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GUEST EDITORIAL

A debt owed to a wonderful mentor, Seymour Reichlin

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Joseph B. Martin, MD, PhD, Edward R. and Anne G. Lefler Professor of Neurobiology, Emeritus, former Dean of Harvard Medical School (1997–2007), and former Dean of the School of Medicine (1989–1993) and Chancellor (1993–1997) of the University of California, San Francisco (UCSF), presents the second guest editorial in this Festschrift issue honoring Dr. Seymour Reichlin's centennial. Martin completed his PhD in anatomy at the University of Rochester, and in 1967 he was one of Dr. Reichlin's earliest fellows. In this account, he provides a personal perspective on his scientific journey under Reichlin's mentorship. He details their groundbreaking work on hypothalamic-pituitary regulation, which laid the foundation for Martin's distinguished career in neurology and academic medicine. Martin describes Reichlin as the "quintessential physician-scientist," highlighting his mentor's exceptional breadth of knowledge and innovative approach to neuroendocrine research. Their decades-long collaboration culminated in co-authoring the definitive 1987 textbook *Clinical Neuroendocrinology* and numerous influential publications. The guest editorial offers unique insights into Reichlin's lasting impact on the field from one of academic medicine's most accomplished leaders, including observations of his mentor's continued scientific contributions at age 100, exploring novel applications of neuroendocrine regulators in cognition and sensory function.

This guest editorial follows Dr. Ronald Lechan's comprehensive overview of Dr. Seymour Reichlin's extraordinary career and scientific contributions in this Festschrift issue (1).

Introduction

I joined Seymour Reichlin's laboratory in Rochester, New York, as a fellow in July 1967, after completing medical school in Edmonton, Alberta, Canada, and neurological residency at Case Western University in Cleveland. Si, as he insisted on being called, emerged as a leader in neuroendocrinology after returning to the United States in 1954, following two years in the laboratory of Geoffrey Harris at the Maudsley Hospital, University College, London. I first became aware of his contributions and the emerging field of neuroendocrinology when I read his extensive three-part review in the *New England Journal of Medicine* published in 1963 (2–4).

My interest in joining his laboratory followed my experience during my neurology residency, treating four patients who suffered from idiopathic orthostatic hypotension. My curiosity led me to wonder about the homeostasis regulation accomplished by the hypothalamus and the endocrine system (5). I was pleased that Reichlin was a Ph.D.-trained academic physician who had spent years in clinical training, including time in psychiatry and endocrinology, in addition to internal medicine.

The Quintessential Physician-Scientist

Seymour was the quintessential physician-scientist, equally at home in the clinical trenches (where he conducted ongoing clinical trials and translational research) as he was in the laboratory. He was a polymath, curious about many things, and I often felt my valuable times with him were constrained by his musings about things that had little to do with my research. Si arrived almost every day with a new idea about the following experiments before I had finished the last. His research often was left partly done as he moved on to bigger ideas. There always seemed to be many laboratory manuals of unpublished research as better ones supplanted older ideas. I accepted all of this, believing that these were genius traits. Having Si's intimate knowledge of the entire landscape of internal medicine, neurology, and psychiatry made him a formidable presence in any conversation we had. The opportunity to work with him was one of the great experiences of my life.

Scientific Journey and Collaboration

My Ph.D. thesis project was to study the dynamics of the hypothalamic-pituitary-thyroid system, which could, by that time, be studied with pituitary hormones measured with highly sensitive radioimmunoassay. I developed an assay for thyroid stimulating hormone (TSH) in the rat and measured fluctuations in circulating levels after manipulating the axis. I was able to show that hypothalamic electrical stimulation with implanted electrodes placed at selected brain sites produced TSH release, mapping the distribution of positive responses to areas that later were shown – after the discovery of thyrotropin-releasing factor (TRF, later TRH for hormone) by Roger Guillemin (6) and Andrew Schally (7), in separate laboratories – to correspond closely to the anatomic localization of TRH neurons. We were working to prove the authenticity of the hypothalamic-pituitary portal system as the key mechanism for endocrine regulation.

I completed my thesis work during a year that I was also in charge of moving his laboratory from the University of Rochester to a new medical school at the University of Connecticut in Farmington.

In addition to his broad insights into biology and medicine (and psychiatry since he had spent a few years in the psychiatry department at Washington University in St. Louis), his political skills in the academic marketplace were even more spectacular. He was friends with everyone. I watched with amazement as the enmity between the scientists Roger Guillemin and Andrew Schally, each at different institutions, escalated as they tried to outdo each other in identifying hypothalamic regulatory (releasing factors) for which they would eventually share the Nobel Prize in 1977 (8). Si got on with both, and they greeted him (separately) with great affection at annual endocrine meetings.

It was my good fortune in 1973 to recruit back to Canada one of Guillemin's research fellows, Paul Brazeau, who had just published the structure and amino acid sequence of somatostatin, the GH release-inhibiting factor (SRIF), from Roger's lab. Paul brought the peptide and antisera to our laboratory, which allowed us to pursue an interest in its role in GH regulation.

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Figure 1. Joseph B. Martin (left) and his mentor Seymour Reichlin (right) photographed during their annual meeting at Il Capriccio restaurant in Waltham, Massachusetts, in the fall of 2024. They joyfully celebrated Reichlin's 100th birthday and their 58 years of friendship.

After completing my degree work, I considered and rejected an invitation to remain in Connecticut as an assistant professor of neurology. Having been supported for three years in his laboratory through a fellowship from the Medical Research Council of Canada, I felt obligated to return to Canada for an appointment in medicine and neurology at McGill University. In 1971, my thesis, *Neural Regulation of the Pituitary-Thyroid Axis in the Rat*, was presented to the University of Rochester.

By that time, Rachel and I had four children ranging in age from a few months to twelve years of age. Si and I continued to stay in close contact as we collaborated on new projects, and my research interests evolved into the brain regulation of growth hormone (GH) secretion. I followed Si's example and published a review on the neural regulation of growth hormone secretion as a medical progress report in the *New England Journal of Medicine* (9). The most striking aspect of this work, with Gloria Tannenbaum and John Willoughby, graduate students (10–11), was the finding that GH is secreted in pulsatile bursts in rats and humans. Despite its actions measured in months and years on metabolism and growth, the dramatic, pulsatile bursts, including enhanced release during early sleep (in the human), provide it with its effective longitudinal impacts.

The availability of somatostatin, and of other hypothalamic neuropeptides that Brazeau was able to obtain, led to a series of electrophysiologic experiments with Leo Renaud showing the neuromodulatory effects of hypothalamic peptides on neuronal excitability (12).

My work during those first six years at McGill led to my appointment in 1976 as Professor of Neurology at McGill University and chief of neurology at the Montreal Neurological Institute.

Building Centers of Excellence

In 1978, I was surprised to be recruited by Harvard Medical School to be chief of the neurology service at the Massachusetts General Hospital (MGH). I settled into a laboratory only a few blocks away across the Boston Common from Si and his group at the New England Medical Center at Tufts University Medical School when he took the important position of head of the Endocrine Unit. He remained there until his retirement in Tucson, Arizona.

My recruitment to The MGH was greatly facilitated by Si's recommendation to the Harvard Medical School search committee, chaired by biologist-psychiatrist Seymour Kety and by an alignment with Dr. Nicholas Zervas, recently appointed chief of the department of neurosurgery at the MGH and a renowned pituitary surgeon, who was adopting the transsphenoidal approach to the pituitary treatment of adenomas. This collaboration with Zervas over the next eleven years was extraordinarily productive. Together, we worked with John Potts, Chair of the Department of Medicine- (and former chief of the Endocrine Unit), to establish an interdepartmental neuroendocrine clinic that became a leading center for the treatment of hypothalamic-pituitary disorders and management of pituitary tumors.

Those were wonderful years for both Si and me as we collaborated on papers and monographs addressing the emerging complexity of the role of brain peptides in neuroendocrine and homeostatic regulations: The discovery of more hypothalamic-releasing (and inhibiting) factors, prolactin inhibiting factor, dopamine, and of the opioid peptides, somatostatin and, gonadotrophin-releasing hormone each result leading to exciting new demonstrations of clinical significance.

My research expanded to the role of genetic causes of neurological disorders, showing, for example, that somatostatin neurons in the cortex are depleted early in Alzheimer's disease but selectively spared in Huntington's Disease, which ravages the nerve cells in the basal ganglia (13–15).

Lasting Legacy and Continuing Friendship

In 1978, we collaborated in planning, with psychiatrist Ross Baldessarini, the 56th meeting in New York City of the Association for Research in Nervous and Mental Disease, which was summarized in a monograph in entitled *The Hypothalamus* (16), and In 1981 with Katherine Bick, a monograph, *Neurosecretion and Brain peptides: Implications for Brain Functions and Neurological Disease* (17). These publications, enlisting more than 80 leading authorities in the medical practice, established neuroendocrinology as a legitimate specialty in medicine, neurology, and psychiatry.

However, the tour de force that brought our collaboration to widespread attention was our joining together on a detailed textbook of Neuroendocrinology published in 1987, entitled *Clinical Neuroendocrinology, 2nd Edition* that covered, in over 750 pages, the entire expanse of hypothalamic-pituitary disorders (18). An earlier edition had been done in collaboration with Gregory M Brown, a fellow graduate student with me in Reichlin's lab, and by then, a professor of psychiatry at the Clark Institute of Psychiatry at the University of Toronto. A much more detailed

and complete treatment of the subject became our goal. The project took five years to complete, which to this day remains one of the contributions I am most proud of. Despite numerous discussions about it, however, we needed more time, focus, and energy to revise it, although we often talked about that.

After Si moved to Tucson, Arizona, to a wonderful small ranch in the suburbs that his dear wife Eleanor (Ellie) loved and which became a home for several animals, he spent the next thirty years in collaboration with individuals who shared his interest in complementary and alternative medicine and the workings of stress-related hormonal and immunological events. He took a particular interest in what he came to call the field of emotional homeostasis, with curiosity about psychotropic drugs and psychedelics. He found a laboratory arrangement at the University there, and we saw each other at least once yearly. Sadly, his wife Ellie died there a few years later of cancer, leaving Si alone to continue his curiosity-driven research that thrives to the present.

I continue to look forward to each summer when Si calls to say that he will be making his annual visit to see his daughter Annie in New York and then on to Boston, where he rents a car, takes a room in the Embassy Suites Hotel in Waltham (on route 128), and invites me to join him for dinner at Il Capriccio, one of our favorite restaurants, with Si later en route to the family coastal Maine ocean retreat.

This happened again this fall (2024), three months after our June celebration of his 100th birthday with friends and former fellows in Boston-see Figure 1. He was still driving but allowed me the privilege of picking him up at the Embassy Suites hotel and again spending a delightful couple of hours with him at Il Capriccio.

Each time we meet, I come away with insights that amaze me. During the last visit, we focused on the remarkable fact that GnRH administered in a pulsatile fashion can improve olfactory performance and enhance memory, with a remarkable publication of its effects on Down's syndrome (19). By this time, it was well known that neurons expressing GnRH send connections to many cortical and subcortical brain regions.

Si remains my greatest hero, one of three or four individuals whose influence on my career trajectory and accomplishments is immeasurable and who evokes wonderfully fond memories and my deepest appreciation.

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