A *Semblanza* for the RegPep26/2027 Named Prize Lectureship Professor Hal Gainer

A life dedicated to understanding the peptidergic neuron (short statement)

In the history of neuroendocrinology, certain names appear not merely as authors of important papers, but as true pioneers who reshape entire fields. Professor Harold "Hal" Gainer, who passed away in November 2023, was precisely such a figure. For over four decades at the National Institutes of Health (NIH), he stood as an internationally recognized leader in the study of peptidergic neurons, those specialized brain cells that express neuropeptides as their primary signaling molecules.

As the International Regulatory Peptide Society (IRPS) prepares to gather in Beijing in 2027, we propose a Named Prize Lectureship to honor this extraordinary scientist, mentor, and human being. Professor Gainer's scientific achievements are monumental: he was the first to demonstrate post-translational processing of neuropeptide precursors within secretory vesicles, the first to identify the oxytocin and vasopressin precursor proteins, and a pioneer in understanding the cell-specific expression of neuropeptide genes. Beyond these discoveries, he was a champion of diversity, a mentor who changed lives with a few kind words, and a bridge-builder who brought neuropeptide science to China through his edited textbook *Peptides in Neurobiology*, which became a graduate-level text.

This lectureship is conceived as a tribute to a scientist who never stopped asking fundamental questions about how peptidergic neurons work, and to a human being whose generosity of spirit touched countless young scientists across the globe.

Foundational Statements:

1. The scientific odyssey: from marine animal sounds to the secrets of vasopressin: early training and diverse beginnings

Harold Gainer's path to becoming a giant of neuroendocrinology was neither linear nor conventional. He earned his undergraduate degree in chemistry from the City College of New York, followed by a Ph.D. in physiology and biochemistry from the University of California, Berkeley. After postdoctoral work at Berkeley and a brief instructorship at UCSF, he moved to Columbia University College of Physicians and Surgeons, where he worked in the laboratory of Dr. Harry Grundfest on the electrophysiology of muscle and synapses.

From Columbia, Gainer accepted a faculty position at the University of Maryland. There, his research took an unexpected turn: he studied the mechanisms of sound production in marine animals and the role of calcium in excitation-contraction coupling. This diverse early career—spanning marine biology, muscle physiology, and calcium signaling, gave him a uniquely broad perspective that would later serve him well when he

turned his attention to the complexities of the brain's peptidergic systems. He maintained his connection to marine biology throughout his career, serving as a summer investigator at the Marine Biological Laboratory in Woods Hole, Massachusetts .

Joining the NIH: a four-decade journey

In 1969, Gainer joined the NIH as a research physiologist at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). This marked the beginning of a remarkable four-decade career at the NIH. By 1983, he had risen to become Chief of NICHD's Laboratory of Neurochemistry and Immunology. In 1987, he was recruited to the National Institute of Neurological Disorders and Stroke (NINDS) as Chief of the Laboratory of Neurochemistry, a position he held until his official retirement in 2012, after which he was named Scientist Emeritus.

At NINDS, Gainer also served as acting scientific director (1994-1995) and as director of the Basic Neuroscience Program (1990-2000), helping to shape the direction of NIH-funded neuroscience research during a period of tremendous scientific expansion.

The Seminal Discoveries

Professor Gainer's scientific legacy rests on several foundational discoveries that fundamentally changed our understanding of how peptidergic neurons function.

First, the identification of neuropeptide precursors: Gainer was the first to identify the oxytocin (Oxt) and vasopressin (Avp) peptide precursor proteins - **the large, inactive molecules from which the biologically active nonapeptides are derived**. This discovery was revolutionary because it established that neuropeptides, unlike classical neurotransmitters, are synthesized as larger precursors that require specific processing to become active.

Second, the demonstration that processing occurs within secretory vesicles: Perhaps his most important mechanistic contribution was demonstrating that the post-translational processing mechanisms that produce biologically active peptides occur not in the cell body but *within secretory vesicles* themselves. This finding established the fundamental cell biology of peptidergic neurons: the large dense core vesicles (LDCVs) are not merely transport containers but active processing factories where prohormones are converted into their final signaling forms.

Third, mapping the oxytocin and vasopressin genes: In a landmark 1990 paper published in *Molecular Brain Research*, Gainer and his colleagues isolated the mouse vasopressin and oxytocin genes and determined their nucleotide sequences. They made a critical discovery: the two genes are linked together in a tail-to-tail orientation, separated by a short 3.5 kb intergenic sequence, and are

transcribed from opposite strands . Both genes share a similar three-exon structure and high similarity in the regions encoding the nonapeptides and the central core of neurophysin .

This genomic arrangement became the focus of much of Gainer's subsequent work. He proposed the **Intergenic Region (IGR) hypothesis**, which posited that the 3.6-kbp region between the mouse OT and VP genes contains the critical enhancer sites responsible for their cell-specific expression. This hypothesis guided the development of transgenic models that continue to inform our understanding of neuropeptide gene regulation.

Fourth, the first intracellular recordings of peptide regulation: Gainer also achieved the first intracellular recordings of peptide regulation of neural activity, providing direct electrophysiological evidence for how neuropeptides modulate neuronal function.

The Intergenic region hypothesis and transgenic innovation

Gainer's laboratory became a world leader in using transgenic approaches to study oxytocin and vasopressin neurons. His team developed organotypic slice-explant cultures of the hypothalamus, which allowed for excellent preservation of highly differentiated magnocellular neurons in long-term culture, a critical tool for studying these cells outside the intact animal .

Using these models, combined with particle-mediated gene transfer (biolistics), Gainer's group identified critical DNA sequences in the IGR responsible for hypothalamus-specific gene expression. They successfully targeted green fluorescent protein (GFP) to large dense core vesicles and studied calcium-dependent secretion of OT-GFP and VP-GFP fusion proteins from individual pituitary nerve terminals, a technical *tour de force* that allowed real-time visualization of neuropeptide secretion .

The neuropeptide textbook legacy

Beyond his primary research, Professor Gainer made another enduring contribution: he edited the first book on neuropeptides, titled *Peptides in Neurobiology* . This seminal volume was subsequently translated into Chinese and used as a graduate-level textbook in China . For a generation of Chinese neuroscientists, many of whom might attend RegPep26/2027 in Beijing, this book was their first systematic introduction to the field that Gainer helped to create.

In his later years, Gainer co-edited (with David Murphy) *Molecular Neuroendocrinology: From Genome to Physiology*, part of the Masterclass in Neuroendocrinology series published by Wiley Blackwell in 2016. This comprehensive volume brought together the latest thinking on everything from

genome expression to post-translational processing, serving as a capstone to his career as a synthesizer and communicator of neuroendocrine science.

2. The mentor: words that changed lives

For all his scientific achievements, those who knew Hal Gainer speak most passionately about his role as a mentor and his extraordinary kindness. The NIH's official memorial notice includes a story that captures his essence perfectly.

Dr. Binta Jalloh, now a postdoctoral fellow at the NCI Center for Cancer Research, recalls meeting Gainer briefly at a dinner party in Woods Hole when she was a college student attending the Marine Biological Laboratory as an underrepresented summer research student . Here is how she remembers that encounter:

> *"He looked into my eyes and said the kindest, most powerful words: 'Binta, from what I can see and have learned about you, you would make a fine scientist one day, just keep going.' He and the others in attendance all had Ph.D.s and careers in their own respective fields. I walked away from that encounter believing that I too could earn my Ph.D. in the sciences and work at NIH if I just keep going like Dr. Gainer says."*

Those few words, spoken not to a promising graduate student but to an undergraduate summer researcher, changed the trajectory of a young woman's life. Dr. Jalloh went on to earn her Ph.D. in genetics and molecular biology from Emory University, with an F31 fellowship funded by NINDS. Today, she works on the NIH campus, just as Gainer had encouraged her to believe she could .

This single anecdote reveals more about Gainer's character than any list of honors could. He saw potential where others might have seen just another student. He took the time to speak words of encouragement when a few kind sentences could have the greatest impact. And he understood, deeply, that the future of science depends not only on discoveries made today but on the young people who will carry the torch forward tomorrow.

NINDS Director Dr. Walter Koroshetz captured this dimension of Gainer's legacy succinctly: "Hal's scientific achievements, mentoring legacy and contributions to NINDS and NIH are described as outstanding by those who knew him. He was a great supporter of the institute and a champion of diversity. The NIH community mourns his passing. We all will miss him" .

3. The human being: humility, generosity, and perseverance

Behind the titles - Scientist Emeritus, Chief of Laboratory, Acting Scientific Director - lay a man of genuine humility and warmth. Those who worked with Gainer describe him as accessible, generous with his time, and deeply committed to the success of everyone in his orbit, from the most junior technician to the most senior collaborator.

A bridge to China

Of particular relevance to the RegPep26/2027 meeting in Beijing is Gainer's special relationship with China. His textbook *Peptides in Neurobiology* was translated and used as a graduate-level text there. This means that many Chinese neuroscientists of a certain generation - now established as professors and PIs - learned their neuropeptide biology from Hal Gainer's book. He was, in a very real sense, a teacher to a generation of Chinese scientists even though he never met most of them in person.

This connection was not one-way. Gainer's own science benefited from international collaboration. His transgenic studies involved collaborators from around the world, and his laboratory welcomed visiting scientists from many countries. He served as an adjunct or visiting professor at George Washington University and Tel-Aviv University in Israel, in addition to his primary NIH appointment .

The marine biological laboratory connection

Throughout his career, Gainer maintained a deep connection to the Marine Biological Laboratory (MBL) in Woods Hole. He served as a summer investigator there. The MBL represented something special to Gainer: a place where scientists from different disciplines and different countries could come together, share ideas, and inspire the next generation. His presence there, year after year, exemplified his commitment to science as a collaborative, international, and deeply human enterprise.

A life of public service

It is worth noting that Hal Gainer spent his entire career, more than 40 years, as an intramural scientist at the National Institutes of Health. In an era when many of his peers moved from institution to institution, chasing higher salaries or more prestigious titles, Gainer chose to serve the public as a government scientist. He could have commanded any salary in the private sector or at a major research university. Instead, he dedicated his life to the NIH's mission: seeking fundamental knowledge about the nature and behavior of living systems and applying that knowledge to extend healthy life and reduce the burdens of illness and disability.

This choice, to serve rather than to accumulate, speaks volumes about his character and values.

4. Why a named lectureship? The unique fit for RegPep26/2027

The proposed **Professor Harold Gainer Named Prize Lectureship** at RegPep26/2027 in Beijing would serve multiple important purposes, each resonating deeply with the values of the International Regulatory Peptide Society.

Honoring foundational contributions to regulatory peptide science

First and foremost, the lectureship would recognize a scientist whose work is directly and centrally relevant to the IRPS mission. Gainer's discoveries about the biosynthesis, processing, packaging, and secretion of vasopressin and oxytocin - the prototypical regulatory peptides - are foundational to the entire field . Every scientist who studies how neuropeptides are made, transported, and released stands on ground that Gainer helped to prepare.

His work on the IGR hypothesis and cell-specific gene expression continues to guide research today. The transgenic tools he developed - including the targeting of GFP to LDCVs - remain in active use. And his textbook *Molecular Neuroendocrinology*, co-edited with David Murphy, stands as a definitive reference in the field .

Celebrating mentorship and diversity

Second, the lectureship would celebrate what Dr. Koroshetz called Gainer's role as "a champion of diversity". In a scientific world where mentoring is often undervalued relative to publishing, a named lectureship in Gainer's honor would send a powerful message: that training the next generation, especially those from under-represented backgrounds, is as important as any discovery published in a high-impact journal.

The story of Dr. Binta Jalloh is not an isolated incident. It is one example of a lifetime of similar gestures, of seeing potential in young people, speaking words of encouragement, and opening doors. The Gainer Lectureship would ensure that his commitment to diversity and inclusion remains a living part of the IRPS's identity.

Honoring international scientific exchange

Third, the lectureship would recognize Gainer's role in building bridges between the American and Chinese neuroscience communities. His textbook *Peptides in Neurobiology* was a crucial educational resource in China. By naming a lectureship in his honor at a meeting in Beijing, the IRPS would be acknowledging that scientific progress is not the property of any single nation but the product of global collaboration.

This fits perfectly with the IRPS's tradition of rotating its meetings across continents and its commitment to fostering international scientific exchange.

A posthumous tribute for a life well lived

Professor Gainer passed away in November 2023. A named lectureship in his honor would be a fitting way to remember him, not with sadness, but with celebration of a life dedicated to science, mentorship, and human connection.

There is a Chinese saying: "A teacher for a day is a father for a lifetime." Hal Gainer was a teacher to thousands.

5. Conclusion: a giant who bowed to no dogma, but lifted countless others

Professor Harold Gainer's career was marked by intellectual courage. He was not afraid to ask the hard questions about how peptidergic neurons work. He was not afraid to challenge established models. And he was not afraid to spend decades focused on a single system, the magnocellular neurons of the hypothalamus, until he had revealed its deepest secrets.

But what truly distinguished Hal Gainer was his humanity. In an increasingly competitive scientific world, he remained generous. In a field that often prizes individual achievement, he remained a team builder. And in a society where senior scientists can be distant and inaccessible, he remained approachable, willing to look a young summer student in the eyes and say the words that would change her life.

As the IRPS gathers in Beijing in 2027, let us create a lectureship that bears his name. Let it be awarded to scientists who embody his values: rigorous science, generous mentorship, and a commitment to building a global, inclusive, and collaborative research community.

In the Chinese tradition, the highest respect is shown through a deep bow. But Hal Gainer taught us something perhaps even more important: that science progresses not only when we bow to truth, but when we lift others up along the way.

Biographical Fast Facts (for citation)

Category	Information
Born	c. 1935
Died	November 2023
Education	B.S. in Chemistry, City College of New York; Ph.D. in Physiology and Biochemistry, University of California, Berkeley
Postdoctoral Training	UC Berkeley; UCSF (Instructor); Columbia University (with Harry Grundfest)
Academic Positions	Faculty, University of Maryland; Adjunct/Visiting Professor, University of Maryland, George Washington University, Tel-Aviv University
NIH Career	NICHD (1969-1987, Research Physiologist, then Chief of Laboratory of Neurochemistry and Immunology); NINDS (1987-2012, Chief of Laboratory of Neurochemistry); Scientist Emeritus (2012-2023)
NINDS Leadership Roles	Acting Scientific Director (1994-1995); Director of Basic Neuroscience Program (1990-2000)

Category	Information
Key Scientific Contributions	First identification of OT and VP precursor proteins; demonstration of post-translational processing within secretory vesicles; first intracellular recordings of peptide regulation of neural activity; mapping of mouse OT and VP genes; IGR hypothesis for cell-specific expression
Major Publications	*Peptides in Neurobiology* (first neuropeptide textbook, translated into Chinese); *Molecular Neuroendocrinology: From Genome to Physiology* (co-editor with David Murphy, 2016)
Mentoring Legacy	Transformed lives of countless young scientists, especially from under-represented backgrounds; champion of diversity at NIH
Special Connection to China	*Peptides in Neurobiology* used as graduate-level textbook in China
Honors	Scientist Emeritus, NINDS; NINDS Director's tribute as "great supporter of the institute and champion of diversity"
IRPS Role	**Long-term supporter and distinguished member**