Upjohn Reichstein's Compound-S Transformation Team (Haines Team)

Discovered use of Streptomyces fradiae and Cunninghamella blakesleana to oxidize Reichstein's Compound-S to hydrocortisone. Discovery allowed use of Percy Julian's Reichstein's Compound-S for manufacture of hydrocortisone and cortisone.

Here's what happened:

- 1948: Percy Julian develops synthesis route for making Reichstein's Compound S, but is unable to find a process for oxidizing Compound-S to hydrocortisone
- 1950: The Upjohn Haines Team discovers that the bacterium *Streptomyces fradiae* directly oxidizes Compound-S to hydrocortisone
- 1950: The Haines Team further discovers that the fungus *Cunninghamella Blakesleana* also directly oxidizes Compound-S to hydrocortisone with improved yield
- 1950's: Reichstein's Compound-S proves to be too expensive to use as an intermediate; Upjohn develops the stigmasterol – progesterone - 11α-hydroxyprogesterone route for manufacture of hydrocortisone and cortisone.

What has been said about the significance of the Compound-S biotransformation discovery

"Now microbial enzymes had achieved the ultimate goal, that of simulating mammalian enzymes exactly by introducing oxygen into the 11-position in the natural 11β-configuration, requiring no further chemical manipulation.
Upjohn would have to make a choice [having] two competing microbial 11-oxygenations in hand, one based on the 11α-hydroxylation of progesterone and the other on the direct 11β-hydroxylation of Reichstein's substance-S"

from: J.A. Hogg. Steroids, the steroid community, and Upjohn in perspective: a profile of innovation. *Steroids*, 1992, 57, 593-616

"Colingsworth, Brunner and Haines, also of the The Upjohn Company, discovered the 11β-hydroxylation of Compound S with the actinomycete, *Streptomyces fradiae* shortly after the original Murray-Peterson findings were made. This was to be the prototype for a second class of hydroxylation of considerable commercial significance."

from: W. Charney, H.L. Herzog. Microbial Transformations of Steroids – A Handbook. Academic Press, New York. 1967, pages 5-6.

"Scientist's from Minnesota's Mayo Clinic made headlines in 1949 when they discovered that the steroid cortisone could ease the symptoms of rheumatoid arthritis. This painful disease, which even today affects more than two million Americans, cripples patients by inflaming their joints and destroying cartilage. But cortisone was extremely scarce, and the sudden demand created by the Mayo Clinic's dramatic announcement drove prices up over $4000 an ounce – and sent scientists scrambling for new ways to make it. While many chemists attempted to produce the chemical from scratch, Julian tried a seemingly simpler approach: synthesizing an almost identical steroid called Compound S, which needed just one oxygen atom to become [hydro]cortisone. Scientists from Michigan's Upjohn Company soon discovered that a common mold could provide Compound S with the needed atom."

from: Percy Julian Forgotten Genius, NOVA special airing on PBS in 2007 (available on DVD).

Team Published Papers

D.R. Collingsworth, M.P. Brunner, W.J. Haines. **A partial microbiological synthesis of adrenal cortex hormones.** J. Am. Chem. Soc., 1952, 74, 2181-2382.

F.R. Hanson, K.M. Mann, E.D. Nielson, H.V. Anderson, M.P. Brunner, J.N. Karnemaat, D.R. Collingsworth, W.J. Haines. **Microbiological Transformations of Steroids. VIII. Preparation of 17α-Hydroxycorticosterone.** *J. Am. Chem. Soc.,* 1953, 75(21), 5369-5370.

Team Patent

W.J. Haines, D.E. Collingsworth. **Steroid Oxidation.** U.S. Patent 2,649,401. Filed 16 September 1950, granted 18 August 1953.