

EDITOR'S NOTE

RITA LEVI-MONTALCINI, 30 YEARS OF HER NOBEL PRIZE

LEONARDO PALACIOS SÁNCHEZ MD.¹ * XIMENA PALACIOS ESPINOSA MSc. PhD²
 JUAN SEBASTIÁN BOTERO MENESES MD.³

¹ Full Professor of Neurology. Neuroscience Department.
 Neuros Research Group Universidad del Rosario

² Full Professor Psychology Program. Universidad del Rosario

³ Professor Research Assistant. Neuroscience Department.
 Neuros Research Group. Universidad del Rosario

Thirty Years have passed since the famed Italian neurobiologist, Rita Levi-Montalcini, was awarded the Nobel Prize of Medicine or Physiology. Her outstanding career in the field of neuroscience was an example for all scientists and researchers, but moreover, her life was an example for all of mankind. This remarkable woman endured a staggering amount of obstacles in order to become a doctor, and a scientist. She prevailed above them, and lived a life of success, wisdom and principle. We wish to honor her achievements and reflect upon her awe-inspiring life.

Key Words: History, Neuroscience, Nobel Prize, Neural Growth Factor (NGF)

In 1986, Italian neurobiologist Rita Levi-Montalcini was awarded the Nobel Prize of Medicine or Physiology alongside biochemist Stanley Cohen, for their discovery of nerve growth factors (1-3). She was the fourth woman to ever receive a Nobel prize. Her life and work are an example of science, humanism, selflessness and perseverance, in spite of the many difficulties she had to endure. Her life, very highly regarded amongst scientists, also stands as an example of a fair and just woman, who fought many years for gender equity, and overall dignity of mankind (3). The purpose of this work is to honor and remember the life of this remarkable scientist, on the 30th anniversary of her Nobel.

Some biographical data

She was born in Turin on April the 22th 1909, she was born with a twin sister, Paola who was a renowned artist past away in the year 2000. Her mother, Adele Montalcini was a very skilled painter herself (3). Rita narrates on one of her autobiographies that she had a very strong bond with her mother and always felt deeply loved and nurtured by her (3-11). Her father Adamo Levi, an electrical engineer, discouraged her from pursuing college and post graduate studies, for it was very unusual in that time for a woman to aspire formal higher education which could distract them from their housekeeping tasks.

Rita unequivocally opposed the decimononic narrow-minded way her family had imposed on women for years and categorically decided against marriage and child-bearing (12,13). It is, however, very possible that many of this decisions and traits of character are a legacy of her father, who from a very young age, taught Rita the importance of being her own woman, and a "free mind" (11). In 1929, her very dear governess died of a lately diagnosed gastric cancer. This planted in the depths of Rita's mind the idea of pledging her life to the noble medical profession. She went to medical school in her hometown of Turin, obtaining a doctorate in Medicine and Surgery in the year 1936 (1,2). Her father had determined that both her and her twin sister Paola, would enroll in an all-female school, where they could learn how to be proper mothers and housewives. When Rita expressed her intention of attending medical school, he opposed. Nonetheless, after some time he gave in and accepted her decisión (14,15).

During her years as a medical student, Rita attended a predominantly male class along with only six other women (one of them her cousin Eugenia). Both girls were, more often than not, the subject of less-than charming comments

regarding their looks, by word of the overwhelming masculine majority of the classroom (11). The whole 300 student group had a total of 294 men students.

Another very important player in her memories, is her anatomy professor Giuseppe Levi. As it is true of many med school teachers, Dr. Levi was quite the character. A man of stern expression and explosive temper, but also gifted with a kind heart and spirit. Professor Levi would become a mentor for Rita, who took the job as her academic assistant after completing her studies. Rita and Giuseppe worked side by side until Benito Mussolini and his nefarious “Manifesto della razza” stood in their way (11). Racial and political persecution were so severe that Levi Montalcini was forced to spend some time away from Italy, working in a Neurological Institute in Belgium. Here, she published a paper showing the anatomical and functional relationship between neural centers and pathways in a chick’s embryo (15).

Nine months later, she returned to Italy and settled in the outskirts of Florence. With some help from her colleagues, Rita hastily arranged a laboratory in her own home, using the bedroom and the kitchen as workspaces (1,3,13). She would often go out into open country to find eggs in nearby farms, telling local farmers she needed them to feed their children, and praised the nutritious qualities of their yield (1).

After her father past away in 1932, Levi-Montalcini took her share of inheritance money and formed a foundation with a sole purpose. To ensure children were the masters of their own future (13).

She graduated “Summa Cum Laude” (1) and she entered a Psychiatry and Neurology residency program, which she would carry out and finish with flying colors. In 1940, by means of recommendation from her former teacher Giuseppe Levi, she read a paper written by Dr. Viktor Hamburger, considered to be one of the fathers of developmental neuroscience. The paper was published in 1943. The reading of this document was paramount for Rita, and it would greatly influence her future Research (1,15).

Towards the ending of World War II, Rita was designated by the Allies forces to travel to northern Italy, where she practiced medicine in favor of extremely poor and ill people, suffering from the scourge of cholera and Typhoid fever. In 1945, when the war ended, Levi-Montalcini returned to Turin and resumed her various academic activities in University.

By 1935, Professor Viktor Hamburger, had reached a near 50-year trajectory in Washington University, St. Louis, during which he spent 25 years as the president of the Zoology department, later known as Biology Department (1).

Hamburger was working in patterns of nerve cell growth and differentiation, and he considered that those processes had to be mediated by some sort of inducing agent. He had read some of Levi-Montalcini’s published work during the war, and invited her and her coworkers to his laboratory in St. Louis for the following semester so they could put their minds together and figure it out. The one semester, became 30 years Levi-Montalcini would spend in Washington University, she would refer to these years as the happiest of her entire life (1).

In Dr. Hamburger’s life, Rita met Dr. Stanley Cohen, who had worked as an associate researcher since 1953. Cohen had shown great interest in cellular biology and embryological development. By the time Levi-Montalcini and Cohen met, Rita had already discovered a neural growth factor (NGF) in tumors found in mice and had extensive work in the field of experimental embryology. ⁽⁴⁾ The molecule Levi-Montalcini discovered was necessary for the growth of both somatosensory and sympathetic nervous systems in vertebrate species (1).

From an experimental stand point, and in order to prove the existence and function of the growth factor she had discovered, Rita, transplanted tumoral cells from mice into chick embryos and observed these induced the development of sympathetic nerve growth. She also observed that the substance found in neoplastic tissue produced cellular growth similar to that found in in vitro nervous system cultures. Stanley Cohen was able to isolate said growth factor and study it’s proteic nature up close (1).

Barely a year before her death, and in honor of medicine, Levi-Montalcini contributed in various publications of great scientific value, regarding her initial discovery. One of them was published with the support of the European Brain Research Institute, Rita Levi-Montalcini Foundation, the Institute of Neurobiology and Molecular Medicine of Rome, and The Normal Superior School of Pisa (6).

In this article, the role of the Nerve Growth Factor in regulating neural and non-neural tissue development in adult organisms is heavily discussed. However, it is the focus of this work to understand the mechanism used by NGF in the early stages of embryonal development. It is concluded that an ontogenetic action of NGF backs and widens the evidence of the vital role this molecule has in the first weeks of development and the neurobiological processes involved.

The discovery of NGF represents an academic achievement essential for modern neurobiology and, in the same way the groundwork for advanced clinical therapy using growth factors for the treatment of complications of neurodegenerative diseases; for example, by reducing the loss of ganglionic retinal cells in glaucoma patients (8). As a matter of fact, in 2009 with the help of various renowned researchers, results were published in regard to the effects of NGF as a neuroprotection agent and apoptotic inhibitor of ganglionic cells in the retina of animal with glaucoma. Three patients with advanced glaucoma, showed great response to treatment with topically applied NGF, restoring in a great deal, visual acuity. These results became a promise that motivated the investigation of new perspectives for the treatment of glaucoma, by reducing nerve cell death which, in turn is the main unsolved problem in many neurodegenerative entities (8). Prior to these findings, in 2005, a study using recombinant nerve growth factor (rNGF) showed promise in being a potential treatment for neurological as well as autoimmune disease (9). The fact that, NGF circulated in almost any organ grants a pivotal role to this molecule in organic homeostasis and is therefore of great importance from a neural, autoimmune and endocrinological point of view (9).

In 1958, Levi-Montalcini was named in St. Louis as Head of the Neurobiological Investigation Center in Rome, as well as for the Molecular Biology lab back in Wash U, she then had no choice but dividing her time between Rome and St. Louis (5). As a result of her interest in clinical and therapeutic applications for NGF, she founded the European Institute of Investigations for The Brain in Rome, in 2002, creating an appropriate place to explore the possibilities regarding neurodegenerative disease (7).

She continued her work with Stanley Cohen and in 1986 they were awarded the Nobel Prize of Medicine or Physiology (1-5). In the words of Rita herself "December 10th 1986 marked the end of NGF's roaming and its official recognition by the scientific community" (10).

Levi-Montalcini was the first Nobel laureate to turn 100 years old, and up until her death in 2012, she was the oldest person to bear the Nobel medal.

NGF was among the first of many growth factors that would be isolated and used in research. We know over a hundred of them today and their role in biology is Paramount (1).

Levi-Montalcini retired from Wash U in 1977 and returned to her homeland where she continued to work for many years (1,2).

She was in her home when she received the call, announcing the award bestowed on Stanley and herself. The decision to leave Dr. Hamburger out of this discovery generated a great deal of controversy. Two of Hamburger's coworkers would later state in "Trends in Neuroscience" journal, that Dr. Hamburger's initial observations and experimental design constituted the foundations of the work Levi-Montalcini and Cohen used to isolate NGF (1).

Rita published an autobiography called "In praise of imperfection" in 1987. The book states mankind is far from perfection, just as one of its more elaborate creations: Science (2).

In 1994 she started a new foundation, that she presided over herself. It was dedicated to offer help to women, mainly in Africa, so they could achieve further education of the highest quality (2,3).

She released another book in 2011, alongside Giuseppina Tripodi titled “The Pioneers”: women that changed society and science, from old age to our days”. In the book, Levi-Montalcini and Tripodi show how women have dedicated themselves to research since the beginning of modern history and have had to overcome tremendous difficulties and unrecognition. Many of them were called witches or devil worshipers and were terribly discriminated. A recount and biography of some of this women are written (2).

Another one of her books “Your Future” is meant for young people to read, so they can be provided with ethics and principles to guide their life (2,5).

Rita Levi-Montalcini died, in her home, on December 30th 2012, she was 103 years old.

Many public and private academic institutions as well as governments and organizations honored her extraordinary work and the principles she stood for her entire life (**Table 1**).

Closing Remarks

Her independence and determination were a role model for many scientists and researchers.

In spite of her father’s wishes, not to pursue higher education, and Mussolini’s dark regime, Rita accomplished many of her goals, became a doctor, an expert in her fields and one of the best neurobiologists in history.

Her scientific achievements are countless and highly praised, but her influence as a humanitarian and a woman of science are not obscured by her published work.

Neural Growth Factor (NGF) described by Levi-Montalcini and Cohen, shifted the established paradigm that proposed a limited and unchangeable number of neurons in the human brain, and changed our understanding of CNS molecular plasticity.

The laureate stated that, the growth and reproduction capabilities of neurons endured into old age. This takes on new importance in a world constantly heading towards an inversion of the population pyramid, and that will be mainly made of elder people.

This finding is a strong argument against stereotypes in the elderly, changing their role in society from burden to protagonist, in the light of the study carried out by Ramírez and Palacios-Espinosa (12), stating positive stereotypes about old age and its protective factors.

The major influence of Levi-Montalcini and her extraordinary life, are founded not only on her skills as a scientist, but on her strong ethics and principles, her perception of womanhood and her ability to see herself as a citizen of the world. Rita-Levi is a non-paralleled and tangible example of human perseverance, courage and implacable strength, brought from passion and commitment to knowledge.

Table 1. *Distinctions Awarded to Rita Levi-Montalcini*

Año	Distinción
1974	Pontifical Academy Scientiarum (23).
1978	Honorary Doctorate - Weizmann Institute of Science (17).
1981	The International Astronomical Union, Minor Planet Center -Official Certificate on assigning the name of the minor planet 9722- Levi-Montalcini (14).
1981	Acad. Européenne des Sciences, des Arts et des Lettres (13).
1983	The Louisa Gross Horowitz Prize in Biology and Biochemistry, Columbia University (22).
1986	Nobel Prize of Medicine and Physiology, Karolinska Institutet (4).
1986	Gold Medal of Merit of the School of Culture and Art, Italy (20).
1987	US National Medal of Science (21).
1987	Cavaliere di Gran Croce Order to the merit of the Italian Repubblica (12).
1995	Foreign member of the Royal Society (ForMeRS) (7).
2001	Gold Medal of good merit of science and culture (20).
2001	Senatore a Vita, Repubblica Italiana (20).
2005	Laurea Honoris Causa - Università degli studi di Milano-Bicocca (18).
2005	Great Cross of the Order of Isabel the Catholic of Spain (7).
2006	Laurea ad Honorem in Ingegneria Biomedica - Polytechnic of Turin (18).
2008	Grand Officer of the Order of the Legion of Honor of France (20).
2008	Doctor Honoris Causa Universidad Complutense de Madrid (16).
2011	Doctor Honoris Causa University of McGill