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## Obituary

**Hervé Paul Marie Antoine ROCHAT**

1937 - 2023



Hervé Rochat was born on May 23, 1937 in Beirut (Lebanon). During his childhood he followed his father, an officer of the Foreign Legion, in his successive posts, starting with Tamanrasset (Algeria), which may explain his love for adventure and discovery and his interest in southern countries. At the end of 1957, to prepare his State Doctorates in Pharmacy and in Physical Sciences (obtained in 1961 and 1969, respectively, and followed by an "Aggregation de Médecine" in 1973), Hervé joined the laboratory of Serge Lissitzky (1919-1986) at the Faculty of Medicine of Marseille, where he met François Miranda (1926-2019), who became his colleague and friend for several decades. Having spent part of their youth in North Africa largely influenced the selection of their research subjects, animal venoms, which some people sometimes described as "exotic". Most of all, they wanted to understand the reasons for the high lethality of the venoms of local scorpions and snakes which

constituted a real threat for the indigenous populations. At that time, only little scientific information on the composition of animal venoms was available. Hervé and François decided to tackle this question, despite attempts to make them study other subjects considered more important for medicine.

With a small contract with the French army for developing an effective antiserum against the venom of the African scorpion *Androctonus australis* ("austral man killer", in Greek), which has been responsible for thousands of deaths per year in the Maghreb countries, they started their research by collecting several thousands of animals around the oases of the Great South of Algeria and Tunisia - at night using a UV lamp, since the chitin cuticula of scorpions is fluorescent. The scorpions were individually housed in the Marseille laboratory and regularly "milked" until enough grams of venom were obtained (1 g requiring 2000 to 4000 milkings) (fig. 1) for attempting the purification of its components, at that time supposed to be a single neurotoxin [Miranda et al., 1960]. With the help of all the members of the team he had recruited and motivated on this project, Hervé carried out this dangerous task twice a month for two decades, despite his administrative functions and responsibilities.



Figure 1 - The scorpion *Androctonus australis* Hector, here in the hands of Hervé, lives in Algeria, Tunisia, Libya and Egypt, where its sting often causes fatal accidents. © Hervé ROCHAT / CNRS Images.

After purifying this first scorpion toxin and showing that it was a small, highly cross-linked protein of about sixty amino acid residues, Hervé spent a sabbatical year with Pehr V. Edman in Melbourne (Australia) to learn automatic protein sequencing based on the “Edman degradation technique”, and established the first peptidic sequence of a scorpion toxin [Rochat et al., 1970]. It was he who introduced in France both this apparatus and this technique, which at the time required at least 15 mg of pure toxin and numerous steps to elucidate a sequence of this size. Hervé's enthusiasm was such that despite his duties as University Hospital Professor, he would come to the lab at night to assist the technicians and students in charge of the experiments.

The structure-function relationships of animal toxins (scorpion, snake, bee, sea anemone, ...) were always the main subject of his laboratory, which was recognized worldwide and was supported by national and local authorities, and by regular contracts with private companies, French and international non-profit organizations, and the French army. To solve these questions, Hervé welcomed researchers specialized in neurobiology, pharmacology, chemistry and immunology in his laboratory. It was first demonstrated that the toxins purified from the venom of the African scorpion, *A. australis*, prolonged the action potential of voltage-activated sodium channels of excitable cells. Then, owing to the milking of 160,000 Mexican scorpions of the genus *Centruroides*, the laboratory discovered a second mode of action, predominant in the toxins of New World scorpions. This new activity could then be related to a specific binding site on sodium channels, distinct from that for Old World scorpion toxins. The lab members were then able to explain the precise mechanism of the different types of toxins, by demonstrating that they block the movement of the voltage sensors of these channels, described as the “voltage-sensor trapping” mechanism. These contributions to the understanding of the mode of action of scorpion toxins stimulated a passion for animal toxins in Hervé's students and lab members, and prompted some of them to continue his research endeavours long after his retirement. For example, in 1988, in collaboration with protein crystallographers, Hervé reported the three-dimensional structure of AaHII, the most lethal of the *A. australis* scorpion toxins that he had identified during his State Thesis in Physical Sciences in the late 60's (fig. 2) [Fontecilla-Camps et al., 1988]. Thirty years later, in 2019, owing to the “resolution revolution” in cryo-electron microscopy, this toxin was finally “viewed” tightly bound to its receptor, and the interactions between the atoms of the toxin and those of this ion channel perfectly identified. These studies and successes were made possible because of the close collaboration between groups of complementary expertise that Hervé managed to set up in his laboratory.



Figure 2 - X-ray crystallography structure of the highly lethal scorpion neurotoxin AaHII, solved at 1.8Å resolution [3]. The polypeptide chain of 64 amino acid residues (the side chains of some of them are shown) is cross-linked by 4 disulphide bridges (displayed in yellow). © Hervé ROCHAT / CNRS Images.

During the mid-70's, Hervé set up a peptide synthesis group in his laboratory, which succeeded in the chemical synthesis of a bee venom toxin, apamin, active on a potassium channel. This proof-of-concept success was quickly followed by the synthesis of short scorpion toxins active on various potassium channels, along with numerous analogues and variants that greatly contributed to the study of their structure-function relationships. These techniques also proved to be particularly useful for understanding the immunochemistry of the toxins. Hervé initiated close collaborations with labs in several countries where venomous animals were a plague, and where the development of antivenoms to protect the population was requested. Immunological studies demonstrated the great polymorphism of animal toxins and the need to produce specific antibodies for them. By obtaining poly- or monoclonal neutralizing antibodies, the epitopes of some of these toxins were identified, a progress that allowed the development of diagnostic kits by ELISA or radioimmunoassay [Rochat et al., 1977] for the detection of very small quantities (~10 ng) of toxin in the blood of envenomed patients.

In the early 90's Hervé encouraged the introduction of molecular biology techniques in his laboratory. As a result, his lab was the first to clone and sequence the cDNA of a scorpion alpha neurotoxin, AaIII [Bougis et al., 1989], then that of *Tityus serrulatus* beta-neurotoxin TsVII, and to define the organization of their genes into promoter, introns and exons. In the late 90's, his last project as a lab director was to support the creation of an "in-lab" proteomics facility, where the first exhaustive analysis of the composition of an animal venom, again that of *T. serrulatus*, by mass spectrometry, was carried out.

Since the early 1970s, Hervé was also interested in snake venom toxins, with a particular predilection for those of the genus *Elapidae* (cobras, mambas, kraits, coral snakes, present on all continents except Europe), and contributed to the identification of curarimimetic alpha-neurotoxins that target the nicotinic acetylcholine receptor [Miranda et al., 1970]. Through collaborations and the welcoming of students or post-doctoral fellows from Maghreb countries, various pro- or anticoagulant constituents were isolated from the venoms of African *Viperidae* snakes, and characterised.

Hervé directed or supervised State or University Ph.D. Theses in "molecular toxinology". Most of those trained in his lab, and often "confirmed" through a post-doctorate stay, became researchers, team or laboratory leaders in France or abroad, and many of them kept working on the structure-function relationships of animal toxins and using them as "molecular scalpels" to study their physiological receptors.

During several decades, researchers and students from all over the world also joined Hervé's laboratory. These include Spanish chemists, Israeli biologists studying insect-specific scorpion toxins, Chilean and Russian protein crystallographers, Mexican pharmacists, and many students or post-docs sent by Institut Pasteur branches based abroad (Maghreb countries, Madagascar, Mali, Senegal, Vietnam...) or by institutes in countries where public health is threatened by venomous animals (Brazil, China, Costa Rica, Egypt...). All were welcomed with great pleasure because they brought both new research subjects and their enthusiasm. Back in their country of origin, occasionally with a French doctorate, some of them became Head of a Laboratory, Professor, Dean and even President of a University. All maintained strong ties of esteem and friendship with Hervé, which enabled the continuation of successful collaboration programs funded by international contracts. For example, in 2003 Hervé and a former PhD student of his founded the first International Associated Laboratory, named "LIA d'Ingénierie Moléculaire", between two CNRS laboratories in Marseille (his own lab) and in Montpellier in France and two laboratories at the Institut Pasteur of Tunis (Tunisia).

Therefore Hervé can be considered as one of the pioneers of French and international toxinology. However, his curiosity also included interest in other types of molecules, such as structural and regulatory proteins of HIV, or adenosine and its metabolism in cardiac or neurological pathologies. The bibliographic databases report more than 250 articles (excluding

books and book chapters) authored by Hervé and published in international journals between 1960 and 2004.

Hervé actively contributed to several Councils and Boards of the Faculties of Sciences and of Medicine of Aix-Marseille University, and to the Boards of several French, European and international societies, such as (e. g.) the “Société Française pour l’Etude des Toxines” (SFET, 1993-2006), the “Association Française de Lutte contre la Mucoviscidose” (AFLM, now Vaincre la Mucoviscidose (VLM) (1990-early 2000’s), the “Collège National de Biochimie et de Biologie Moléculaire Médicale” (CNBBMM), or the International Society of Toxinology (IST) as its President from 2000-2003. In 1981, he organized the 4<sup>th</sup> European Symposium of the IST in Marseille [Hider, 1981; Proceedings], and in 2000, he was involved in organizing the 13<sup>th</sup> World Congress in Paris. Hervé was also Editorial Board member of international scientific journals dedicated to protein biochemistry and toxinology.

In addition to fundamental research, which was his first passion, and to his duties as the Director of his research laboratory (1977-1999), Hervé held important positions at the French research organisations CNRS and INSERM and at the Faculties of Sciences and of Medicine of Aix-Marseille University. For the CNRS, he was Deputy Director of the Life Sciences Department (1985-1989). For the Faculty of Sciences, he coordinated two academic grade levels, the “DERBH” in Biochemistry of Interactions (1978-1984) and the “DEA” (now Master-2) in Neurosciences (1985-1999). For the Faculty of Medicine, from 1973 he taught biochemistry to several generations of future M.D.’s. As a hospital practitioner, he headed three Biochemistry Laboratories and one Clinical Investigation Center, and in one of them he created a robotic chain of biological analyses (1988-2003).

In recognition of these achievements, Hervé was awarded the Charles Dhéré prize in biological chemistry by the “Académie des Sciences de Paris” (1983); awarded the rank of “Chevalier de l’Ordre National du Mérite” (1989); included in the Who’s Who in France (2003); and appointed Honorary Professor of the newly renamed Faculty of Medical and Paramedical Sciences of Aix-Marseille University (early 2000’s). The scorpion *Buthus rochati* was named after him [Lourenço, 2003; Sousa et al., 2017].

Once retired, Hervé, always faithful to his vocation as a teacher and his interest in the southern countries, became actively involved in a long-term twinning between two dioceses located in Provence and in northern Benin. There, he contributed to the development of a primary school and a middle/high school, and enabled the integration of out-of-school and destitute children, whom he met regularly.

Hervé Rochat passed away quietly on January 30, 2023, at the age of 85, in his house in Mimet, a small, perched village near Marseille. He leaves behind his spouse for 50 years, four children, eight grandchildren, and many former colleagues, students, collaborators, and friends. Passionate in everything he undertook as a patient, persevering and hard worker, he brought people together through his kindness, gentleness, humour and simplicity.



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