

## THE ENDOCRINE SOCIETY 2002 ANNUAL AWARDS

### Citation for the 2002 Fred Conrad Koch Award of The Endocrine Society to Dr. Jan-Åke Gustafsson

Jan-Åke Gustafsson, the recipient of the 2002 Fred Conrad Koch Award, is Professor and Chairman of both the Departments of Medical Nutrition and of Bioscience at the Karolinska Institute in Sweden. Since the early 1980s, he has played a key role in the development of the new south campus in Huddinge, now the most rapidly expanding part of the Karolinska Institute, at the same time making the exciting scientific discoveries for which he is being honored.

Prof. Gustafsson is a native Stockholmer who received his graduate education at the Karolinska Institute, where he has spent his entire professional career. In 1964, he started as a young M.D./Ph.D. student in the Department of Chemistry, chaired by the legendary Nobel Laureate Sune Bergström, and in 1968 he presented his Ph.D. thesis on steroid metabolism, in tails according to Karolinska tradition at that time. He completed his M.D. studies in 1971, and he has since devoted essentially all his effort to basic biochemical research. During the 1970s, he established a group of young research students with an initial focus on imprinting of hepatic steroid metabolism, but this later shifted to steroid receptors, which remained as his principal interest.

Jan-Åke Gustafsson has a distinguished record of seminal contributions to endocrinology, especially the action mechanism of steroid hormones. Before its eventual cloning, he

purified the glucocorticoid receptor (GR) to homogeneity and showed that it contains three distinct functional regions. These findings, the first for a steroid hormone receptor, were achieved through biochemical and immunochemical methods developed in the Gustafsson laboratory and provided much of the early understanding of nuclear receptor structure. Based on this work, and on previous studies by Keith Yamamoto on mouse mammary tumor virus, a collaboration was established, and, after several years of an air bridge of purified hepatic receptor between Stockholm and San Francisco, it succeeded in identifying specific binding sites for liganded GR in the MMTV genome. This finding led to the concept of hormone-response elements in target DNA with which steroid receptors interact to function as transcription factors. The Gustafsson/Yamamoto collaboration also achieved the first partial cloning of a steroid hormone receptor, employing antibodies to GR developed in the Gustafsson laboratory. Later, Gustafsson and his collaborators determined the three-dimensional structure of the DNA-binding domain of GR, the first structural information of a nuclear receptor.

Especially outstanding is Jan-Åke's discovery and cloning of a second estrogen receptor, now called estrogen receptor (ER)  $\beta$ , produced from a separate gene and showing different ligand affinities, tissue distribution, and intracellular functions from the original receptor, ER $\alpha$ . These observations provided new understanding of many hitherto puzzling actions of estrogens. He showed that ER $\beta$  can react with target DNA as a heterodimer with ER $\alpha$ , and that in the rat uterus it can modulate the stimulatory action of the latter. He prepared antibodies specific for ER $\beta$ , which permit its distinction from ER $\alpha$  in tissues and tumors at the cellular level. These permitted the surprising finding that ER $\beta$ , rather than ER $\alpha$ , is associated with known proliferation markers in breast cancer, suggesting that, for optimal characterization of hormone dependency in breast tumors, both receptor isoforms should be measured.

In collaboration with others, Jan-Åke obtained mice lacking the ER $\beta$  gene, which he used to delineate the involvement of the new isoform in female reproduction, cardiovascular, and central nervous system function, learning behavior, bone development, and prevention of prostatic hyperplasia, possibly of neoplasia. Gustafsson's findings have opened new horizons in understanding estrogen effects in various tissues, including breast and prostatic cancer.

In recognition of his scientific accomplishments, Jan-Åke Gustafsson has received many awards, including the Sweden Prize in Chemistry, Fernström Prize, Anders Jahre Prize, Medal of Collège de France, Gregory Pincus Award, Söderberg Prize in Medicine, Lundberg Foundation Medal, Curt Nicolin's Prize, European Medal of British Society for Endocrinology, and Lorenzini Foundation Medal. He is a member of the Swedish Academy of Sciences, Swedish Academy of Engineering Sciences, Nobel Assembly (Chairman, 2002), Japanese Biochemical Society (honorary), American Acad-



emy of Arts and Sciences (foreign honorary), and Foreign Associate, U.S. National Academy of Sciences.

In spite of his many professional obligations and busy international lecture schedule, Jan-Åke somehow finds time to pay personal attention to his many students, enjoy the collegial atmosphere that he has established in Huddinge, jog several kilometers on mornings when the snow is not too deep in Stockholm, and inspire the admiration of all of us who have had the privilege of knowing him. Jan-Åke Gustafsson is a worthy recipient of the Fred Conrad Koch Award, the highest honor that The Endocrine Society bestows for scientific achievement.

*Elwood V. Jensen*

#### **Citation for the 2002 Ernst Oppenheimer Award of The Endocrine Society to Dr. Leonard P. Freedman**

Leonard Paul Freedman was born in Detroit, Michigan, on May 8, 1958. After Kalamazoo College, Len moved to the University of Rochester, where he received his Ph.D. in Molecular Genetics in 1986. Len's work in the laboratory of Lasse Lindahl focused on nutritional control of ribosomal gene expression in *Escherichia coli*, and presaged his future and unbroken interest in regulated transcription. Whereas single-celled bacteria respond individually to environmental stimuli, complex organisms require coordinated communication among different cell types. The endocrine system is the major regulator of this homeostatic process, and thus the study to hormone action was a logical next step for the young Dr. Freedman. And what better way to pursue this progression than to move across the U.S. to the University of California San Francisco, to train in the laboratory of one of the world's leading molecular endocrinologists, Keith Yamamoto.



In Yamamoto's lab, Len focused on the regulation of transcription by glucocorticoids. The glucocorticoid receptor (GR) had just been cloned, and Len's first breakthrough was to demonstrate the presence and functional role of zinc atoms within the domain of GR that binds DNA. He was also part of the collaboration with Paul Sigler and Ben Luisi that led to the crystal structure of the GR DNA-binding domain, a first for eukaryotic transcription factors. In addition, Len was the first to use GR for cell-free transcription. These studies were critical to understanding the molecular mechanisms by which glucocorticoid hormones regulate gene transcription.

In 1990, Len moved back East to an independent position at the Memorial Sloan-Kettering Cancer Center in New York City. During the exciting period from 1985–1990, numerous nuclear hormone receptors had been cloned and found to have sequences and functions that were much more similar than previously suspected. In branching out from his mentor, Len took advantage of this by turning his attention to the nuclear receptor for vitamin D<sub>3</sub>. Here, Len made one important contribution after another. Consistent with his expertise from the Yamamoto lab, Len initially focused on DNA binding by the vitamin D<sub>3</sub> receptor (VDR), determining its optimal DNA binding site, and the role of vitamin D<sub>3</sub> and dimerization. In the mid-1990s, Len turned his attention to biological roles of VDR in bone biology, where he became a leading figure, as well as hematopoietic differentiation. This led to novel insights into mechanisms by which vitamin D<sub>3</sub> turns genes on or off. A particularly important finding was the identification of the cell cycle inhibitor p21 as the transcriptional target, linking vitamin D's effects on cell cycle arrest to differentiation.

Throughout this period, Len was advancing up the ranks at Sloan-Kettering, where he became a tenured member of the Cell Biology Program and received the Boyer Research Award given to the outstanding investigator under the age of 40. He received numerous grants, including a MERIT award from the NIDDK, and trained numerous predoctoral and postdoctoral students that have gone on to independent positions in academia and industry. Len serves on numerous scientific review panels and has been a member of the Editorial Board of two leading Endocrine Society journals, *Molecular Endocrinology* and *Endocrine Reviews*, as well as *Molecular and Cellular Biology*; he is currently an Editor of *MCB*. Len has given plenary talks throughout the world, and his lectures are frequently highlights of the nuclear receptor-related Keystone Symposia, as well as meetings of The Endocrine Society and the American Society for Bone and Mineral Research. He can be counted on to deliver an enjoyable, enlightening talk, using receptor systems to illuminate novel mechanisms of transcriptional regulation and cell differentiation.

Len's productivity has never been greater than during the past few years, when he turned his attention to the cellular factors mediating transcriptional activation by vitamin D<sub>3</sub> working through the VDR. This work led to the identification of a novel complex containing an extraordinary number of factors that he named "DRIPs," (D<sub>3</sub>-receptor interaction proteins). Len's group identified and cloned these factors, demonstrated their importance for vitamin D<sub>3</sub>-activated transcription, and joined forces with other transcriptional luminaries, to show that the DRIPs, were nearly identical to

Bob Roeder's TRAPs ( $T_3$ -receptor associated proteins) as well as Robert Tjian's ARC (activator-recruited factor) complex. This may seem like alphabet soup to some, but to the transcription community this represented the beginning of a unified understanding of activated gene regulation.

What next for Len? Having accomplished so much in the academic arena, he very recently joined Merck Research Laboratories as Senior Director of the Bone Biology Department. There are many more basic questions relating to nuclear receptor mechanisms that he is likely to solve. In addition, because the activities of the receptors are regulated by ligands, he is now positioned to use his insight into basic mechanisms of receptor function to develop novel drugs that work on nuclear receptors to improve the human condition.

While obviously a busy man, Len Freedman has remained a great colleague and mentor, husband to Gilya Hodos, and father to three boys, David, Daniel, and Elie. He is highly deserving of recognition by The Endocrine Society as the 2002 recipient of the Ernst Oppenheimer award.

*Mitchell A. Lazar*

**Citation for the 2002 Robert H. Williams Distinguished Leadership Award of The Endocrine Society to Dr. Samuel Refetoff**

Dr. Samuel Refetoff is a uniquely gifted, creative, and brilliant individual who has been an outstanding leader in both fundamental and clinical endocrinology. He is probably best known as the investigator who discovered and defined the molecular basis of the syndrome of resistance to thyroid hormone (RTH), sometimes called appropriately the Refetoff syndrome. He has also made other important contributions to many areas of endocrinology and has been remarkably



successful in bridging bench research and clinical practice. He has awed and inspired many young scientists, and has an exceptional training record. Indeed, his fellows now include 22 full-time faculty members at universities and research institutes around the world.

Samuel Refetoff was born in Bulgaria but emigrated to Belgium as a teenager. There, he obtained his high school diploma from a French-speaking high school in Antwerp. A second emigration led him to Montréal, where he received a baccalaureate degree in 1959, in French again. He then completed medical school in English at McGill University in 1963. Subsequently, he was an intern in Montréal and resident at The Hospital of the Good Samaritan in California in 1964. It was during this year that he initiated studies on a victim of a car accident who presented with the combination of stippled epiphyses, goiter, deafness, and an elevated protein-bound iodine fraction. As a part of his evaluation of this condition, he sought to obtain urine samples from the family members who lived in Watts, California. Riots were in full force in that area at that time but this did not deter Refetoff, who collected the urine samples under the supervision of armed guards. It was with this index family that RTH was first identified. Refetoff then moved to the Peter Bent Brigham Hospital to complete an endocrine fellowship in 1966–1968. It was during this time, and partly through his interactions with Dr. Leslie DeGroot, that he developed the clinical description of RTH. In 1969, Dr. Refetoff moved to the University of Chicago. Despite numerous offers from prestigious institutions, he has remained at the University of Chicago, where he is currently the Frederick H. Rawson Professor in Medicine and Professor of Pediatrics and Genetics.

Dr. Refetoff's research has virtually covered every area of molecular as well as clinical thyroidology. In addition to RTH, he also provided the basis for understanding another hormone resistance syndrome, resistance to TSH (RTSH). He was the first to describe the molecular basis for familial dysalbuminemic hyperthyroxinemia. He was also the first to identify mutations in the thyroxine-binding globulin gene and most recently, a mutation in the TTF1 gene that produces predominantly neurological defects. Outside of thyroidology, he has made major contributions to pituitary physiology (including the first isolation of prolactin mRNA) and hormonal rhythms.

Samuel Refetoff is the recipient of many prestigious national and international awards. He has received two honorary doctorate degrees, one from the University of Cagliari (Italy) in 1990 and one from the Université Libre de Bruxelles (Belgium) in 1989. He has received the Sandoz Lecture of the Canadian Society of Endocrinology and Metabolism and the Knoll Pharmaceutical Mentor Award from The Endocrine Society as well as the Rhône-Poulenc Rorer Clinical Investigator Award. The American Thyroid Association honored him with the Paul Starr Award, and in 1996 he was given this society's highest award, the Sidney Ingbar Award. In 1997, he was the Chaire Francqui Interuniversitaire in Belgium, and in 1998 he received the Merck KgaA prize from the European Thyroid Association. He was honored by the Japan Thyroid Association with the Shizume Lecture Prize in 1999. His bibliography includes more than 350 publications.

Dr. Refetoff directs the Endocrinology Training Program at the University of Chicago but has also mentored endocrinologists all over the world. His curiosity, tireless energy, and talent for languages has led him to conduct research in Venezuela, Central Africa, the Andes, Australia, Japan, and, most recently, the Azores islands. He is fond of Latin cultures and may lecture in French, Spanish, or Italian when needed. Samuel Refetoff has devoted friends and excellent colleagues in many countries, and they often relish in sharing stories about some of his recent scientific and personal feats. To many young investigators and clinicians, Dr. Refetoff has been a mentor not only professionally, but personally as well. His high moral and intellectual standards, his passion for science, his vast culture, and his compassionate approach of medical care win him the love and admiration of all around him.

*Eve Van Cauter*

**Citation for the 2002 Edwin B. Astwood Award  
Lecture of The Endocrine Society to  
Dr. P. Reed Larsen**

Dr. P. Reed Larsen has been an outstanding contributor to our understanding of thyroid hormone action for more than 30 yr. One of his earliest discoveries was the demonstration, with his co-worker Dr. Enrique Silva, that the  $T_3$  in the nuclei of pituitary cells is not produced by the thyroid but is generated locally from circulating  $T_4$  by the type 2 deiodinase. They went on to show that the same mechanism generates the active hormone in both the central nervous system and brown adipose tissue, and over the years Reed has continued to focus on the function of the three deiodinases.

A major achievement in this area was the initial isolation of a deiodinase cDNA clone. I followed these dogged efforts

closely, and I believe that their success exemplifies Reed's remarkable talents. After considering a number of strategies, he and Dr. Marla Berry, then a post-doc, used a laborious approach based on injection of *Xenopus* oocytes to identify a clone with appropriate enzyme activity. Perplexingly, this cDNA appeared to encode only a tiny protein that could not correspond to the desired enzyme. Instead of dropping this lead, as the majority of investigators would have done, Reed was convinced by his own results and soon discovered that this cDNA encoded one of the first mammalian selenoproteins. In these highly unusual proteins, the UGA codon, which normally directs the termination of translation, instead directs the incorporation of the modified amino acid selenocysteine. Reed and Marla went on to unravel the unique mechanism employed by mammalian cells to ignore the termination function of the UGA codon and recode it to insert selenocysteine. In marked contrast to the strategy used by bacteria, this mechanism is based on the presence of a particular sequence in the 3' untranslated region of the mRNA that they termed SECIS, for selenocysteine insertion sequence. This was truly a molecular biology tour de force.

In a dramatic and recent example of the flow of insight from the bedside to the bench, Reed and his co-workers have discovered that deiodinase expression by hemangiomas can cause consumptive hypothyroidism. Based on the clinical features of a single infant with such a tumor, they deduced that it was overexpressing the type 3 deiodinase and thereby inactivating thyroid hormone. They also demonstrated similar results with other hemangiomas. Hemangiomas are the most common tumor in infants, and each month of hypothyroidism during the first year results in the loss of three to five IQ points. Clearly, this work has significant clinical implications.

Reed's efforts have been sustained by the support of his wife Jane and his children. In turn, his impact on the field of thyroid hormone action has been amplified by the remarkably talented group of thyroidologists, too numerous to name, that he has trained. His students, fellows, and colleagues have all been inspired by his boundless drive and curiosity, by his relentless focus on physiologically relevant questions and, perhaps most importantly, by his unstinting support and friendship. At a personal level, it was Reed's sabbatical in my laboratory that started my own interests in thyroid hormone action. His efforts and talents—including those at the bench in the earliest stages—were essential for the successes that we achieved in that area. He is a very worthy recipient of the Edwin B. Astwood Award.

*David D. Moore*



**Citation for the 2002 Clinical Investigator Award  
Lecture of The Endocrine Society to  
Dr. Anne Klibanski**

Dr. Anne Klibanski was born in New York City and obtained a B.A. *magna cum laude* with honors in literature at Barnard College in New York City in 1971. She obtained her M.D. degree in 1975 from New York University School of Medicine. She stayed in New York City serving as Intern, Resident, and Senior Resident in Medicine at Bellevue Hospital. In 1978 she moved to Boston, Massachusetts, where she



became a Clinical and Research Fellow at the Massachusetts General Hospital under the stewardship of Dr. Janet McArthur and Dr. Inese Beitins. This mentorship guided Dr. Klibanski in the clarity and durability of her interest in clinical research. In 1980 she became a Clinical and Research Fellow within the Thyroid Unit of the Massachusetts General Hospital working with Dr. E. Chester Ridgway. It was here that she developed her long-term interest in prolactin and pituitary physiology, and established long-term relationships with Drs. Robert Neer, David Cooper, Paul Ladenson, Bill Chin, Larry Jameson, Margaret Shupnik, and Susan Greenspan. These associations nurtured a 24-yr career within the Department of Medicine at the Massachusetts General Hospital, rising from Instructor in Medicine to Professor of Medicine in 1997 and becoming the first woman Professor of Medicine at Harvard Medical School at the Massachusetts General Hospital.

Dr. Klibanski's research interests have been in two distinct yet interrelated areas. First, she was the first to describe the profound effect of hyperprolactinemia and its subsequent hypogonadism on skeletal integrity in both women and men. She subsequently showed that reversal of the hyperprolactinemia could not only halt the deterioration of bone mineral density, but in fact, result in improved skeletal health when PRL function, and therefore gonadal function, were restored to normal. She subsequently extended these studies to other causes of hypothalamic/pituitary dysfunction, showing that patients with anorexia nervosa and nutritionally deprived individuals developed not only hypogonadism, but also decreased bone density. Her studies looking at the impact of acquired growth hormone and IGF-1 deficiency on bone mass were critical in establishing the importance of

gonadal steroids and growth hormone on skeletal integrity in both women and men. These studies opened up novel areas of investigation into how the hypothalamic/pituitary axes control bone mass.

Shortly after starting her basic research studies in the Thyroid Unit at the Massachusetts General Hospital, Dr. Klibanski developed her second major area of interest involving the pathogenesis and therapy of pituitary tumors. Dr. Klibanski's legendary contributions in the area of pituitary tumors include prolactinomas, GH-secreting tumors, and  $\alpha$ -secreting pituitary adenomas. Her early work emphasized the importance of dopamine, somatostatin, and adrenergic hormones in the regulation of the hypothalamic-pituitary axis. She played an integral role in the initial descriptions of not only pure  $\alpha$ -subunit-secreting tumors, but the rare LH-secreting pituitary tumors. Dr. Klibanski's basic studies shifted to the pathogenesis of pituitary tumors, demonstrating the monoclonal origins of nonfunctioning and corticotroph pituitary adenomas. Subsequently, her studies have emphasized the importance of growth factors such as activin, activin/TGF- $\beta$  receptors, and somatostatin receptor subtype gene expression in the pathogenesis of pituitary adenomas. As a result of the breadth of her scientific achievements in the area of pituitary pathophysiology, Dr. Klibanski established the first Neuroendocrine Unit at the Massachusetts General Hospital and has served as Director since its inception. She was instrumental in the creation of the multidisciplinary Neuroendocrine Clinical Center at Massachusetts General Hospital, ultimately creating a clinical and research program integrating endocrinology, neurology, neurosurgery, and radiation oncology. This center has become an important national prototype for the research and care of neuroendocrine patients.

Ultimately, all of Dr. Klibanski's hypotheses become tested and her insights refined within the hallowed halls of the famed Mallinckrodt Clinical Research Center (CRC) of the Massachusetts General Hospital. She has been a quintessential translational research investigator, testing hypotheses in patients, taking clinical insights to the bench, and finally reintroducing these discoveries to human subjects. Her abiding interest in clinical research awarded her the Associate Director position of this Unit between 1986 and 1990, and in 1989 she became Co-Director of the CRC, a position she holds to this day. Dr. Klibanski's career is a perfect example of the vanishing academician. She has excelled at every level and is a true credit to The Endocrine Society. Dr. Klibanski developed important hypotheses about serious health problems, accepted guidance from durable mentors, and encouraged the development of imaginative projects from her colleagues and fellows. In turn, she has successfully mentored a number of academicians and received a Harvard Medical School Award for these contributions. Her research is marked by the creative pursuit of questions without regard to traditional boundaries or subspecialty restrictions. Ultimately, Dr. Klibanski achieves wisdom at the bedside of her clinical research patients, a process that enriches all of us in The Endocrine Society.

*E. Chester Ridgway, III*

**Citation for the 2002 Gerald D. Aurbach Award  
Lecture of The Endocrine Society to  
Dr. Agnes Schonbrunn**

The Gerald D. Aurbach Award for 2003 is given to Dr. Agnes Schonbrunn, Professor of Integrative Biology and Pharmacology at the University of Texas–Houston, School of Medicine. Dr. Schonbrunn obtained her B.Sc. degree with First Class Honors in Biochemistry in 1970 at McGill University in Montreal, Canada. She received her Ph.D. in Biochemistry in 1975 at Brandeis University, working on the mechanism of flavin coenzyme catalysis in the laboratory of Dr. Robert Abeles. For her postdoctoral training, Dr. Schonbrunn made a major switch in research area—she turned her attention from the mechanisms of enzyme action to understanding the function of membrane receptors, joining the laboratory of Dr. Armen Tashjian at Harvard School of Dental Medicine and Harvard Medical School. Here she embarked on a prolific career pathway that has resulted in important scholarly contributions, especially in the field of G protein receptor functions. Agnes Schonbrunn has made continuous novel contributions to the field of somatostatin receptors. She has selected important questions and, undaunted by technical difficulties and generating new investigative tools, has contributed much of our current understanding of somatostatin receptor family biology. Dr. Schonbrunn began her studies of neuropeptide receptors as a postdoctoral fellow in the laboratory of Armen Tashjian. Somatostatin had been discovered 3 yr before she began her fellowship, but little was known about receptors for this peptide, mainly because the assay of somatostatin receptors was plagued by technical problems resulting from high non-specific binding of the available ligands. Developing new



procedures and using her rigorous biochemical training, she succeeded in identifying and characterizing high affinity somatostatin receptors, being the first to do so and opening up an important area of endocrine research. After establishing her own laboratory, first at the Harvard School of Public Health in 1979 and then, in 1988, at the University of Texas Medical School in Houston, she has consistently continued to work on many different aspects of somatostatin receptors, including mechanisms of signaling, biological functions, and mechanisms of regulation. These studies included numerous “firsts”—first demonstration of homologous and heterologous somatostatin receptor regulation; the first evaluation of how different signaling pathways contribute to somatostatin inhibition of hormone secretion; one of the first demonstrations that somatostatin activates K<sup>+</sup> channels; the first evidence for the involvement of a protein phosphatase in somatostatin regulation of channel activity; the first synthesis of a photoaffinity analog of somatostatin and the use of this analog to correctly identify the receptor protein for the first time; the first to develop an efficient method for purification of somatostatin receptor-G protein complexes and its subsequent use to identify the specific G proteins involved in somatostatin receptor signaling; the first generation of specific somatostatin receptor subtype antibodies, and the use of these antibodies to determine the distribution of somatostatin receptors in different targets; the first demonstration that the subcellular distribution of somatostatin receptor varies in different tissues; and the first to show that somatostatin receptors are regulated by phosphorylation.

The spectrum of her contribution ranges from fundamental biochemistry (identification of receptor proteins by photoaffinity labeling, characterization of receptor phosphorylation sites) to clinical applications (identification of the distribution of different somatostatin receptor subtypes in human tissues and tumors). She has applied information and tools developed from biochemical and molecular studies to investigate somatostatin receptor physiology and pathology and their ultimate application to therapy and diagnosis of endocrine tumors.

Her contributions have resulted in development of peptide therapies for neuroendocrine tumors and related disorders, and for precise radioactive scanning for endocrine tumor diagnosis. Agi Schonbrunn is a personification of vision, rigor, persistence, and intellectual honesty in science. Her fundamental observations have been translated directly to clinical application and impacted novel modes of therapy for neuroendocrine tumors.

*Shlomo Melmed*

**Citation for the 2002 Sidney H. Ingbar Distinguished  
Service Award of The Endocrine Society to  
Dr. John Funder**

John Watson Funder was born the day after Christmas, 1940, in Adelaide, South Australia. He was educated at the University of Melbourne, where he was awarded both the M.D. and Ph.D. degrees in 1971. He was a medical officer at St. Vincent’s Hospital in Melbourne, followed by a postgraduate period at the Howard Florey Laboratory of Experimental Physiology. He also spent postgraduate time in the Car-



diovascular Research Institute in San Francisco, at the Necker Hospital in Paris, and at Prince Henry's Hospital in Melbourne. A number of positions of responsibility followed in quick succession: Associate Director of the Medical Research Center at Prince Henry's Hospital, Deputy Director of the Medical Research Center in 1983, and Director of the Baker Medical Research Institute since 1990; he is currently Professor of Medicine in the Department of Medicine at Monash University.

Funder's research began with a publication in 1968 on the "Effects of Adrenal Steroid Withdrawal on Chronic Renovascular Hypertension in Adrenalectomized Sheep." In this paper, the effects of glucocorticoids and mineralocorticoids on cardiovascular biology were examined. Five hundred papers and 34 yr later, Funder's most recent paper examines "Experimental Cardiac Fibrosis, Differential Time Course of Responses to Mineralocorticoid-Salt Administration," exploring the role of glucocorticoid and mineralocorticoid on the cardiovascular biology. Between these papers is an investigative tour de force that explains the core concepts defining the physiology and molecular biology of steroid hormone action and the effects of the steroid hormone on the kidney and cardiovascular system. These studies span the animal kingdom from bacteria to man, and touch all aspects of adrenal steroid biology—synthesis, secretion, transport, binding, signal transduction, and biological effect. It is a truly remarkable body of work.

Funder's role as a leader in endocrinology is equally substantial. For example, he was chairman of the Program Organizing Committee of the 1996 International Congress of Endocrinology in Sydney Australia, and from 1996–2000, he was the chairman of the International Society for Endocri-

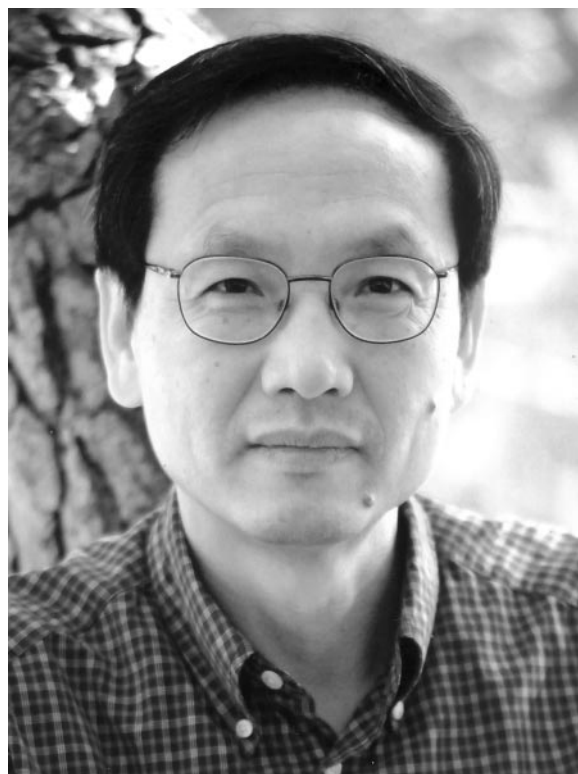
nology; he is a council member of The Endocrine Society; he has served on the Advisory Board of *Endocrine Reviews*; he has served on the editorial boards of *Circulation Research*, *Journal of Steroid Biochemistry*, *Endocrine Reviews*, *Steroids*, *Neuroendocrinology*, *Journal of Neuroendocrinology*, *Clinical Endocrinology*, *Endocrinology*, *Journal of Hypertension*, and *The Journal of Clinical Endocrinology & Metabolism*. He has been the President of the Australian Endocrine Society, and President of the Australian Society for Medical Research. In short, he has been a guiding force in the development of modern endocrinology for three decades. Dr. John Funder is a most deserving recipient of the Sidney H. Ingbar Distinguished Service Award from The Endocrine Society.

D. Lynn Loriaux

#### Citation for the 2002 Roy O. Greep Award Lecture of The Endocrine Society to Dr. Aaron Hsueh

The Roy O. Greep Award for 2002 is awarded to Dr. Aaron Hsueh, Professor of Reproductive Biology at Stanford University, in recognition of his contributions to the advancement of ovarian physiology and for implementing genomic approaches to discover novel ligands and receptors.

Aaron Hsueh received his undergraduate education in zoology from the National Taiwan University. After obtaining his Ph.D. degree from the Department of Cell Biology at Baylor College of Medicine under Dr. James H. Clark, he spent 1 yr as a postdoctoral fellow at the National Institutes of Health under Dr. Kevin J. Catt. In 1976, he established his own laboratory at the University of California, San Diego, where he spent the next 15 yr, achieving a promotion to full Professor in 1984. In 1991, he moved to the Stanford University School of Medicine to head the new Division of Re-



productive Biology in the Department of Gynecology and Obstetrics.

Dr. Hsueh has focused his research on ovarian physiology. In addition to his earlier work on gonadotropin receptor down-regulation and gonadal cell desensitization, he investigated paracrine regulation of granulosa cell differentiation and set up a sensitive *in vitro* bioassay for FSH. His laboratory contributed to the understanding of the molecular biology, structural-functional relationship, and pathophysiology of gonadotropin receptors. His group has also demonstrated the role of oocyte-derived growth differentiation factor 9 (GDF-9) in the development of early follicles in the ovary, and has isolated several ovarian Bcl-2 genes to construct the intracellular apoptosis pathway during follicle atresia. The identification of novel Bcl-2 genes, Bok (Bcl-2-related ovarian killer), and BOD (Bcl-2-related ovarian death agonist), provides a paradigm to characterize tissue-specific apoptosis pathways in endocrine tissues. Recently, Dr. Hsueh set up the Ovarian Kaleidoscope database (<http://ovary.stanford.edu/>) in which genes expressed in the ovary could be searched to allow a global understanding of gene regulation and expression in the ovary.

Taking advantage of the recent genomic revolution, Dr. Hsueh and his co-workers have analyzed and reclassified all cystine-knot proteins in five model organisms and established a Cystine-Knot Polypeptide Hormone database (<http://hormone.stanford.edu/>). Based on GenBank searches, Dr. Hsueh and his colleagues have identified multiple leucine-rich repeat-containing G protein-coupled receptors (LGRs) in human, fly, and worm, thus illustrating the evolutionary origins of these orphan receptors and providing the opportunity to discover their ligands. Recently, he and his co-workers found that the classic hormone relaxin is the ligand for LGR7 and LGR8, and a new heterodimeric glycoprotein hormone (thyrostimulin) is a ligand for the TSH receptor. In addition, they discovered stresscopins as selective ligands for the type II CRH receptor and demonstrated the anorexic, gastric stasis, and antiedema actions of these peptide hormones. The pioneering use of bioinformatic approaches by Dr. Hsueh and his colleagues allows the discovery of novel polypeptide hormones, receptors, and intracellular signaling molecules.

The significance of Dr. Hsueh's research has been recognized by his colleagues worldwide. He received the Research Career Development and MERIT Awards from NIH as well as an Honorary Doctor of Medicine from the University of Umea, Sweden. He was the recipient of the Society for the Study of Reproduction Research Award in 1986 and the President's Achievement Award from the Society for Gynecological Investigation in 1988. In his work with The Endocrine Society, Dr. Hsueh was an editor of *Endocrinology* (1986–88) and the Chairman of the Scientific Program of the Society's 75th meeting. In 1987, Dr. Hsueh was awarded the Ernst Oppenheimer Memorial Award.

Aaron Hsueh has been the mentor of over 120 postdoctoral fellows and graduate students, many of whom are successful researchers in reproductive endocrinology. He received President's Mentorship Award from Society for Gynecological Investigation in 2000 for recognition of his role as a teacher.

For his contributions to endocrine research and training of fellows, The Endocrine Society recognizes Aaron Hsueh as the recipient of the 2002 Roy O. Greep Award.

P. Michael Conn

#### Citation for the 2002 Distinguished Educator Award of The Endocrine Society to Dr. William Ganong

The Endocrine Society takes great pleasure in announcing that William Francis Ganong, M.D. (or Fran as colleagues and friends know him), is the recipient of the Distinguished Educator Award in 2002.

Fran grew up in Northampton, Massachusetts, and matriculated at Harvard in 1941. His education was interrupted by service in the army. He received the bachelor's degree from Harvard in 1946 on the basis of army and correspondence credits. In 1949, he received the M.D. from Harvard and did his internship, residency, and research fellowship at the Brigham Hospital in Boston. In 1951–1952, he served as Lieutenant and then Captain in the Army Medical Corps in Japan and Korea.

Fran chaired the Department of Physiology at the University of California San Francisco from 1970–1987, building a strong group of researchers and teachers. He has been Emeritus since 1991. He has served on the governing councils of a number of professional societies, including The Endocrine Society, and was President of the American Physiological Society in 1977. He was Editor-in-Chief of the journal *Neuroendocrinology* from 1979–1984 and co-editor of *Frontiers in Neuroendocrinology* (with Luciano Martini) from 1989–2002.

His research over the years has focused principally on the neuroendocrinology of aldosterone regulation. His investigations, initiated in collaboration with Pat Mulrow starting



in the 1950s, of the renin-angiotensin-adrenal system were central to the acceptance of the integrating role played by that signal cascade. Ganong's laboratory was among the first to probe the role of the central nervous system (particularly the hypothalamus) in ACTH and adrenal regulation.

Fran Ganong has received numerous awards during his career. Among these is the Award for Outstanding Contributions to the Teaching of Physiology presented by the Association of Chairmen of Departments of Physiology. He actually won this award twice, first in 1978 and then again in 1988! In 1985, he received the A.A. Berthold medal of the German Endocrine Society. In 1986, he served as the Transatlantic Lecturer of the English Society for Endocrinology. In 1995, he received the Lifetime Achievement Award of the Council for High Blood Pressure Research.

His textbook, *Review of Medical Physiology*, has undoubtedly been used by more medical and premedical students to learn physiology than any other published text. The first publication of the book was in 1963, and it has sold over two million copies worldwide since then. The 20th edition was published in March 2001. The book has been translated into 17 languages, including Indonesian, Malaysian, Czech, Serbo-Croatian, and Turkish. It is also available recorded on tape in English for the blind. Additionally, there is now a searchable CD-ROM text.

Fran's colleagues at the University of California San Francisco have revealed at least one secret of his success in this multifaceted career. I am told that he always carries a pack of index cards with him, noting new things in physiology and thus keeping his textbook remarkably up-to-date and fresh. With respect to his research, he has always adhered to the minimalist concept of Occam's Razor in interpreting experimental research, undoubtedly fostering his successful research career.

Many years ago when I was teaching physiology to students at the University of Illinois Medical School, I invited Fran to lecture to my class. During his presentation, he offered the students 25 cents for every error they could spot in the text. He claims that at the end of his lecture "they mobbed the podium" and he nearly went broke paying them off. My own memory of the incident is not nearly so drastic in its outcome.

When I agreed to write this citation, the most recent copy of his book in my possession was the 17th edition (published in 1995). I decided to take a look at the latest edition to see how much it had changed. Many of the diagrams were new and I noted that a "self-exam" is now included. I looked up what he had to say about inhibin and the ovary, finding the material remarkably up-to-date. Then I looked up another topic about which I knew nothing (sleep apnea) and found the discussion cogent and very helpful. So like many generations of students worldwide who have preceded me, I turned to Fran's book for help in understanding facets of physiology and it was not found wanting.

Thus, we honor this distinguished endocrinologist, physiologist, and educator who has had a major influence for nearly 40 yr on students of biology and medicine in many countries.

Neena B. Schwartz

### Citation for the 2002 Distinguished Physician Award of The Endocrine Society to Dr. Lisa H. Fish

Dr. Lisa H. Fish is a highly respected clinician who has made numerous contributions to endocrinology. Most notable has been her work through professional organizations to bring recognition to and support for the practicing endocrinologist. Being in private practice has given Dr. Fish the perspective needed to be a very strong advocate for the specific needs of the clinical endocrinologist. She has gained this perspective through her role as an endocrinologist and medical director of the Diabetes in Pregnancy Program at the Park Nicollet Clinic and Medical Center and as medical director of the Inpatient Diabetes and Diabetes Intensification Programs at the International Diabetes Center at the Methodist Hospital in Minneapolis. She is active in improving the quality of patient care, as evidenced by her role as physician leader of the Diabetes Care Initiative at the Methodist Hospital. In addition to her private practice activities, she is also on the clinical faculty of the University of Minnesota, and is a member of the editorial board of *Endocrine*. She has also been a relevance reviewer for the American Board of Internal Medicine for the Endocrinology, Diabetes and Metabolism Boards.

In the early 1990s, when Dr. Fish became involved in The Endocrine Society, it was just beginning an evolution into a much broader organization that included all aspects of the professional endocrine community. The inclusion of the practicing endocrinologist as an equal partner in the affairs of The Society was a paradigm shift for The Society, a shift that did not come about without some growing pains. Dr. Fish played a key role in bringing about these changes in The Society. She was a tireless advocate for the special needs of



the practicing endocrinologist. Through her work on the Clinical Initiatives Committee, the first Committee constituted to specifically address the needs of the practicing clinician, Dr. Fish slowly won over the leadership of The Society as to the importance of including practitioners, patients, and the public in the affairs of The Society. She did this by using her substantial powers of persuasion and diplomatic skills. She played a key role in initiating programs and activities that were focused on the practicing endocrinologist. The success of these initiatives, brought about through Dr. Fish's leadership, is reflected by the number of practicing endocrinologists who are now members of The Society. As she moved from being Chair of the Clinical Initiatives Committee to an elected representative on Council, her ideas and leadership skills contributed to the continued evolution of The Society. In recognition of Dr. Fish's contributions to The Society, she received the Presidential Citation for Leadership in Clinical Endocrinology in 1997.

At the same time that Dr. Fish was working with The Society, she also became very active in the American Medical Association (AMA). She has been recognized three times by the AMA with its Physician's Recognition Award. She was The Endocrine Society representative to the Specialty Services Society of the AMA, as well as The Society's delegate to the AMA. It is through Dr. Fish's efforts that The Endocrine Society became a member organization of the AMA. She initiated a drive that encouraged enough of The Society's members to join the AMA to meet membership requirements. It is truly due to her perseverance that The Endocrine Society gained a major presence within the AMA, a presence that continues today.

Dr. Fish continued to play a groundbreaking role in The Society by becoming a founding member of the Board of Directors of The Hormone Foundation. Through the Foundation, Dr. Fish has been able to make a new contribution, *i.e.* to the area of patient education. During the first formative years of The Hormone Foundation, Dr. Fish has played an important role in guiding the Foundation to become the premier resource for patients and the public. She played a pivotal role in serving as a liaison between the Endocrine Council and the Foundation. During The Society's recent strategic planning effort, Dr. Fish has been a strong advocate for the Foundation as a key element in the future goals of The Society. She has also provided the leadership in the Foundation's program on Hormone Abuse. There is no doubt that Dr. Fish will continue to make significant contributions to the Foundation as it expands its role into fund raising activities.

Dr. Fish received her M.D. degree from Brown University Medical School, and she received her postgraduate training at the University of Minnesota Hospitals, completing residency training in internal medicine and fellowships in endocrinology and diabetes.

*M. Susan Smith*

**Citation for the 2002 Richard E. Weitzman Award of The Endocrine Society to Dr. Jonathan L. Tilly**

Jon Tilly earned his Ph.D. degree in 1990 from Rutgers University under the mentorship of Dr. Alan Johnson, and completed postdoctoral work with Dr. Aaron Hsueh at



Stanford University. In 1993, Jon joined the faculty at Johns Hopkins as an Assistant Professor and established his now world-renowned research program on ovarian cell death (apoptosis). In 1995, he relocated to Boston to accept his current faculty position as Associate Professor of OB/GYN and Reproductive Biology at Harvard Medical School. In addition, Jon serves as the Director of the Vincent Center for Reproductive Biology and Chief of the Division of Research in the Department of OB/GYN at Massachusetts General Hospital.

Jon's principal research interest has been to elucidate the regulation and functions of apoptosis in the ovary. Over the past 8 yr, Jon has methodically and meticulously woven many seemingly diverse topics into a highly respected and extremely well-funded scientific enterprise that spans basic, translational, and clinical research. As a brief chronology, in 1995 Jon's laboratory was the first to report on the possible function of *bcl-2* gene family members in granulosa cell death during follicular atresia. Given that, at the time, *Bcl-2* family members were believed to act by affecting the reduction-oxidation status of the cell, Jon's lab simultaneously explored and published on this topic in the context of granulosa cell apoptosis. Jon published several additional papers in *Endocrinology* in 1995, three of which were the first to report on the role of p53 in follicular atresia, the consequences of *bcl-2* gene knockout on the ovary, and the function of caspases in granulosa cell death.

After arriving at Massachusetts General Hospital, Jon initiated one of his most important areas of scientific research. This work, detailed in *Nature Medicine* in 1997 and 2000, elegantly dissected the molecular mechanisms underlying oocyte death and ovarian failure caused by exposure to anti-

cancer therapies. Briefly, these investigations showed that chemotherapy and radiation engage a cell death pathway in oocytes involving the proapoptotic messenger ceramide, and that the resultant death of oocytes requires both Bax and caspase-2. Jon's lab took these seminal findings one step further by validating both transgenic and small molecule therapy-based approaches to protect the ovaries from the damaging side-effects of anticancer treatments. From these efforts, Jon has a patent application in review that describes novel technologies to maintain fertility and ovarian function in female cancer patients.

While this accomplishment is, in itself, a clear indication of the novelty and significance of Jon's work, he has simultaneously pursued another paradigm of premature menopause with equal focus and intensity. These investigations, which took over 6 yr to accomplish, were published in *Nature Genetics* in 2001 and in *Endocrinology* in 2002. From this work, Jon's lab uncovered a novel apoptosis-signaling pathway involving the aromatic hydrocarbon receptor-transcription factor. In addition, he beautifully documented the cascade of proapoptotic events set in motion in oocytes exposed to a class of toxic chemicals, present in the environment and in tobacco smoke, that are known to cause premature ovarian failure.

However, Jon's story of scientific discovery to date does not end here. Since 1993 Jon has been in hot pursuit of the first, and to date only, animal model that fails to exhibit ovarian senescence with advancing age. Working under the hypothesis that attenuating follicle atresia could extend ovarian life span, Jon first showed that a key apoptosis-regulatory gene, termed *bax*, was required for primordial follicle loss. Upon long-term evaluation of *bax*-mutant female mice, Jon's lab went on to prove that these animals indeed failed to undergo their equivalent of menopause at very advanced ages. With the development of this unique animal model, reported in *Nature Genetics* in 1999, follow-up studies to determine if and how the aging female body may benefit from prolonging ovarian function will finally be possible.

Because of these and many other accomplishments, Jon has been invited to speak of his work in over 100 lectures at scientific meetings, universities, and pharmaceutical companies. Moreover, the broad importance of Jon's research was most recently underscored by his appointment last year as an Investigator of the Steven and Michele Kirsch Foundation, one of only eight such named Investigators in the country. It is indeed rare that the efforts of a scientist as young as Jon impact so profoundly on a field as competitive as ovarian biology; however, Jon's brilliant career to date has done just that. Therefore, it is most befitting that The Endocrine Society recognizes Jon this year as the recipient of the Richard E. Weitzman Award.

John Cidlowski

### **Citation for The Endocrine Society and Pharmacia Corporation International Award for Excellence in Published Clinical Research in *The Journal of Clinical Endocrinology & Metabolism* in 2001**

#### **First Prize**

"What Are the Physical Characteristics Associated with a Normal Metabolic Profile Despite a High Level of Obesity in Postmenopausal Women?" Vol. 86, No. 3, 2001, pp. 1020–1025. Authors: Martin Brochu, André Tcherno, Isabelle J. Dionne, Cynthia K. Sites, Georgia H. Eltabbakh, Ethan A. H. Sims, and Eric T. Poehlman. Department of Medicine, Divisions of Clinical Pharmacology and Metabolic Research (M.B., A.T., I.J.D., E.T.P.), Cardiology (M.B.), and Obstetrics and Gynecology (C.K.S., G.H.E.), and Endocrinology, Diabetes, and Metabolism Unit (E.A.H.S., E.T.P.), University of Vermont College of Medicine, Burlington, Vermont 05405.

#### **Finalist**

"Differential Regulation of Gonadotropin Secretion by Testosterone in the Human Male: Absence of a Negative Feedback Effect of Testosterone on Follicle-Stimulating Hormone Secretion." Vol. 86, No. 1, 2001, pp. 53–58. Authors: Frances J. Hayes, Suzunne Decruz, Stephanie B. Seminara, Paul A. Boepple, and William F. Crowley, Jr. Reproductive Endocrine Unit of the Department of Medicine and National Center for Infertility Research, Massachusetts General Hospital, Boston, Massachusetts 02114.

#### **Finalist**

"TSH-Controlled L-Thyroxine Therapy Reduces Cholesterol Levels and Clinical Symptoms in Subclinical Hypothyroidism: A Double Blind, Placebo-Controlled Trial (Basel Thyroid Study)." Vol. 86, No. 10, 2001, pp. 4860–4866. Authors: Christian Meier, Jean-Jacques Staub, Carl-Bénédict Roth, Merih Guglielmetti, Maya Kunz, André R. Miserez, Jürgen Drewe, Peter Huber, Richard Herzog, and Beat Müller. Divisions of Endocrinology (C.M., J.J.S., C.B.R., M.G., M.K., A.R.M., B.M.) and Clinical Pharmacology (J.D.), and Department of Central Laboratories (P.H.), University Hospital Basel, CH-4031 Basel, Switzerland.

#### **Finalist**

"Insulin Inhibits Intranuclear Nuclear Factor  $\kappa$ B and Stimulates I $\kappa$ B in Mononuclear Cells in Obese Subjects: Evidence for an Anti-Inflammatory Effect?" Vol. 86, No. 7, 2001, pp. 3257–3265. Authors: Paresch Dandona, Ahmad Aljada, Priya Mohanty, Husam Ghanim, Wael Hamouda, Ezzat Assian, and Shakeel Ahmad. Division of Endocrinology, Diabetes & Metabolism, State University of New York at Buffalo and Kaleida Health, Buffalo, New York 14209.

*Photos of the winners will be available after the Annual Meeting of The Endocrine Society and will be published in a future issue.*