Topical Corticosteroids, Structure-Activity and the Glucocorticoid Receptor: Discovery and Development—A Process of "Planned Serendipity"

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ABSTRACT: This is a personal recounting of the way in which the original steroid chemists and biologists worked closely together, often by trial and error, to use cortisol as the template to develop increasingly improved systemic glucocorticoids. In doing this, they learned how certain chemical functional groups affected efficacy and safety negatively and positively. When the more promising systemic glucocorticoids were subsequently applied topically, the skin barrier impaired their activity. This led to new research, this time employing in vitro percutaneous absorption evaluations coupled with *in vivo* vasoconstrictor studies, to screen and develop effective new topical delivery systems. A subsequent stage of this glucocorticoid research revealed that these molecules had to "fit" into receptor sites and the approximate spatial structure of such receptor sites. It also disclosed the way that the various chemical functional groups affected that "fit" and the resulting effect upon safety and efficacy. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:2936–2947, 2008

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GLUCOCORTICOIDS

Cortisone: from Discovery to Therapy

In the late 1930s, miniscule amounts of active steroids were isolated from adrenal glands by several groups, including those led by Tadeus Reichstein in Switzerland, Edward Kendall at the Mayo Clinic, and Oskar Wintersteiner at Columbia. Among these steroids, labeled compounds A–E, were the yet-to-be-identified hormones cortisone and cortisol.[1,2] The National Research Council convened a meeting of scientists during WWII in response to troubling rumors that the Polish underground reported to the U.S. "At the conference it was stated on good authority that German scientists had beaten all others in the race to unravel the secret of the adrenal cortex. They were said to have made an extract that counteracted hypoxemia and permitted the pilots of the Luftwaffe to fly at 40000 feet with impunity."[3,4] This rumor was false, but it triggered a major research program by the U.S. government in 1942 to synthesize sufficient cortisone and/or cortisol for testing.[5] The ability of cortisone to alleviate inflammation was eventually confirmed by Hench et al.[6,7] The first human injection of compound E was made at

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St. Mary's Hospital of the Mayo Clinic on September 21, 1948.[3] The astounding success in patients with severe rheumatoid arthritis was immediately acclaimed worldwide. In an incredibly short amount of time, Hench, Kendall, and Reichstein were awarded the Nobel Prize in 1950.

Many medicinal chemistry groups immediately sought suitable starting materials and synthetic processes that could be used for producing large amounts of cortisone (Fig. 1). Placing an oxygen at C-11 presented the greatest single obstacle to synthesizing cortisone. No available starting material had an oxygen at C-11, and no practical method was known for adding this. One approach started with a compound derived from diosgenin (from a Mexican yam); it was perfused through fresh cow adrenal glands, which biochemically added the C-11 β hydroxyl. Syntex developed a synthetic method starting from a chemical found in hemp. Finally, Upjohn developed an efficient microbiological conversion method starting with progesterone supplied by Syntex. In this way enough cortisone became available for clinical trial and therapeutic use.[8]

CORTISONE: IMPROVING ITS ACTIVITY AND/OR REDUCING UNDESIRABLE EFFECTS (THE ROLE OF THE MEDICINAL CHEMIST)

It was soon found that after long-term use the wonderful systemic anti-inflammatory activity of cortisone was accompanied by severe side effects such as electrolyte disturbances that disrupted the metabolic balance of the body. Medicinal chemists searched for ways to modify cortisone to increase its systemic activity and/or reduce its undesirable side effects.

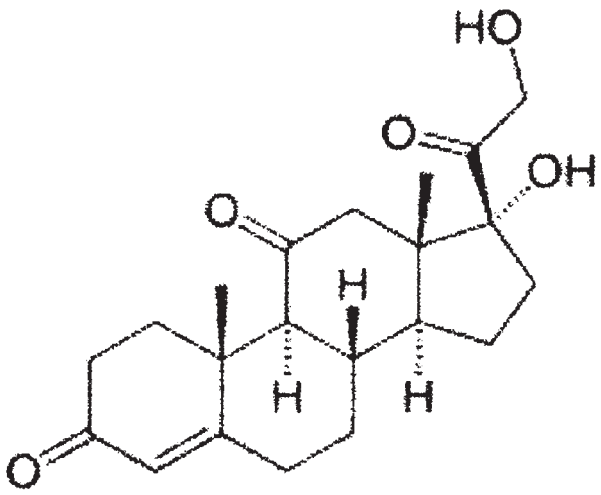

Figure 1. Structure of cortisone. Systematic name, 17,21-dihydroxypregn-4-ene-3,11,20-trione; chemical formula, $C_{21}H_{28}O_5$.

Attaching functional groups to the various steroid positions required developing novel chemistries. The syntheses were multi-step, requiring blocking of some groups in the molecule while trying to change or introduce other groups. Complex mixtures often resulted, requiring novel separation techniques. Yields diminished with each step. (For example, fluocinonide required as many as 32 stepwise reactions.)

Most importantly, there were no established guidelines to follow. It was as if the chemists were assigned the task of modifying the pins of a key to make it fit and turn a lock whose configuration they could only imagine. Changing a pin on the key might affect one of the tumblers on the lock for better or for worse. Different combinations could and would produce unexpected results.

Much of the synthetic work was empirical. It was often trial and error, intuition, guesswork, and gleaning leads from other not necessarily related chemistry. In order to gain some guidance, the dozens of compounds that were laboriously synthesized and isolated were forwarded to the biology labs for testing in various biological assay models described below. In this way, comparisons of activity might be observed and logic and/or serendipity might produce a good result.

These compounds were then tested in animal models of human diseases in the uncertain hope that what was "sauce for the goose" would also work in humans. Drugs developed from such a methodology had the potential of causing as many unwanted side effects in humans as satisfying the therapeutic needs.[9]

There was a slow and steady progression of "molecular acrobatics" as scientists learned how to add functional groups at various positions on the steroid molecule and gradually discerned which of these had been either beneficial or detrimental from the results of the various biological assays.[10] For instance, changes that stabilized a corticoid to metabolic inactivation would enhance potency, although they might negatively affect other processes.[11] Table 1 presents an approximately chronological sequence of the step-by-step additions of functional groups to systemic corticosteroids, resulting in improvements in biological activity. It might seem that the addition of valuable functional groups at key positions on the molecule in the development of