John D. Baxter

1940–2011

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
Paul Webb
and Robert J. Fletterick

NATIONAL ACADEMY OF SCIENCES

JOHN D. **BAXTER**

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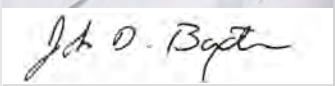


By Paul Webb and Robert J. Fletterick

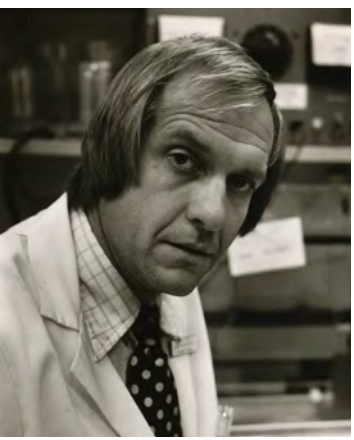
John Baxter was one of the most influential leaders in the fields of endocrinology and thyroid hormone actions, achieving nearly four hundred highly regarded academic publications during his lifetime. He was equally well known as one of the pioneers and a stalwart of the biotechnology industry. Translational medicine—the integration of basic science research with strategies to treat and prevent human disease—has rightly become fashionable in recent years; both coauthors believe, however, that John entered science in the mid-1960s with this concept already firmly articulated in his mind.

John consistently geared his research efforts toward improvement of human health. He loved the theory and practice of endocrinology and felt that understanding the endocrine system could lead to treatments for many diseases, notably metabolic disturbances that have become menacingly prevalent in the modern world.

He was a tireless advocate of The Endocrine Society (TES); of its educational arm, the Hormone Foundation (now the Hormone Health Network); and of the American Thyroid Association (ATA). John served as president of TES from 2002 to 2003, and served with great pride on the committees and Council of TES. It was fitting that he received major awards from both of his favorite professional organizations: the Koch award from TES at its Toronto meeting in 2007 and the Sydney H. Ingbar award from the ATA in 2009.

John was among the first to develop and adopt early genetic engineering efforts in the late 1970s and early 1980s and, typically, he directed this research towards clear, achievable goals in medicine. This work, which focused mostly on growth hormone, had important consequences in medicine, the integration of science and business, and in our society at large.

When John first began this work, it was well known that growth hormone could correct growth deficiencies, but therapies of the era were based on growth hormone that had been purified from human pituitaries, which were far from ideal because of the poor availability of source tissues and the risk of infection. John and his coworkers isolated growth hormone genes, including partial cDNA sequences that allowed isolation of the human gene, from a variety of mammalian species. They went on to show, in July of 1979, that it was possible to express growth hormone protein in bacteria and to purify it. This opened the door for the translation of basic genetic engineering concepts to large-scale industrial purification processes, which ultimately led to widespread application of growth hormone as a practical and relatively low-cost therapeutic for growth hormone deficiency and, recently, for other applications in children and adults.



Baxter in 1979.
(Photo by David Powers.)

As a direct result of this contribution to molecular medicine, John's picture was featured on the cover of *The New York Times Magazine* in 1980 relating to an article on the new molecular biology in medicine, titled "On the brink of altering life." Patents on engineered human and bovine growth hormone generated huge royalties for his home institution, the University of California, San Francisco (UCSF). John's group made other significant discoveries during this time. For example, their work on the ß-endorphin gene led to the first demonstration that recombinant proteins could be biologically active. His group characterized expression patterns of atrial natriuretic peptide and also made seminal discoveries on the biology of prolactin and epidermal growth factor expression and action.

Within the academic scientific community, John was best known as an internationally renowned expert on the actions of thyroid hormone. His earliest papers focused on links between thyroid hormone and hypercalcemia in patients with thyrotoxicosis, and, as he achieved independence at UCSF, he turned again to analysis of the way that thyroid hormone regulates cell behavior. His group produced several landmark papers that paved the way for the modern understanding of thyroid hormone receptors, including their nuclear localization and classification as nuclear hormone receptors, their association with chromatin and DNA binding properties, and the relationship between receptor activation and changes in gene expression.

Baxter, 1979 with Walter L. Miller now chief of Endocrinology at the University of California San Francisco.
(Photograph by David Powers.)

John became increasingly concerned about the epidemic of metabolic diseases affecting the United States, and he was convinced that selective modulation of thyroid signaling pathways offered opportunities to safely treat dyslipidemias and prevent heart disease, as well as treat and reverse obesity. His single-minded determination to achieve these goals provided the spark for two major achievements in thyroid hormone action that stand out from all others.

First, John believed that intelligent drug design could never truly be attained without detailed knowledge of the molecular mechanism of thyroid hormone receptor action. With Robert Fletterick, he set out to understand thyroid hormone receptor structure and function in detail, which culminated with the landmark publication in 1995 of an x-ray structure of the thyroid hormone receptor ligand-binding domain complexed with hormone. This success led to strategies for producing large amounts of purified protein, based on several important biochemical insights from Baxter's laboratory.

The structural model produced a major surprise: hormone formed the central core of the domain. This understanding paved the way for greatly improved understanding of thyroid hormone receptors and revealed the core mechanism of action of members of the nuclear hormone receptor family, which includes receptors for steroids, vitamins A and D, and many other biologically active molecules. Knowledge of the receptor structure also seeded studies that revealed basic mechanisms of nuclear receptor coregulator interaction, dimerization, and altered receptor function in disease.

The second major achievement of John's investigations into thyroid hormone action stemmed from this newfound understanding of receptor structure: he discovered ways to create selective thyroid hormone mimetics that retain the beneficial effects of thyroid

hormone excess states on cholesterol levels and body fat while avoiding harmful effects on heart, muscle, and bone. This work was initiated in long-term academic collaborations with Tom Scanlan, a talented chemist in UCSF's Department of Pharmaceutical Chemistry, and it continued with the pharmaceutical company Karo Bio AB in Stockholm. The result was a partial realization of John's dream: two drugs (sobetirome and eproterome), which accumulate in liver and display preferential binding to the thyroid hormone receptor beta isoform that mediates cholesterol lowering, reached clinical trials for patients who have dyslipidemias. These drugs continue to be considered for other human genetic and metabolic diseases.

His collaboration with Scanlan and Fletterick also led to methods for creating nuclear receptor antagonists from first principles. The trio applied these principles to create the first thyroid hormone antagonists, which may someday be used to provide rapid relief from dangerous symptoms of thyroid hormone excess states.

Often forgotten in the wake of his success are the important discoveries that John made early in his career, which related to actions of the steroid hormone receptors. He was a leading postdoctoral scholar, both at the National Institutes of Health and at UCSF, in the laboratory of one of the founders of this research field, Gordon Tomkins. John's seminal early discoveries included specific receptors for glucocorticoid hormones in liver and immune cells, their site of action in the nucleus and the relationship of the receptor proteins to hormone-dependent changes in protein expression, killing of lymphoma cells and other biological effects, and demonstrations of hormone binding activities for mineralocorticoids and estrogens. A particularly striking finding was that glucocorticoid receptor defects led to hormone resistance, the first time that a receptor defect was linked to a defect in hormone signaling. This concept paved the way for our modern understanding of many other forms of hormone resistance, both in the nuclear receptor and peptide hormone fields.

The consistent theme of John's work was finding a connection between academic science and medicine. It should be obvious that therapeutic development was the driving force behind all of the research achievements listed above, even though many of them required difficult and intellectually challenging advances in basic science. John applied this principle to the structure of the Metabolic Research Unit, a department at UCSF that he led from the 1980s onward. It was common for the mix of basic scientists, clinical researchers, and pure clinicians that were members of the department to share laboratory space, attend the same seminars, and meet as a group to exchange ideas.

In the late 1990s, the formal notion of translational research became important. There was a moment at UCSF when a guest speaker introduced the concept in a seminar and described how basic science must become integrated with clinical needs. Audience members exchanged puzzled looks and a whisper passed through the crowd: "Isn't this what we already do?"

John also pursued international biotechnology interests. Remarkably, his faith in the fledgling industry was such that he was prepared to resign his prestigious position with the Howard Hughes Medical Institute, along with the generous research support that came with it, in order to pursue these international projects, which were not restricted to drug development.

John's enthusiasm and charisma were essential factors in his successful with the emerging biotechnology industry, which turned into one of his lifetime's passions. He founded several companies, including California Biotechnology, which developed peptide hormones for heart failure (brain natriuretic peptide) and wound healing (fibroblast growth factor); SciClone, which developed hepatitis B/C therapeutics (Zadaxin); Serra, a nuclear receptor company; and Calhoun Vision, which developed implantable, remodellable lenses for treatment of poor vision. Together, these companies created thousands of jobs and great economic value for the state of California.

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His perception of inefficiency in the nursing home industry, drawn from visits with his mother in assisted living facilities, also led him to create OneTouch, a company dedicated to improved automated information management in health care. He also consulted with and served on boards of many other companies, and he took these responsibilities very seriously.

John Baxter's work figured prominently in a well-prosecuted disagreement in early biotechnology history. In 1999, Genentech settled a decade-long patent suit with UCSF relating to engineered human growth hormone. Genentech made a $50 million donation

toward a spectacular research building, Genentech Hall, at the university's new Mission Bay campus, and John was one of five UCSF researchers who each received $17 million from the settlement.

His time in biotechnology also revealed a capacity for interesting left-field solutions to problems. Worried by a clash in culture between scientists and administrators at one of his companies in the 1980s, he came up with the solution of hiring a specialist in corporate therapy to visit and help fix the culture. Naturally, he became great friends with this person, whom he always referred to as "my shrink," and he often returned to this solution in situations where he perceived that emerging culture clashes might harm the future productivity of a company or department.

Within academia, John took great pride in his record as a mentor. Many of the leading scientists in the United States who passed through his laboratory, including several National Academy of Sciences members, will doubtless tell similar stories about his leadership style. While always ready with advice and support, he felt very strongly that it was important to allow his postdoctoral scholars independence in their research, the chance to think for themselves and develop their own projects.

Such willingness to grant freedom and independence was not always accompanied by a similar attitude toward presentations and writing papers. In these cases, he insisted that his group strive for exacting standards of clarity of expression and communication and that the significance of the work must always be clearly stated so that everyone in science, from the most technically adept to the beginning graduate students, would appreciate why the work was performed and what the results meant. This exercise, though sometimes painful for participants (including, sometimes, the coauthors of this article), often brought out new interpretations that might easily have passed by unnoticed, and they always improved the quality of the paper.

John never forgot his home state or either of his alma maters. He was born in Lexington, Kentucky, and graduated from the University of Kentucky with a BA in chemistry. He never lost his accent or his love for the University of Kentucky basketball team. John went to medical school at Yale, where he received his MD in 1966 and stayed on for an internship and residency in internal medicine, which overlapped a brief stay at Guy's Hospital in London. He enjoyed his times at the University of Kentucky and Yale greatly, and in later life, he was quietly proud to have supported these institutions as a benefactor, and to have endowed the Baxter lecture series at Yale. He would gleefully relate an unfortunately unprintable tale about life at Yale in which he learned to correctly place a

preposition in a sentence, and he clearly felt very warmly about the institution and many of its current generation of professors.

As anyone who met John in person will know, his days as a star athlete were also never forgotten. He lettered in both basketball and track during high school, became the first Kentucky schoolboy to run a mile in under 4 minutes and 30 seconds, and received a track scholarship from the University of Kentucky, where he set track records in the 880 meter and mile events.

Baxter running during his student-athlete days.

His involvement in athletics led him into some remarkable situations. He had bested and then befriended many of the greatest runners in the United States over his years as a track star, represented the UCSF basketball team in a road game within the confines of the notorious San Quentin prison, and was not above challenging himself to race solo against a representative 4 x 880 meter relay team of his fastest postdoctoral scholars in Golden Gate park, even while in his forties.

After arthritis slowed his athletic career, he threw himself into a new sporting pursuit, fishing. Surprising no one, he became an avid and enthusiastic practitioner of the art and set half a dozen or more world records (for catches of yahoo and tuna), often attained in exotic South Pacific locales. Perhaps his best loved fishing times were spent on the Tularik River in Alaska, where he fished for salmon and did not break many records, but nevertheless usually filled the cooler with his catch.

It is probably already apparent that John was a man of rare intellect and unstoppable energy, drive, and talent, and that these qualities were reflected in his academic record. Those who worked closely with him know that he also had a unique and open personality, and that he tried his best to make sure that no possible opportunity for enjoyment passed him by, whether it was in science, sport, in fine wine or food, exotic world travel, or in simply passing the time with his family.

He searched enthusiastically for the best in every situation and was never afraid to give credit to his colleagues. John would frequently cede the senior author designation of a publication to junior members of his group if he felt that their efforts deserved it, and he always made sure that his colleagues were credited for their efforts. John also consistently and openly sought new collaborators. He was delighted to maintain strong relationships with many of his former students and postdoctoral scholars, notably in Brazil, where several collaborations that were seeded by John in the mid-1990s persist, two decades later.

Baxter in Alaska.

John's career enjoyed a final and unexpected chapter from 2008 to 2011, when he was invited to join The Methodist Hospital Research Institute in Houston, Texas. He became chief of the Division of Endocrinology at the Methodist Hospital, a senior member of the institute, director of medicinal genomics, deputy director of the diabetes center run by Willa Hsueh, and co-founder of the Center for Nuclear Receptors and Cell Signaling, with one of his long-term collaborators, Jan-Åke Gustafsson.

John felt strongly that his work in the last three years of his life matched some of the best of his career. He continued his ongoing efforts on selective thyroid hormone receptor modulation and nuclear receptor structure-function, and introduced genomics to his arsenal of weapons for studying thyroid hormone receptors. He also took the opportunity to branch out into several new areas, including modulation of peroxisome proliferator activated receptors, hormonal regulation of basal metabolic rate, and analysis of the roles of nuclear hormone receptors in adipose tissue inflammation, neuroinflammation, mesenchymal stem cell lineage determination, and hard-to-treat cancers. Ironically, the latter included cholangiocarcinoma, which led to his death. Although he did not know that he was already suffering from this insidious and partic-

ularly deadly disease when he green-lighted the project, he was delighted with the rapid progress of the studies and with the possibility of their clinical applications.

John was a loyal and true friend. His last public appearance was at a memorial service for the wife of one of the authors. He was very ill, but through force of will he made it to the podium one last time to express his thoughts and support. The next morning he went in for surgery, from which he never recovered.

One final memory of John merits particular attention. Upon election to the National Academy of Sciences, members are invited to contribute an article summarizing their lifetime's work. Despite constant cajoling from one of us (PW) after his 2003 election to the Academy, John never completed this article. His reasoning was simple: He felt that the ongoing research of his group was always likely to bring new breakthroughs and ideas for new applications of drugs, and he felt that it would be a shame to write an article that might miss some of these achievements. He simply could not bear the thought that any review might exclude ongoing work of his younger colleagues. In this regard, he may have been partly correct. Posthumous publications of work that was commenced during his time at The Methodist Hospital Research Institute have begun to emerge and his surviving colleagues expect that his name will continue to be featured in PubMed for several years to come.

SELECTED BIBLIOGRAPHY

1966 With P. K. Bondy. Hypercalcemia of thyrotoxicosis. *Ann. Intern. Med.* 65:429–442.

1976 Glucocorticoid hormone action. *Pharmacol. Ther. B.* 2:605–669.

With K. M. MacLeod. Chromatin receptors for thyroid hormones. Interactions of the solubilized proteins with DNA. *J. Biol. Chem.* 251:7380–7387.

1977 With P. H. Seeburg, J. Shine, J. A. Martial, and H. M. Goodman. Nucleotide sequence and amplification in bacteria of structural gene for rat growth hormone. *Nature* 270: 486–494.

With P. H. Seeburg, J. Shine, J. A. Martial, A. Ullrich, and H. M. Goodman. Nucleotide sequence of part of the gene for human chorionic somatomammotropin: purification of DNA complementary to predominant mRNA species. *Cell* 12:157–165.

1978 With P. H. Seeburg, J. Shine, J. A. Martial, R. D. Ivarie, J. A. Morris, A. Ullrich, and H. M. Goodman. Synthesis of growth hormone by bacteria. *Nature* 276:795–798.

1979 With N. L. Eberhardt, J. W. Apriletti, L. K. Johnson, R. D. Ivarie, B. S. Schachter, J. A. Morris, P. H. Seeburg, H. M. Goodman, K. R. Latham, J. R. Polansky, and J. A. Martial. Thyroid hormone receptors and responses. *Recent Prog. Horm. Res.* 35:97–153.

With J. A. Martial, P. H. Seeburg, D. T. Matulich, and H. M. Goodman. Regulation of growth hormone messenger RNA. *Monogr. Endocrinol.* 12:279–289.

1980 With J. Shine, I. Fettes, N. C. Lan, and J. L. Roberts. Expression of cloned betaendorphin gene sequences by Escherichia coli. *Nature* 285:456–463.

With W. L. Miller and J. A. Martial. Molecular-cloning of DNA complementary to bovine growth-hormone messenger-RNA. *Jour. Biol. Chem.* 255(16):7521-7524.

With L. K. Johnson, I. Voldavsky, and D. Gospodarovicz. Nuclear accumulation of epidermal growth-factor in cultured rat pituitary cells. *Nature* 287(5780):340-343

1982 With N. E. Cooke. Structural analysis of the prolactin gene sugests a separate origin for its 5' end. *Nature* 297(5867):603-606.

1987 With D. G. Gardner, G. P. Vlasuk, J. C. Fiddes, and J. A. Lewicki. Identification of atrial-natriuretic-factor transcripts in the central nervous system of rats. *Proc. Natl. Acad. Sci. U.S.A.* 84(8):2175-2179

1995 With J. W. Apriletti, K. J. Lau, and B. L. West. Expression of the rat alpha 1 thyroid hormone receptor ligand binding domain in Escherichia coli and the use of a ligand-induced conformation change as a method for its purification to homogeneity. *Protein Expr. Purif.* 6:363–370.

With R. L. Wagner, J. W. Apriletti, M. E. McGrath, B. L. West, and R. J. Fletterick. A structural role for hormone in the thyroid hormone receptor. *Nature* 378:690–697.

1998 With R. C. Ribeiro, J. W. Apriletti, R. L. Wagner, B. L. West, W. Feng, R. Huber, P. J. Kushner, S. Nilsson, T. Scanlan, R. J. Fletterick, and F. Schaufele. Mechanisms of thyroid hormone action: insights from X-ray crystallographic and functional studies. *Recent Prog. Horm. Res.* 53:351–92; discussion 392–394.

2002 With P. Webb, N. H. Nguyen, G. Chiellini, H. A. Yoshihara, S. T. Cunha Lima, J. W. Apriletti, R. C. Ribeiro, A. Marimuthu, B. L. West, P. Goede,K. Mellstrom, S. Nilsson, P. J. Kushner, R. J. Fletterick, and T. S. Scanlan. Design of thyroid hormone receptor antagonists from first principles. *J. Steroid Biochem. Mol. Biol.* 83:59–73.

2009 With P. Webb. Thyroid hormone mimetics: potential applications in atherosclerosis, obesity and type 2 diabetes. *Nat. Rev. Drug Discov.* 8:308–20.

2010 With T. S. Scanlan. Sobetirome: a case history of bench-to-clinic drug discovery and development. *Heart Fail. Rev.* 15:177–82

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