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**Title:** The development of novel anti-inflammatory drugs for IBD  
**Issue Date:** 2015-11-12
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A brief history
The field of glucocorticoids and the glucocorticoid receptor is quiet extensive. Currently (2015) a simple search on PubMed will return close to 200,000 hits. This is related to the ever increasing interest but also for a part to the long history of glucocorticoid research which dates back to the eighteen hundreds. In 1855 Thomas Addison, a British physician, described a progressive destructive condition of the adrenal glands [1] which we now know renders patients glucocorticoid and mineralocorticoid deficient. Symptoms include low blood pressure, muscle weakness and low blood sugar. If left untreated patients may develop a severe condition termed Addisonian crisis which may be life-threatening. Nowadays patients suffering from adrenal insufficiency can be easily compensated by supplementing the lacking cortisol in the form of a tablet.

Not long after Addison’s publication, a Mauritian physiologist named Charles-Edouard Brown-Sequard used animals to show that removal of the adrenal glands results in death which, as he correctly suggested, was due to a lack of hormones. It took another forty years before the next step was taken. In 1898 the Canadian physician Sir William Osler treated an Addison’s patient with crude preparations of adrenal glands taken from animals, thereby temporarily improving symptoms of the disease [2]. His results strongly suggested that the adrenal glands produced a substance that was vital to the body. To establish this, both Hartman and Swingle adrenalectomized rats, cats and dogs, and prepared extracts with which the life of these animals could be maintained [3, 4]. These extracts have also been used effectively for the treatment of Addisons patients and at the time it was believed they contained a substance that could extend life in general. Therefore an international competitive search commenced which culminated in the discovery of cortisone in 1934. The American chemist Edward Kendall was the first to successfully isolate it. He discovered that the adrenal glands did not contain just one substance but that the effects caused by adrenalectomy are related to different groups of molecules, which he labeled alphabetically. Only four of these seemed to have a physiological effect in animals. 11-dehydrocorticosterone (compound A), corticosterone (compound B), dehydrocorticosterone (compound E, known to Reichstein as compound Fa) and 17-
hydroxycorticosterone (compound F)[5]. Importantly, its use as an anti-inflammatory drug was completely unknown. Investigations were driven by a rumor during WWII that the Germans were performing large scale isolations from bovine adrenal glands in order to prevent hypoxia of Luftwaffe pilots enabling them to fly on higher altitudes. As a consequence it was in the interest of the war to quickly find a way to synthesize adrenal hormones. And although a use for these hormones in warfare could not be found, the first large scale synthesis of cortisone was completed by Kendall at the Mayo clinic (in collaboration with Lewis Sackett of Merck) in 1948.

Dr. Philip S. Hench was Chief of the Medical Service and Director of the Army's Rheumatism Centre at the Army and Navy General Hospital during the war. When the war came to an end he specialized in arthritic disease at the Mayo clinic. There he noticed that particular conditions, such as pregnancy or jaundice, caused a remission of pain. From these observations he became convinced that this effect was caused by a steroid hormone. In 1949 Hench, in collaboration with Kendall, reported the successful treatment of rheumatoid arthritis patients with Compound E [6]. In 1950, for their work on hormones of the adrenal cortex, Hench, Kendall and Reichstein received the Nobel Prize in physiology or medicine. Interestingly to isolate 1 gram of cortisone, Kendall required 500 kilogram of adrenal glands, which he collected from 20,000 cows. It was not until 1952 before a means of biological production was found, using the fungus *Rhizopus nigricans*.

References

2. Osler, W., *On six cases of Addison's disease with the report of a case greatly benefited by the use of the suprarenal cortical extract*. Int Med Magazine. , 1896.
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