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Biographical note

Tribute to Roger Guillemin, a pioneer in neuroendocrinology (1924–2024), Nobel Prize in Physiology or Medicine

Christiane Mougin [a], **Jean Rossier** [b,c] **and Bertrand Bloch** [*,d]

[a] Department of Cellular Biology, University of Franche-Comté, France

[b] Academy of Sciences, Institut de France, France

[c] Royal Academy of Medicine, Belgium

[d] University of Bordeaux, France

E-mail: bertrand.bloch@u-bordeaux.fr (B. Bloch)

Abstract. Roger Guillemin discovered and characterized the hypothalamic factors that control anterior pituitary functions. He consequently demonstrated that these brain peptides regulate a large number of major body activities through neuroendocrine mechanisms. This especially include growth, fertility and reproduction, endocrine gland functions and stress. These seminal works paved the way to major applications in many fields of physiology and medicine for diagnosis, pharmacology and therapy, far beyond the initial discovery and properties of these molecules, including in cancerology, immunology, inflammation, drug addiction and behavior.

Keywords. Neuroendocrinology, Releasing factors, Hypothalamus, Anterior pituitary, Endorphins.

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Roger Guillemin, Nobel Prize in Physiology and Medicine in 1977, died at the age of 100 on February 21, 2024, in San Diego (California) where he was living.

Roger Guillemin was born in Dijon on January 11, 1924. He was a student at the Carnot High School, and then began his medical studies in 1943. His youth was nourished by the "Franche-Comté" roots of his father's family. A great-grandfather was an ironmaster in Vuillafans; his father was born in Dole, and it was through this family that, as a child, teenager and later medical student, he became very close to the Duvernoy family in Besançon. He strongly contributed to the French resistance during World War II, during the German occupation of Besançon, within a group of smugglers founded by Doctor Maurice Duvernoy. It was from Maurice Duvernoy, director of the Besançon School of Medicine, that he later got his first anatomy lessons. By a fair turn of events, Roger Guillemin's first works inspired some of the neuroanatomical work of his son, Henri Duvernoy, on the vascularization of the hypothalamic-pituitary arterial system.

Very early on his career, Roger Guillemin became passionate about endocrinology. At the end of his medical course, he met Hans Selye in Paris, a pioneer in stress studies. Fascinated by his lecture dealing with the adaptation of the body to stress, Roger Guillemin left France to work with him at the University of Montreal. His research work allowed him to first defend his medical thesis in Lyon, then subsequently his PhD in 1953 in Montreal. He then started

* Corresponding author

Figure 1. Roger Guillemin at the Salk Institute in 2017 (Personal collection, Bertrand Bloch).

to work for several years at Baylor University College of Medicine (BUCM) in Houston (Texas).

At the end of the 1940s, Geoffrey Harris, one of the pioneers in neuroendocrinology at Oxford University, proposed that substances present in the hypothalamus could reach the pituitary gland through the portal vascular system, and control the release of pituitary hormones and consequently many body functions, including stress. From this concept, Roger Guillemin decided to isolate and characterize these factors and synthesize them. This work will lead him to the Nobel Prize. Between 1960 and 1963, he came back to the Collège de France in Paris where he developed his very first experiments devoted to hypothalamic factors through innovative bioassays [1]. But according to his words, the working conditions and administrative obstacles encountered in France at that moment were at odds with his vision of the ambitious and innovative research he wanted to develop. Roger Guillemin then returned to BUCM in Houston in 1963. In his laboratory, he created the material, technical, and organizational conditions necessary for the isolation of these molecules.

He hypothesized that these factors were small proteins ("peptides") produced by neurons in the hypothalamus. Even though his concepts and his first results were strongly criticized by part of the scientific community, he relentlessly developed innovative strategies to isolate these substances present in minute quantities inside the brain. He collected several tons of hypothalamic fragments from millions of sheep in slaughterhouses. At the end of 1968, Roger Guillemin and his team, including his students Roger Burgus, Wylie Vale, Catherine and Jean Rivier, and Nicholas Ling, obtained 1 mg of the first hypothalamic peptide from 300,000 sheep hypothalamus [2]. This peptide, called TRF, stimulates the production of thyroid hormones through action on the pituitary gland. Thanks to this first pioneering discovery, neuroendocrinology became a major field in biology and medicine. The structure of this peptide was established in 1969. Simultaneously, his competitor Andrew Schally identified with his team the same TRF from pig hypothalamic fragments.

In 1970, Roger Guillemin founded and directed the Laboratories for Neuroendocrinology at the Salk Institute in San Diego (California), and focused his research on the purification, isolation and characterization of the hypothalamic peptide which stimulates the release of hormones acting on the gonads (Gonadotropin-releasing hormone or GnRH). He also tried to isolate the peptide that stimulates the production of growth hormone. It took many years of sometimes unexpected research results, because the first peptide he discovered was an inhibiting substance, somatostatin. And it was a few years later that GRF, the peptide activating the production of growth hormone, was unexpectedly isolated from a pancreatic tumor responsible for acromegaly [3]. This last discovery had direct consequences for clinical medicine. The search for hypothalamic releasing hormone ended in early eighties with the identification, by his former student Wylie Vale, of CRF, the peptide that controls ACTH release [4].

Following the discovery of enkephalins, these endogenous morphines, by John Hughes and Hans Kosterlitz in 1975, Roger Guillemin also discovered several other opioid peptides, work to which one of us (JR) contributed [5].

Roger Guillemin therefore made a decisive contribution to the understanding of the mechanisms

Figure 2. Henri Duvernoy (left) next to the future Nobel Prize in Medicine Roger Guillemin, himself next to his mentor Maurice Duvernoy (Personal collection, C. Mougin; gift of H. Duvernoy).

Figure 3. Roger Guillemin and his team at the Salk Institute in 1983 (Personal collection, Bertrand Bloch).

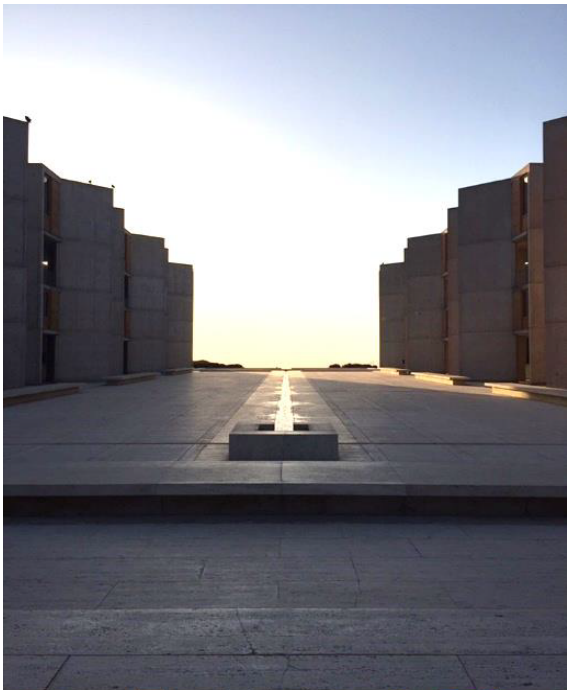

Figure 4. The Salk Institute for Biological Studies (Personal collection, C. Mougin).

by which the brain controls the secretions of the pituitary gland and the endocrine system. The consequences of his discoveries went quickly beyond the scope of neuroendocrinology and are of particular interest for endocrine physiology and pathology, control of fertility (contraception, medically assisted reproduction, sterility…), tumor and inflammatory pathologies, regulation of mood disorders and psychiatry and, of course, pharmacology [6]. These achievements also found numerous applications in the veterinary field, something Roger Guillemin liked to point out.

His work therefore led him to the Nobel Prize in Physiology or Medicine in 1977, that he shared with Andrew Schally and Rosalyn Yalow. Roger Guillemin also received the highest international honors. He was elected as a member of the American Academy of Sciences in 1974 and as a member of the Academy of Arts and Sciences in 1976; in France, he was appointed foreign associate member of the Academy of Sciences in 1984. His work has been recognized by numerous other prizes and honors. He was "commandeur de la Légion d'honneur". Several universities have conferred on Professor Roger Guillemin the title of Doctor Honoris Causa, including the University of Burgundy (November 4, 1978) and the University of Franche-Comté (November 20, 1998).

Roger Guillemin has indeed trained and inspired dozens of students and researchers around the world. Those who knew him have been impressed by his ingenious mind combined with a sound science and willingness, and a serenity associated with constant authority. Each of us had the privilege to be part of his team in the late 1970s and early 1980s, like several researchers from France, in this science paradise that is the Salk Institute. His laboratory was a hive of world citizens, where young researchers and skilled scientists of all origins were interacting. Roger Guillemin's scientific demands went together with a generosity and benevolence that permanently stimulated creativity. Roger Guillemin was fully committed to promoting a science without ideological or geographical borders; he has been involved on numerous occasions with many other researchers in promoting this humanist vision of science, open to the world and anchored in the needs of our societies. This is evidenced by the numerous personal relationships established with colleagues from all over the world, including in France, throughout his life. Among many examples, let's remind his deep ties of friendship and science with Professor Etienne Emile Baulieu, inventor and promoter of RU486, the molecule for safe termination of early pregnancy. Well beyond scientific discoveries and borders, his personal influence allowed each of his students and collaborators to create unwavering friendships and to promote his spirit and his values.

Roger Guillemin was also an elegant esthete, a very distinguished oenologist, an artist and a lover of innovative art. He painted on screen using his computer and basic softwares. No one knows what painter he would have become if he had not decided to devote himself completely to science.

He explained that the process leading to the creation of each of his "computer paintings", as he called them, was not very different from the intellectual process of research carried out in the laboratory about a scientific fact or a concept. However, according to him, there is a major difference between the approach of a scientist and that of an artist:

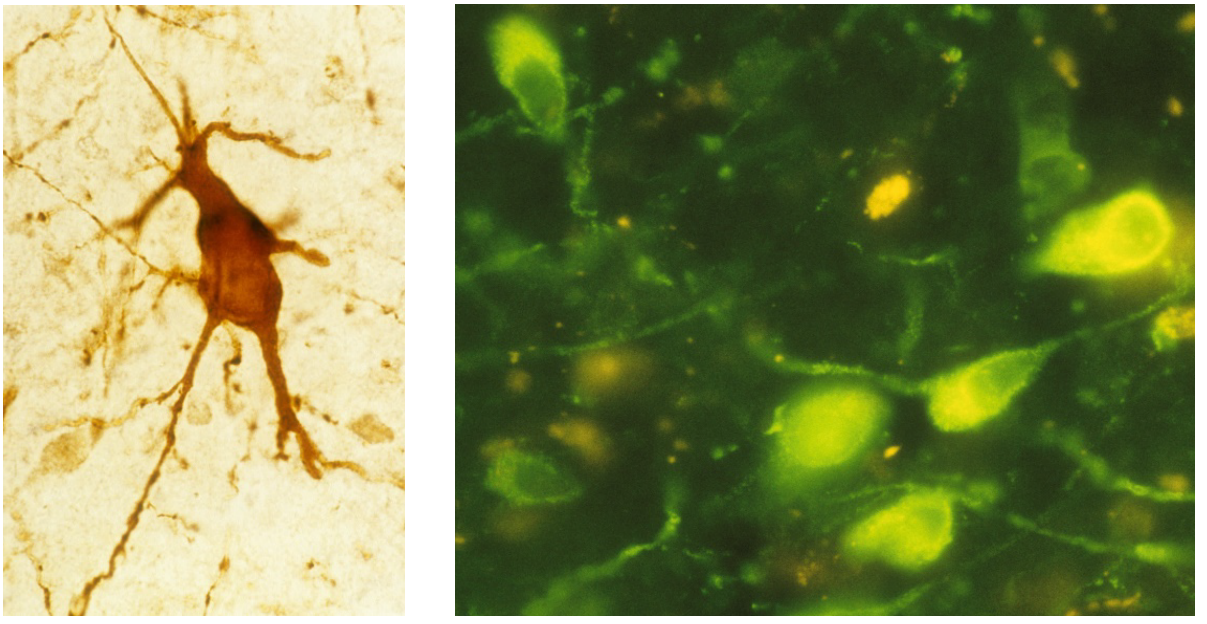

Figure 5. Hypothalamic neurons producing peptides (Immunohistochemical detection) (Documents Bertrand Bloch).

Figure 6. Roger Guillemin during the "Honoris causa" ceremony at the University of Franche-Comté with Henry Duvernoy (on his left), Bertrand Bloch and Christiane Mougin (on his right) (Personal collection, Christiane Mougin).

"There are rules and laws from which the scientist cannot escape: the laws of gravity, the fact that such a DNA sequence encodes such a protein and not another, that gold melts at such and such a temperature and not another, etc., while the rule for the contemporary artist is precisely that there are no rules. It is probably a higher level of what neuroscience and cognitive sciences call qualia." His sculptures and pottery of pre-Columbian origin from Mexico, Vanuatu and New Guinea, his relationships with numerous artists, including Nikki de Saint Phalle, illustrate his refined interest for art. His six children reflect this passion for art: a son who is a sculptor in Princeton, a daughter who is a gallery owner, another a dancer... and his late wife Lucienne Guillemin, a talented pianist, and accomplished painter, deceased in 2021 at the age of 100. With his family, Roger Guillemin always enjoyed being on his farm in an outstanding natural site, in Truchas, New Mexico, far from any urbanization; this haven of peace has constantly been a specific location for him to think and work.

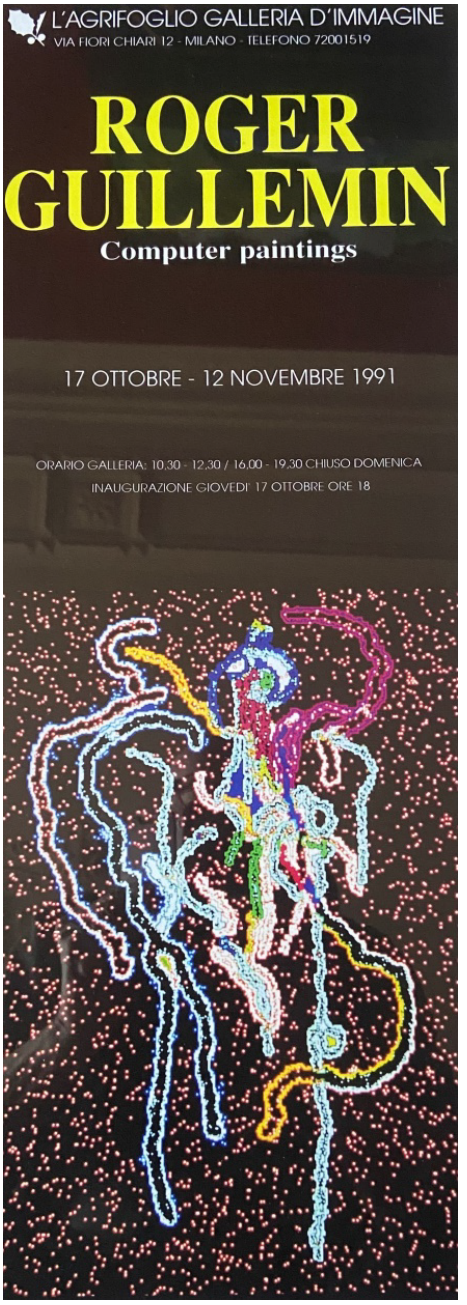

Figure 7. Computer painting exhibit from Roger Guillemin in Milano (1991) (Personal collection, Bertrand Bloch).

Declaration of interests

The authors do not work for, advise, own shares in, or receive funds from any organization that could benefit from this article, and have declared no affiliations other than their research organizations.

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