

Major Upjohn researchers (team leaders) of the work presented in this nomination

Reaearcher	Overview of Contribution
George Cartland, PhD	1930's-1940's - developed a method of manufacturing a stable extract of adrenal cortex extract activity, which was marketed in 1935 as ACE. Their analytical unit of measure for adrenal hormone potency, the Cartland-Kuizenga unit, became the worldwide standard.
Marvin Kuizenga, PhD	
Frederick Heyl, PhD	1949 - developed commercial chemical synthesis process for converting stigmasterol to progesterone
Milton Herr, PhD	
Herbert Murray, PhD	1952 - discovered microbiological route for oxygenating progesterone to hydroxyprogesterone, opened the door for low-cost synthesis of cortisone
Durey Peterson, PhD	
W.J. Haines, PhD	1952 - discovered microbiological route for oxygenating Reichstein;s Compound S to hydrocortisone
B.J. Magerlein, PhD	1952-1954 - developed commercial direct synthetic process for converting hydroxyprogesterone to hydrocortisone and cortisone
W.P. Schneider, PhD	
J. Ward Greiner	1956 – developed counter-current processing method for extracting corticosteroid manufacture starting materials stigmasterol and sitosterol from soy sterols
The combined work of these scientists reduced the synthesis of cortisone from Merck's 37 steps to 11 steps from an abundant sterol, stigmasterol, reducing the selling price about 100-fold and allowed Upjohn to dominate the market.	
John Hogg, PhD	1950's – 1960's – developed commercial routes next generation corticosteroid products. The combined work of these scientists lead to commercialization of cortisone-analogue, next generation steroids, which became even more important medicines than cortisone, boosting Upjohn into becoming the largest steroid producer in the world.
Frank Lincoln, Jr., PhD	
George Spero, PhD	
W.E. Dulin, PhD	
Merle Wovcha, PhD	1974 – discovered microbiological route for converting sitosterol to hydroxyandrostenedione, opened the door for sitosterol to become another starting material for steroid synthesis
Verlan Van Rheenan, PhD	1974-1990 – developed commercial routes for converting androstenediones into useful steroid manufacturing intermediates and products. The combined work of Wovcha and these scientists expanded even further the Upjohn steroid portfolio.
E.J. Hessler, PhD	
Doug Livingstone, PhD	

Major patents granted for the work presented in this nomination

US 2,601,287 – Partial synthesis of progesterone

Inventors: Frederick Heyl, Milton Herr

Filed: 18 Aug 1949, Granted: 24 Jun 1952

US 2,602,769 – Oxygenation of steroids by Mucorales fungi

Inventors: Herbert Murray, Duey Peterson

Filed: 23 Feb 1952, Granted: 8 Jul 1952

US 2,649,401 – Steroid oxidation

Inventors: W. Haines, D. Collingsworth

Filed: 16 Sep 1950, Granted: 18 Aug 1953

US 2,670,358 – 14- α -Hydroxyprogesterone

Inventors: Herbert Murray, Durey Peterson

Filed: 28 Aug 1952, Granted: 23 Feb 1954

US 2,715,621 – Steroids

Inventors: Philip Beal, John Hogg, Frank Lincoln Jr.

Filed: 30 Mar 1953, Granted: 16 Aug 1955

US 2,751,402 – Oxidation of hydrocortisone esters to cortisone esters

Inventor: William Schneider

Filed: 13 Aug 1953, Granted: 19 Jun 1956

US 2,759,004 – Recovery of oxygenated steroids from aqueous fermentation media

Inventors: S. Eppstein, Hazel Marion Leigh

Filed: 13 Aug 1953, Granted: 15 Aug 1956

US 2,839,544 – Countercurrent extraction of steroids

Inventors: John Ward Greiner, Glen Fevig

Filed: 4 Sep 1956, Granted: 17 Jun 1958

US 2,875,200 – 9 α -Halo-11 β ,21-dihydroxy-4,17(20)-pregnadiene-3-one compounds and process of preparing thereof

Inventors: John Hogg, Frank Lincoln Jr.

Filed: 17 Dec 1954, Granted: 25 Feb 1959

US 2,897,217 – 6-Methyl analogues of cortisone, hydrocortisone and 21-esters thereof

Inventor: George Spero

Filed: 23 Nov 1956, Granted: 28 Jul 1959

US 2,897,218 – 6-Methyl-1-dehydro analogues of cortisone, hydrocortisone and 21-esters thereof

Inventors: Oldrich Schek, George Spero

Filed: 23 Nov 1956, Granted: 28 Jul 1959

US 2,923,720 – 2-Lower-alkyl pregnanes and process thereof
Inventors: Frank Lincoln Jr., John Hogg
Filed: 31 Jan 1955, Granted: 2 Feb 1960

US 3,359,287 – 16-Methylene-17 α -hydroxy progesterones and derivatives thereof
Inventors: John Babcock, J. Allan Campbell
Filed: 16 Nov 1959, Granted: 19 Dec 1967

US 4,035,236 - Process for preparing 9 α -hydroxyandrostenedione
Inventor: Merle Wovcha
Filed: 25 Oct 1975, Granted: 12 Jul 1977

US 4,102,907 – Disulfinylation process for preparing androsta-4,9(11)-diene-3,17-dione
Inventor: Kenneth Shephard
Filed: 7 Mar 1977, Granted: 25 Jul 1978

US 4,216,159 – Synthesis of 16-unsaturated pregnanes from 17-keto steroids
Inventors: Edward Hessler, Verlan Van Rheenan
Filed: 25 May 1978, Granted: 5 Aug 1980

US 4,345,029 – *Mycobacterium Phlei* mutants convert sterols to androsta-1,4-diene-3,17-dione and androsta-4-ene-3,17-dione
Inventors: Merle Wovcha, C. Biggs
Filed: 8 Sep 1980, Granted: 17 Aug 1982

US 4,977,255 - Steroidal 17 α -silyl esters and process to corticoids and progesterones
Inventors: Douglas Livingston, Bruce Pearlman, Scott Denmark
Filed: 5 Nov 1987, Granted: 11 Dec 1990

Major references providing the information in this nomination

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

D.A. Livingston. Application of Silicon Chemistry in the Corticosteroid Field. *Advances in Medicinal Chemistry*, 1992, volume 1, pages 137-174

W. Charney, H.L. Herzog. *Microbial Transformations of Steroids – A Handbook*. Academic Press, New York. 1967

N. Applezweig. Steroid Drugs From Botanical Sources: Future Prospects. Renewable Resources – A Systemic Approach. Edited by Enrique Campos-López. Academic Press, New York, 1980

R.D.B. Carisle. A Century of Caring: The Upjohn Story. Benjamin Co., New York, 1987

G. Hetenyi, Jr., J. Karsh. Cortisone therapy: a challenge to academic medicine in 1949-1952. *Perspectives in Biology and Medicine*, 1997, 40(3), 426-440.

M. Whitehouse. Drugs to treat inflammation: a historical introduction. *Current Medicinal Chemistry*, 2005, 12(25), 2931-42.

L. Millikan. Drug therapy in dermatology. *Basic and Clinical Dermatology*, 25 July 2000

P. Weindling (Ed.). Healthcare in Private and Public from the Early Modern Period to 2000. Routledge, 2014.

A. Gelijns. *Innovation in Clinical Practice: The Dynamics of Medical Technology Development*. National Academies, 1991.

L. Engel. Medicine Makers of Kalamazoo. McGraw-Hill, 1962.

M.P. Ladish. Biotechnology (Bioprocess Engineering), page 5, Van Nostrand's Encyclopedia of Chemistry. Published On-line 15 Jul 2005.
DOI:10.1002/0471740039.vec0422.

P.J. Pitts. Making Drug Manufacturing Great Again. *Investor;s Business Daily, Potics, Commentary*, 21 April 2017. <http://www.investors.com/politics/commentary/making-drug-manufacturing-great-again/>

Major Steroids and Intermediates Manufactured by The Upjohn Company (1987)

THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001, U.S.A.
TELEPHONE (616) 323-4000

PHARMACEUTICAL CHEMICAL MARKETING DIVISION

BULK PRODUCT LIST

Corticosteroid

Betamethasone
Betamethasone Phosphate
Betamethasone Valerate
Cortisone Acetate
Dexamethasone
Dexamethasone Acetate
Dexamethasone Phosphate
Fludrocortisone Acetate
Fluorometholone
Hydrocortisone
Hydrocortisone Acetate
Hydrocortisone Hemisuccinate
Prednisolone Anhydrous
Prednisolone Hydrous
Prednisolone Acetate
Prednisone
Prednisone Acetate
Triamcinolone
Triamcinolone Acetonide

Steroid Intermediates

Androstenedione (AD)
11 α Hydroxyprogesterone
17 α Hydroxyprogesterone
17 α Acetoxyprogesterone
DBXI [17 α , 21-Dihydroxy-16 β -methyl-9 β ,
11 β -epoxy-pregna-1,4-diene-3,20-dione]
SD-V [17 α , 21-Dihydroxy-16 α -methyl-pregna-
4,9(11)-diene-3,20-dione,21-acetate]
SD-VI [17 α , 21-Dihydroxy-16 α -methyl-pregna-
1,4,9(11)-triene-3,20-dione]
SD-VII 17 α , 21-Dihydroxy-16 α -methyl-pregna-
1,4,9(11)-triene-3,20-dione,21-acetate]
I-1D [16 α , 17 α , 21-Trihydroxypregna-1,4,9
(11)-triene-3,20-dione,21-acetate]
3TR [21-Hydroxypregna-1,4,9(11)-16-tetraene-
3,20-dione-21-acetate]
1-2 Dihydrotriamcinolone [9 α Fluoro-11 β , 16 α ,
17,21-tetrahydroxypregna-4-ene-3,20-dione]

Antibiotics

Erythromycin
Erythromycin Stearate
Erythromycin Ethyl Succinate
Neomycin Sulfate
Novobiocin

Hormones

Ethisterone
Hydroxyprogesterone Caproate
Methyltestosterone
Progesterone
Testosterone
Testosterone Cypionate
Testosterone Enanthate
Testosterone Propionate

Sterols

Sitosterol
Stigmasterol

Specialty Chemicals

Cycloheximide
Streptozocin

1987