Upjohn Progesterone Transformation Team (Murray-Peterson Team)

Discovered use of *Rhizopus nigricans* to oxidize progesterone to 11α-hydroxyprogesterone. Discovery allowed first low-cost, high-quality manufacture of hydrocortisone and cortisone from progesterone. Team went on to discover additional valuable steroid microbiological transformations, leading to manufacture of multiple steroid medicines.

Here's what happened:

- 1949: researchers at the Mayo Clinic make a major medical breakthrough by showing that cortisone is an effective treatment for the inflammation caused by rheumatoid arthritis.

- 1940's: Marker shows that progesterone, a potential intermediate for the synthesis of cortisone, could be made from botanical sterols, but is unable to find a process for oxidizing progesterone in order to make cortisone.

- 1950: Djerassi (at Syntex), following on Marker's work, develops a chemical process for conversion of progesterone to cortisone, but the process is not developed for commercialization.

- 1950: Upjohn formed research teams to investigate potential chemical and microbiological routes for oxidizing progesterone, Reichstein's Compound S and other steroid intermediates. Teams were unique mixes of chemists, biochemists and microbiologists.

- 1950: The Murray-Peterson Team discovers that Rhizopus fungi selectively transform progesterone to 11α-hydroxyprogesterone. The process is optimized using *Rhizopus nigricans* and the biotransformation step becomes part of the most successful commercial process for manufacture of hydrocortisone and cortisone.

- 1950's – 1960's: Murray-Peterson Team goes on to discover multiple steroid microbiological transformations useful for the manufacture of corticosteroid analogs with improved therapeutic activities and/or safety profiles. In a male dominated enterprise a female scientist (H. M. Leigh) becomes a co-author of team papers and a co-inventor on team patents (See Photos supporting document).

What has been said about the significance of the progesterone biotransformation discovery:

"The 11alpha-hydroxylation of progesterone was the trigger shortly after the beginning of the cortisone era in 1949 that reshaped steroid research strategy throughout the pharmaceutical industry."

"Within the framework of a discliplined and well-coordinated project Murray and Peterson, individuals of sharpley contrasting nature, had made a history-making discovery of the unobvious, the hallmark of invention by definition and hailed as 'the neatest trick of the year'."

from: J.A. Hogg. Steroids, the steroid community, and Upjohn in perspective: a profile of innovation. *Steroids*, 1992, 57, 593-616, (with reference to: *Chem, Eng. News*, 7 April 1952).

"The importance of the Murray-Peterson discovery was many-fold. It led to a new technology for the manufacture of adrenocortical hormones and, eventually, of their synthetic analogs. It introduced the use of fungi, heretofore unexplored as a source of enzymes for microbiological transformations. And perhaps most important of all, it caused a surge of interest in the field. Much new, basic information for science was developed subsequently from the study of microbiological transformation of steroids."

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

"The pragmatic and the programmatic strains of biotechnic thinking of the 1930s came together in the years after World War II. Medicine, energy and the environment were each seen to be served by a potentially powerful new technological paradigm. The manufacture of antibiotics and then steroids by means of fermentation technologies grew enormously. This provided a context for the formalizing of biotechnology as a distinct applied science."

Michael R. Ladisch, M. 2005. Biotechnology (Bioprocess Engineering). Van Nostrand's Encyclopedia of Chemistry. pg 7. Published Online: 15 JUL 2005 DOI: 10.1002/0471740039.vec0422

"One research program led by Djerassi focused on the conversion of diosgenin to cortisone."
"At that time, cortisone could only be made by a laborious 36-step Merck & Co. process that started with desoxycholic acid isolated from ox bile. Syntex completed its synthesis of cortisone from diosgenin; however, this achievement immediately was overtaken by another scientific breakthrough.
In 1951, scientists at the Upjohn Co. introduced a microbiological process, which specifically oxidized progesterone to a product that was easily converted to cortisone."

From: The "Marker Degradation" and Creation of the Mexican Steroid Industry 1938-1945. ACS International Historic Chemical Landmark. Dedicated 1 Oct 1999.

Team Published Papers

D.H. Peterson, H.C. Murray. **Microbiological Oxygenation of Steroids at Carbon-11.** *J. Am. Chem. Soc.*, 1952, 74(7), 1871-1872.

D.H. Peterson, H.C. Murray, S.H. Eppstein, L.M. Reineke, A. Weintraub, P.D. Meister, H.M. Leigh. **Microbiological Transformations of Steroids. I. Introduction of Oxygen at Carbon-11 of Progesterone.** *J. Am. Chem. Soc.,* 1952, 74(23), 5933-5936.

P.D. Meister, D.H. Peterson, H.C. Murray, S.H. Eppstein, L.M. Reineke, A. Weintraub, H.M. Leigh. **Microbiological Transformations of Steroids. II. The Preparation of 11α-Hydroxy-17α-progesterone.** *J. Am. Chem. Soc.,* 1953, 71(1), 55-57.

S.H. Eppstein, P.D. Meister, D.H. Peterson, H.C. Murray, H.M. Leigh, D.A. Lyttle, L.M. Reineke. A. Weintraub. **Microbiological Transformations of Steroids. III. Preparation of 11-Epi-cortisone and 6β-Hydroxy-11-desoxycorticosterone.** *J. Am. Chem. Soc.,* 1953, 75(2), 408-412.

D.H. Peterson, S.H. Eppstein, P.D. Meister, B.J. Magerlein, H.C. Murray, H.M. Leigh, A. Weintraub, L.M. Reineke. **Microbiological Transformations of Steroids. IV. The 11-Epimer of Compound F and Other New Oxygenated Derivatives of Reichstein's Compound S. A New Route to Cortisone.** *J. Am. Chem. Soc.,* 1953, 75(2), 412-415.

P.D. Meister, D.H. Peterson, H.C. Murray, G.B. Spero, S.H. Eppstein, A. Weintraub, L.M. Reineke, H.M. Leigh. **Microbiological Transformations of Steroids. V. The Oxygenation of 17α-Hydroxyprogesterone to 6β,17α-Dihydroxyprogesterone and 11α,17α-Dihydroxyprogesterone.** *J. Am. Chem. Soc.,* 1953, 75(2), 416-418.

D.H. Peterson, A.H. Nathan, P.D. Meister, S.H. Eppstein, H.C. Murray, A. Weintraub, L.M. Reineke, H.M. Leigh. **Microbiological Transformations of Steroids. VI. Preparation of 11α-Hydroxy-6-dehydroprogesterone.** *J. Am. Chem. Soc.,* 1953, 75(2), 419-421.

S.H. Eppstein, D.H. Peterson, H.M. Leigh, H.C. Murray, A. Weintraub, L.M. Reineke, P.D. Meister. **Microbiological Transformations of Steroids. VII. Preparation of 11α-Hydroxypregnane-3,20-dione and 11α-Hydroxyallopregnane-3,20-dione.** *J. Am. Chem. Soc.,* 1953, 75(2), 421-422.

D.H. Peterson, S.H. Eppstein, P.D. Meister, H.C. Murray, H.M. Leigh, A. Weintraub, L.M. Reineke. **Microbiological Transformations of Steroids. IX. Degradation of C_{21} Steroids to C_{19} Ketones and to Testolactone.** *J. Am. Chem. Soc.,* 1953, 75(22), 5768-5769.

S.H. Eppstein, P.D. Meister, H.M. Leigh, D.H. Peterson, H.C. Murray, L.M. Reineke, A. Weintraub. **Microbiological Transformations of Steroids. X. The Oxygenation of Androgens by Rhizopus.** *J. Am. Chem. Soc.,* 1954, 76(22), 5679-5682.

P.D. Meister, D.H. Peterson, S.H. Eppstein, H.C. Murray, L.M. Reineke, A. Weintraub, H.M. Leigh Osborn. **Microbiological Transformations of Steroids. XI. The Transformation of 3-Ketobisnor-4-cholen-22-al to 11α,22-Dihydroxybisnor-4-cholen-3-one and 6β,11α,22-Trihydroxybisnor-4-cholen-3-one by Rhizopus.** *J. Am. Chem. Soc.,* 1954, 76(22), 5679-5682.

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S.H. Eppstein, P.D. Meister, D.H. Peterson, H.C. Murray, H.M. Leigh Osborn, A. Weintraub, L.M. Reineke, R.C. Meeks. **Microbiological Transformations of Steroids. XV. Tertiary Hydroxylation of Steroids by Fungi of the Order Mucorales.** *J. Am. Chem. Soc.,* 1958, 80(13), 3382-3389.

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G.S. Fonken, H.C. Murray. **Microbiological Transformations of Steroids. XVII. Dehydrogenation of 5β-Prenane-3-11,20-trione 20-Ethylene Ketal by Septomyxa affinis.** *J. Org. Chem.,* 1962, 27(3), 1102-1104.

Team Patents (partial list)

H.C. Murray, D.H. Peterson. **Oxygenation of Steroids by Mucorales Fungi**. U.S. Patent 2,602,769. Filed 23 February 1952, granted 8 July 1952.

H.C. Murray, D.H. Peterson. **14-Alpha-Hydroxyprogesterone.** U.S. Patent 2,670,358. Filed 28 August 1952, granted 23 February 1954.

S.H. Eppstein, H.M. Leigh. **Recovery of Oxygenated Steroids From Aqueous Fermentation Media.** U.S. Patent 2,759,004. Filed 13 August 1953, granted 14 August 1956.