of adrenocortical hormones between 1935 and 1938 (Hillier 2007). They were produced by *partial synthesis*, i.e. synthesis that began with structurally elaborate starting materials, complex natural products. A total synthesis referred to a synthesis starting from simple and inexpensive materials whose composition was known, such as air and coal. Robert Burns Woodward achieved a total synthesis of cortisone in 1951 (Woodward et al. 1951). The discovery of cortisone and its therapeutic efficacy led to what Hillier (2007) called the "diamond decades" of steroid chemistry that started in the 1950s.

Cortisone success, however, is often described as a mixture of knowledge and luck. "A fascinating tale of good science, perseverance, and luck" which, as Burns says, "might not be possible in today's regulatory environment" (2016:1), or a "discovery resulted from 19 years of imaginative and deductive observation together with an element of serendipity which seems to characterise many fundamental discoveries" (Glyn 1998: 822). Leo Slater (2000) used cortisone research to show that the boundaries between the disciplines were flexible and the way the networks of research interpenetrated one another. Several factors played a role in the cortisone case: the rise of steroid chemistry, simultaneous individual accomplishments as well as a continuous cooperation among scientists, military competitiveness, and cooperation among pharmaceutical companies.

Kendall, Reichstein, and Hench

Edward Kendall at the Mayo Clinic in Rochester, Minnesota and Tadeus Reichstein at the Eidgenössische Technische Hochschule (ETH) in Zürich independently identified the structure of cortisone in the 1930s from extracts of bovine adrenal glands (Mason et al. 1936, Reichstein 1936). Kendall isolated eight crystalline cortical compounds from some 1.250.000 cattle carcasses, while Reichstein isolated twenty-eight crystalline compounds from the adrenals of 20.000 head of cattle (Shoppee 1956: 319-322). Reichstein established his reputation with the synthesis of vitamin C in 1933, and Kendall had previously discovered thyroxin, a hormone of the thyroid gland, in 1918 (Simoni et al. 2002). Kendall's interest switched to the hormones of the adrenal cortex in 1929 when Albert Szent-György[4] from Cambridge vis-

[4] Albert Szent-Györgyi was awarded the Nobel Prize in Physiology or Medicine in 1937 for his discoveries in connection with the biological metabolic processes, with special reference to vitamin C and the catalysis of fumaric acid.



Edward Calvin Kendall

ited Kendall at the Mayo Clinic. Szent Györgyi was at the time pursuing the isolation of vitamin C from adrenal glands. (See Quirke 2005: 648).

We learn that Kendall had the assistance of commercial agreements and contracts with Parke-Davis in Detroit and Wilson Laboratories of the Wilson Packing Company of Chicago. Between 1934 and 1949 they provided some 150 tons of adrenal glands for his research. Kendall also produced about $9 million worth epinephrine, sold as Adrenalin, for Parke-Davis (Slater 2000). Kendall's program was a mixture of industrial process, chemical investigation, and basic medical research, being neither inherently pure nor applied. His work on the adrenals was expensive and laborious, and until the discovery of cortisone it seemed to be yielding no significant results. At the same time Reichstein worked with crude extracts provided by Organon, Inc. of Oss, Holland, not with adrenals (Slater 2000).[5] Reichstein and Kendall independently assigned their new compounds letter designations; Reichstein's "substance Fa" and Kendall's "compound E" later proved to be identical, and Kendall named them cortisone in 1949 to avoid confusion with vitamin E.

Philip Showalter Hench

Independent biochemical investigations were still far from discovering therapeutic efficacy. This was the accomplishment of Kendall's colleague, Philip Hench, the head of the Department of Rheumatic Diseases at the Mayo Clinic. Hench hypothesised the presence of a therapeutic agent X that emerged in conditions of jaundice and pregnancy, and relieved arthritic patients from rheumatic symptoms (Hench 1964). His physiologic research of an unknown therapeutic agent began in 1929, and it took twenty years, until his announcement at the Seventh International Congress of Rheumatology in New York in May 1949, to demonstrate that certain corticosteroids were able to reverse many of the acute manifestations of rheumatoid arthritis. Simultaneous discoveries made identification of the features of cortisone possible. One was biochemical, related to the steroid structure of the hormones isolated from

[5] Reichstein also tried to use plant material as a starting point for the synthesis of cortisone. In 1947 two of his assistants went on an expedition to Africa to search for the seeds of *Strophantus* species, especially *Strophantus sarmentosus*. They spent nine months on the Gold Coast, Togo, the eastern Ivory Coast and Southern Nigeria collecting samples of this species, but it proved inadequate for the production of cortisone. (Reichstein 1964: 304-305)

the adrenal cortex, and the other was physiologic, related to therapeutic possibilities for rheumatic patients. The discovery of a biological therapeutic substance was undertaken in ignorance of its site of origin, relying solely on its function in the organism. Hench eliminated the possibility that agent X is a sex hormone, because patients of both sexes were relieved from arthritis pain with the occurrence of jaundice. Successful converging of the two discoveries made at the same clinic presents the special serendipitous moment in the cortisone chronology.

World War II

The outset of World War II played a significant role in the reinforcement of collaboration between scientists on the issue of adrenocortical hormones. In 1941, as the United States became involved in World War II, adrenal research became an "internationally competitive effort" (Simoni et al. 2002: 21). As Viviane Quirke notes:

> *"The therapeutic potential of adrenal cortical hormones in rheumatic and other inflammatory diseases might never have been investigated, had it not been for the rumour in 1941 that Luftwaffe pilots were taking these hormones to increase their resistance to oxygen deprivation and be able to fly at higher altitudes." (2005: 649)*

A German submarine was captured with cargo that was believed to be adrenal glands. A report saying that the Germans were buying adrenal glands from slaughterhouses in Argentina reached Washington (Slater 2000). It was later revealed that the cargo in the submarine was in fact liver for Otto Bayer's work on vitamin B12 at IG Farbenindustrie (Quirke 2005).

It is true that steroids were being produced out of extracts of sex organs between 1920 and 1940 in Germany, but none of them was cortisone. The first European adrenal product was Doca (Deoxycorticosterone Acetate), a chemical sold by Swiss Ciba, identical to the later Cortiron, launched by the German Schering (Gaudillière 2013). Ciba became involved very early with steroid chemistry through its collaboration with the ETH in Zurich and later on with the University of Basel (Heusler, Kalvoda 1996). Ciba had an agreement with ETH in Zürich, and therefore benefited from Reichstein's work. All patent rights on steroids were assigned to Ciba. However, it was Schering that dominated the German drug market, and Dutch Organon which supplied Reichstein with research material. So the three companies, Schering, Ciba, and Organon, signed an agreement in 1939 called *Cortin*, which organized and limited competition among these corporations, providing

important resources for circulation of research information and for mutual licensing of patents (Gaudillière 2013). Early uses of Schering's Cortiron remained limited because its usefulness was not clear, and cases of Addison's disease, that it hoped to alleviate, were rare.[6] That did not change during the war, even though steroids were given military priority because of their use in healing wounds (Gaudillière 2013). We can see how the boundaries between basic and applied were vague, and how European pharmaceutical and academic communities exchanged information and material, and facilitated intensive research. The line connecting ETH, Organon, Ciba, and Schering can be traced to the University of Basel in Switzerland, where Reichstein continued his work.

In America, a similar cooperation of industry and academics took place. The rumour about German usage of steroids motivated the American National Research Council to rank steroids at the top of wartime research agenda, above penicillin and antimalarials. Merck and the Mayo Clinic, as well as other academic and industrial groups, were collaborators in the steroid research program set up by the Office of Scientific Research and Development (OSRD), which intensified the research on adrenals and promoted the crossings of disciplinary boundaries. (Slater 2000) It was also in 1941 when the decision was brought to administer compound E (cortisone) to a patient. Hench and Kendall met at a conference, where Kendall remarked that his compound E increased the resistance of animals against reactions to typhoid vaccine. Hench made note of this in his pocket notebook, and eight years would elapse before there would be enough of this substance to administer to a rheumatoid patient (Hench 1964).

The priority of adrenal research was the reason why Lewis Sarett from Merck and Company worked for three months in Kendall's laboratory in 1942. The idea was to gain knowledge and return to Merck with a goal of developing large-scale synthetic methods for the compounds that were chosen for the initial studies, compounds A and E, because of their relative structural simplicity. After several years funds waned as the effectiveness of the research for various war-related uses did not meet the expectations. Eventually, only Kendall's group at Mayo and his collaborators at Merck continued. By the end of the war, in 1945, enough compound A had been available for clinical testing. It was a big disappointment it's proven ineffectiveness in cases of Addison's disease (Kendall 1964).

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[6] Addison's disease is a chronic condition of adrenal insufficiency, deadly if not treated with hormone replacement therapy.

Synthesis and first supplies

Kendall and his associates pursued the research. Lewis Sarett synthesised cortisone in 1946 in 37 steps at Merck (Sarett 1946). A partial synthesis from desoxycholic acid that had been pioneered by Reichstein's group in Basel produced the first 18 milligrams of cortisone. Shortly after the war ended Merck management decided to make cortisone available for clinical investigations. Jacob Van de Kamp, Max Tishler, along with Kendall, Sarett and Merck's development staff improved Sarett's partial synthesis, and by April 1948 sufficient amount of cortisone was available (Patchett 2002, Slater 2000). In September 1948 Philip Hench administered 100 milligrams of cortisone intramuscularly to a patient suffering from rheumatoid arthritis.[7]It showed a rapid success in relieving pain and reducing inflammation. Subsequent trials with cortisone andadrenocorticotropic hormone (ACTH) gave similar symptomatic relief (Hench 1949, 1964).

The patent was assigned to the non-profit Research Corporation (Kendall 1964, Slater 2000). The Research Corporation had been founded in 1912 partly to prevent the commercial exploitation of academic research. The Corporation held patents for scientists at universities and foundations and licensed these patents, producing income for the support of other research, and providing for the redistribution of research income (Slater 2000: 457-458). In August 1949 the Committee of the National Academy of Sciences on the Investigation of Cortisone posed the problem of distributing the limited amount of cortisone. It was decided that the small amount available will be used only for clinical and experimental research and that it will be made available to selected investigators from the USA and Canada.Since the Academy had no funds with which to buy cortisone or to support research, it was

> *"confidently expected that the needed funds will become available from both public and private sources. (...) The Academy committee has accepted this responsibility because of the deep conviction that a new discovery of the greatest importance to the health and welfare of countless people has been made and that it is vital to promote its most rapid and intelligent development." (Science, August 5, 1949)*

In the autumn of 1949the Research Corporation held the Cortisone Conference, where seventeen scientists to whom the Corporation provided support were invited (Slater 2000). Topics included a total synthesis, natural

[7] In 1950 cortisone started to be given by mouth, in the form of 100 mg tablets (BMJ 1 (4701) 1951: 288).

raw materials for partial synthesis, hormone analogues, toxicity, and clinical testing. The second conference was held in Chicago in September 1950, and the third in New York in 1951.

We can say that the outbreak of World War II had a crucial role for the investments in adrenal research, understandable in the light of the emerging steroid research activity. Luckily enough, one of the compounds turned out to be physiologically active in a way no one could anticipate. However, the work on steroids had begun several decades earlier. Companies like Ciba, Schering, Organon, as well as French Roussel (Gaudillière 2013) industrialized steroid research in the 1930s, including adrenal research, as we can see from Doca and Cortiron.

Kendall, Hench and Reichstein were awarded the 1950 Nobel Prize in Physiology or Medicine for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects. On November 1 1950, cortisone became available to physicians of the United States through drug supply houses. Merck's brand of cortisone was named Cortone. The price was falling: In July 1949, the price per gram was $200.00. In 1950, it was reduced five times, from $150.00 in January to $35.00 on November 1 (Kendall 1964: 276-277). However, in 1951 we can still read that cortisone "cannot yet, or perhaps ever, become a cheap medicament". (BMJ 2 (4728) 1951: 406-408) This was mostly due to the lack of supplies of bile acid. Foreign sales were minimal, regulated by the US government, and were made primarily to those countries that would contribute the starting material, cattle bile, or participate in clinical development (Slater 2000: 467).

Successes and controversies

Jean-Paul Gaudillière called cortisone "an iconic product of the 'therapeutic revolution'" (2013: 190). Cortisone was used in treating excessive inflammation, allergy, acute infections, and autoimmune disorders. Eventually, it had a deep impact on several medical specialties, including ophthalmology, gastroenterology, respiratory medicine, dermatology, nephrology, endocrinology and rheumatology. John H. Glyn, a British rheumatologist and Hench's friend and colleague, wrote in 1998 that the discovery of cortisone transformed rheumatology from its "Cinderella status of the BC (before cortisone) era" (1998: 823), though its clinical usefulness remained controversial. The dramatic effects in rheumatic patients and its anti-inflammatory agency were challenged by serious side effects brought on by high dosage levels and prolonged therapy (Beckett et al. 1956), as well as by relapse of the treated

condition once the treatment was ended (Wilson 1950, Carlisle 1950, Thorn 1951). It was clear that "cortisone supresses rheumatoid arthritis but does not cure it" (BMJ 2(4725) 1951). It was discussed with caution, considered to be "a real danger if (...) it is used anything like as empirically by medical men generally as were the sulphonamides and penicillin" (Emery 1949). Glyn wrote in his memoire:

> *"In the United States a black market developed which had serious medical and social repercussions. Patients who had experienced great relief of their symptoms were not prepared to relapse when supplies ran out. They became totally dependent on the drug. Overdosage led to devastating side effects, and the ever escalating cost of maintaining their supplies resulted all too often in financial destitution. Such patients had no alternative but to seek relief by registering as guinea pigs to research groups such as the one at the Bellevue Hospital in New York which I joined in 1952." (1998: 823)*

Alternative sources of starting material and new methods of production were investigated because of shortages of bile acids and of money (BMJ 1(4668) 1950: 1477-1478). Kendall reported at the American Chemical Society meeting that 40 head of cattle were needed to provide cortisone needed daily by one patient(The Science News-Letter 57(8) 1950: 120-121).Merck officials-expected the production to be tripled or quadrupled by the middle of 1952. (The Science News-Letter 59 (11) 1951: 168-169) The increased output was expected from recently investigated botanical sources as well as from total synthesis.

John Glyn led the first UK cortisone studies. Small quantities of cortisone and ACTH were distributed to hospitals in Britain (BMJ 2 (4693) 1950: 1375). Hench gave two well attended lectures in London in 1950 (BMJ 2 (4693) 1950: 1375), and Glyn published the preliminary results in the British Medical Journal in 1950 (Copeman et al. 1950), and the next in 1952 (Copeman et al. 1952). In 1954 the results of the first multi-centre crossover trial of cortisone and aspirin organised by the British Nuffield Foundation and the Medical Research Council were published in the British Medical Journal.[8] The trial concluded that there was no evident difference between the two groups. This led to a sharp correspondence between Glyn and Austin Bradford-Hill, who designed the trial (Glyn, Todd 1954, Bradford-Hill 1954). Glyn criticized the design, the selection of patients, and the dosage:

[8] The trial was organised in six centres and included 61 patients with rheumatoid arthritis (BMJ 1 (4873) 1954: 1223–27).

> *"My comments on this trial are largely a text on which to hang a plea to the statisticians to modify their rigid approach to clinical trials. Perfect statistical techniques are not possible when dealing with biological material, nor is it possible at the early stage at which the Medical Research Council generally formulate their trials for them to lay down the optimum regimes which are not liable to subsequent criticism. (...) In other words, the pendulum away from therapeutic empiricism has swung too far." (Glyn, Todd 1954: 1376-1377)*

We learn that in the later years, in a personal conversation, Bradford-Hill "graciously agreed" that some of Glyn's comments "were justified in the light of subsequent events" (Glyn 1998: 823).Sir Austin Bradford-Hill was an English epidemiologist and statistician who pioneered randomized control trials and established a criterion of causation (Bradford-Hill criteria of causation). Randomized control trials have been the cornerstone of evidence-based practice since then. They established the procedure and dominate delivery of health care. Their critics focus on the problems of statistical inference and generalisability of population-based research findings to particular instances of clinical decision-making. Evidence-based practice has been accused for being de-personalised, and the person-centred approach has recently gained new attention (see Anjum et al. 2015). Similar reluctance and criticism can be traced in Glyn's 1954 letter to Bradford-Hill. Cortisone brought additional awareness of a need for individualised therapy and patient approach.

By 1955, analogues with reduced toxicity and enhanced physiological activity were developed (BMJ 1 (4929) 1955: 1520). Though Kendall believed it "highly improbable" (1964: 278) that any product would occur that would be used in the place of cortisone and cortisol, generic formulations of prednisone, prednisolone (see Jenkins, Sampson 1967) and dexamethasone remain in widespread use to this day. In chemistry, a development of the method of conformational analysis facilitated the study of the relationship between structure and activity, providing a more rational approach to drug design (Quirke 2005). In medicine and pharmacology cortisone was an important incentive for a new attention to chronic diseases that occurred in the post-war research (Quirke 2005). It is now known that intracrine[9] metabolism of cortisone to cortisol sustains local amplification of glucocorticoid action at sites of inflammation throughout the body (Hillier 2007).[10]

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[9] "Intracrine" denotes a type of hormone function in which a regulatory factor acts within the cell that synthesizes it by binding to intracellular receptors. (Dorland's Medical Dictionary for Health Consumers 2007)

[10] Cortisol is the closely related compound F, in Kendall's notation.

Conclusion

The aim of this paper was to expose a fragment of the history of adrenocortical steroid research. The case of adrenal research between 1930s and 1950s shows the evident cooperation between academic and industrial in both European and American research activity (ETH-Ciba-University of Basel, Ciba-Shering-Organon, Mayo-Merck). Adrenal steroid research was expensive and depended on the providers of research material, such as Organon, Parke-Davis, and Merck Company. A continuous cooperation between scientists generated intense exchange of hypothesis and material, which led to both fundamental and practical achievements. Cooperation between pharmaceutical companies (the Cortin agreement) and non-profit organisations (the Research Corporation) provided a stabile drug market and sound research climate through licensing of patents and exploitation of new drugs. We have also seen the way political circumstances created research priorities and the way wartime posed time-constraints on achieving research goals, which intensified research activity.

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Sažetak

Otkriće, sinteza i terapijska primjena kortizona predstavljaju paradigmu moderne translacijske medicine (Hillier 2007, Saenger 2010) jer združuju otkrića biokemičara Edwarda Calvina Kendalla i Tadeusa Reichsteina; otkriće kemijske sinteze za široku primjenu industrijskog kemičara Lewisa Hastingsa Saretta i otkriće terapijske primjene reumatologa Philipa Showaltera Hencha. Cilj je translacijske medicine ubrzati proces između bazičnog istraživanja i kliničke prakse te integrirati različite discipline da bi se razumjeli različiti ishodi (Zhang et al. 2014). U ovome radu predstavit ću uvjete koji su omogućili ovu suradnju bazičnog, primijenjenog i kliničkog istraživanja: uspon steroidne kemije, istovremena pojedinačna dostignuća, kao i kontinuirana suradnja između znanstvenika, vojna kompetitivnost i suradnja između farmaceutskih kompanija.

Key words: *kortizon; translacijska medicina; Edward Kendall; Philip Hench; društveni aspekti farmakologije.*