RETROSPECTIVE

Elwood V. Jensen (1920–2012): Father of the nuclear receptors

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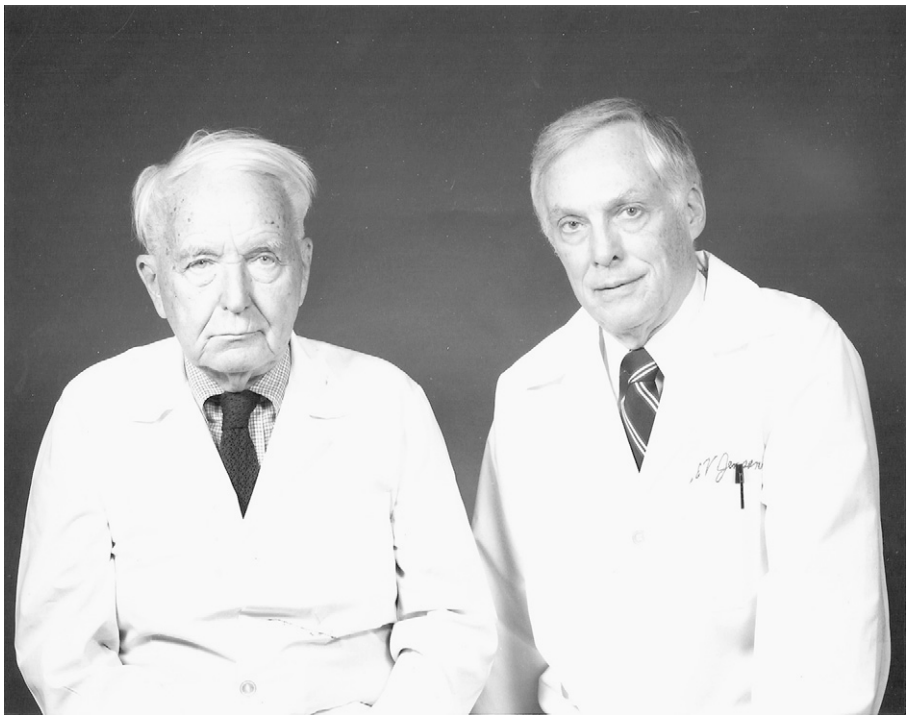
With the passing of Dr. Elwood Jensen, the field of Molecular Endocrinology recently lost another of its major pioneers. Jensen is popularly credited with the discovery of the mammalian estrogen receptor, and the promulgation of this important molecule as a key player in female endocrine function and as a diagnostic tool and therapeutic target for breast cancer. His work led to treatments that extended and saved the lives of many women.

Elwood V. Jensen was born in Fargo, North Dakota, in 1920. He was preschooled by his mother, a teacher, and entered grade school in Ohio, where he grew up and later matriculated at Wittenberg College. He received his doctorate in organic chemistry at the University of Chicago in 1944. Jensen entered the faculty as an Assistant Professor in the Ben May Laboratories at University of Chicago in 1947 and later did a sabbatical at the Swiss Federal Institute of Technology. While in Switzerland, he climbed the Swiss face of the Matterhorn—one of the highest peaks in the Alps—even though he had no mountaineering experience. In 1951, Jensen returned to the Ben May Laboratories for Cancer Research and became Director there in 1969 (Fig. 1). On a leave of absence in 1983 through 1988, he served as worldwide Research Director for the Ludwig Institute for Cancer Research, based in Zurich. After retirement from Chicago in 1990, Jensen was Scholar-in-Residence at Cornell Medical College, Alexander von Humboldt visiting professor at the University of Hamburg, and Nobel visiting professor at the Karolinska Institute in Stockholm before his appointment at the University of Cincinnati in 2002 as the Distinguished University Professor, George and Elizabeth Wile Chair in Cancer Research, to perform his late and final scientific work. Jensen passed away on December 16, 2012, at the age of 92. His first wife, the former Mary Collette, died in 1982. In addition to his son, Thomas, Jensen is survived by his second wife, the former Hiltrud Herborg; a daughter, Karen C. Jensen; and a sister, Margaret Brennan.

Jensen made his mark in the field of hormone action in the late 1950s, when the popular notions for steroid actions in growth were via enzyme activation, chemical and biosynthetic metabolism, and cellular transport of nutrients. His early association with the Nobel Laureate Charles Huggins in the mid 1950s led him to focus on the major growth effects in rat reproductive tissues emanating from administration of tiny amounts of estrogen. Realizing that certain estrogens could not be metabolized to downstream active products led him to synthesize a radioactive estrogen in the Fermi laboratory at the University of Chicago and administer it to ovariectomized rats. Surprisingly, Jensen found that the hormone was not metabolized and the radioactivity became localized and retained in the uterus and other reproductive tissues: the same that resulted in growth from estrogens. Thus was born the estrogen receptor theory. This theory resulted in considerable debate as to whether what was found was really a "receptor" because of a lack of downstream function. Although Jensen relented and termed it "estrophilin" for a few years, he was correct in all respects that it represented a true intracellular receptor, the latter theory substantiated by solubilization of the estrophilin and a series of sucrose gradient analyses performed first by Jack Gorski in 1967 and used effectively by Jensen, followed by the discovery of progesterone and other intracellular receptors by other laboratories. A nuclear concept was formalized by the O'Malley laboratory through the discovery of the estrogen-mediated induction of specific proteins and mRNAs by the steroid



Elwood Jensen (*Right*) with his mentor Dr. Charles Huggins (*Left*), Ben May Laboratory for Cancer Research, 1975.

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hormone. This body of work established Jensen's estrogen receptor as a nuclear transcription factor.

Jensen proceeded to publish work on the biochemistry of estrogen receptor translocation to the nucleus. In a monumental piece of work in the late 1970s, Geof Greene and Jensen used an estrogen affinity column to purify the estrogen receptor from reproductive tissues and then constructed a specific monoclonal antibody to estrogen receptor. The antibody was of critical use in two respects. First, it allowed quantification of the amount of estrogen receptor in tissues and it was quickly found that estrogen receptor-positive tumors had a better prognosis than estrogen receptor-negative tumors. This diagnostic procedure was applied as a standard diagnostic by many laboratories from the 1980s onward to assess the presence of estrogen receptor in female breast cancer samples. The procedure became a reliable prognostic factor to identify the subgroup of women that were destined to respond to antiestrogen therapy with selective estrogen receptor modulator drugs, such as Tamoxifen, that bind to the estrogen receptor and inhibit the growth of estrogen receptor-containing cancer cells. Craig Jordan had discovered and promoted selective estrogen receptor modulators as the logical therapy for women with breast cancer because of its selective ability to allow estrogen function in bone and nonbreast tissues yet inhibit breast cancers. The subsequent clinical results from simply "taking a pill" saved patients from undergoing the more aggressive antihormone approach: removal of the ovaries and the adrenal glands, which had been known to stop tumor growth in one-third of patients.

A second major use for the antibody to estrogen receptor was for the cloning of the estrogen receptor. After earlier work by the Evans, Gustafsson, and the Yamamoto laboratories on the cloning of the glucocorticoid receptor, Jensen provided his antibody and teamed up with Pierre Chambon to effect the first cloning of the estrogen receptor in the Chambon laboratory in 1986. The work of Evans on the nuclear receptor superfamily awakened scientists to the realization that the estrogen receptor was a member of a large superfamily of nuclear receptors, many of which were orphans with no known ligand.

Jensen received numerous honors and awards from around the globe for his work and was a respected member of major national societies, such as the National Academy of Sciences. Notably, he received the Albert Lasker Award for Basic Medical Research in 2004 for his work on estrogen receptors. In addition to his monumental research accomplishments, Elwood Jensen was a warm, optimistic, and gracious man who was admired and well liked by all of his peers in the Hormone Action Field. His close friends and his extremely wide circle of acquaintances will miss him a great deal.