
RITA LEVI-MONTALCINI



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No one word can describe Rita (as I was once asked), but many can: joy and passion for science, compassion, duty/devotion, trust in her friends and colleagues, loyalty, grace, graciousness, kindness, generosity of spirit, and a strong sense of equality and fair play. Those who knew Rita during the middle and later phases of her career may have seen only the elegant woman with upswept hair, wearing a silk dress and pearls. Scientists in the new field of nerve growth factor (NGF) research may have felt a chill of criticism from the woman who started it all. Any chill would have been gone, however, by the realization that she was responsible for scientific interest in NGF and growth factors.

In the frontispiece to her book of letters, *Cantico di una vita*, Rita quotes from the Old Testament: "I found that which my heart was searching for, I grasped it and will never let it go" (*Cantico dei cantici* III, 4), a quote which is not commonly used in a general sense. She described this as a "joyous state of mind" from her work and life experiences.

Rita was born in 1909 in Turin, Italy to an upper-class family, who did not value academic education for women. Her father, Adamo Levi, finally acceded to her pleas to pursue a career in medicine. She needed to quickly catch up on her missing knowledge of Latin, Greek, and mathematics before beginning medical school. When Rita began to work with Professor Giuseppe Levi of the Institute of Histology and Embryology at the University of Turin, she realized that her true interests were not as a physician but as a research scientist. Her studies on the development of chick embryo spinal ganglia with Professor Levi were the foundation of the work leading to the discovery of NGF. Using quantitative analysis of silver-stained specimens, she predicted that neurons grow and develop, but then some will die. During this period, her colleagues in Professor Levi's group included Salvador Luria and Renato Dulbecco, both from Turin and both eventual awardees of a Nobel Prize for their research.

When the Racial Manifesto was issued by the Italian government on July 14, 1938, Rita and other Jewish coworkers could no longer work at the University of Turin. After a brief sojourn in Belgium, ended by Nazi invasion, she chose to go into hiding in the Tuscan countryside. The stories of Rita working in her bedroom with a microscope and homemade instruments are well-known, as is the tale of utilizing "more nutritious" fertilized eggs requested from the local farmer so that she could continue her studies of neuronal development in peripheral ganglia.

After the war, Rita briefly joined the Stazione Zoologica of Naples, known for work in developmental biology of marine invertebrates. The

letters during this period showed her joy in her work and in life, including strolls with Giuseppe Reverberi and reading in the extensive library in between experiments. Some days they would take one of the institute's fishing boats to Ischia or Capri to collect flora and marine fauna for the laboratory, also spending time swimming and enjoying the sea.

During those years, Viktor Hamburger at Washington University in St. Louis had noticed Rita's work. It intrigued him that she had described neuronal cell death as a normal part of ganglion development, not in line with his hypothesis. He invited Rita to join his laboratory to resolve differences, to determine the mechanism governing the differentiation of motor and sensory neurons destined to innervate the limbs in chick embryos. The journey lasted not six months, but 30 years.

When Rita arrived in St. Louis, she worked in Hamburger's laboratory to pursue their joint project. The research first utilized *in vivo* models in chick embryos. To mimic Hamburger's experiments with amphibian larvae, in which he extirpated a limb or transplanted supernumerary limbs and then observed changes in the ganglia innervating these regions, tumors were transplanted to the chorioallantoic membrane of the chick. Surprisingly, hypertrophy of the ganglia was observed, with nerve fibers reaching to the implanted sarcoma 180 tumors. Rita realized that in order to determine whether this effect was due to having a larger physical "field" of innervation or to the presence of a soluble factor, a new approach was required. She traveled to the laboratory of Herta Meyer in Rio de Janeiro, Brazil, which led to the development of a tissue culture system that would permit testing of these hypotheses. They developed the plasma clot, inverted tissue culture of neuronal ganglia used for many years, even for assaying the purification of the NGF protein, the molecular factor eventually discovered. This method was one of the first tissue culture models useful for routine experimental investigation.

As time went on and Rita's project flourished, Hamburger gave her free rein to continue the work on NGF independently. He offered her a position as lecturer in zoology. She enjoyed the casual spirit of the American students, who often greeting her with a "hey, doc" and were interested in learning from their professors. In letters to her sister Paola, Rita explained why it would be difficult to return to work in Italy. She was not interested in becoming a departmental chair, nor in returning to work for Professor Levi in Turin where she would be at the mercy of an eventual, unknown successor. Positions with the Consiglio Nazionale delle Ricerche (CNR) were few and poorly paid. This situation made it more attractive to remain in St. Louis, where she could work

more effectively and with joy. Her colleagues Luria and Dulbecco also chose to follow scientific and academic careers in the United States.

Daily letters to her family and frequent trips to Italy were Rita's links to home. In St. Louis, she beautifully decorated a faculty apartment and had many friends. She would prepare wonderful dinners for her guests, whether famous or not. Rita took pride in her cooking but, because of her devotion to her work, would prepare as much as possible of her food in advance. Dinners at her home started with appetizers in the living room, usually Belgian endive with crème fraîche and caviar, with the Turinese aperitif Punt e Mes. Her entrée of *filet en chemise* was accompanied by *gnocchi di semolino*, salad, and vegetables, followed by fruit and cheese. Rita made zabaglione ice cream herself, preparing four dozen filled champagne glasses that she kept in her ample freezer, ready for an impromptu dinner party. She roasted her own beans for coffee. Conversation was always lively, and guests departed late in the evening. Rita later noted that her large dining table was also important in her writing and in preparation of work that led to the Nobel Prize.

When the biochemist Stanley Cohen (co-Nobel) joined the Department of Zoology at Washington University in St. Louis, a new phase of the research began. Facilitated by Rita's new assay, Cohen set out to determine if the nerve outgrowth observed with extracts of sarcoma 180 was due to a protein, nucleic acid, or other molecule. Snake venom DNase was routinely used to digest DNA present in a sample. To great surprise, this enzyme preparation, crude by today's standards, appeared to increase nerve outgrowth in ganglion cultures. Further experiments showed that snake venom itself contained nerve growth promoting activity, and that this activity was due to a protein molecule. The presence of the activity in snake venom also suggested that it might be present in mammalian salivary glands, related to venom glands. This proved to be the case, and the growth promoting activity, now called NGF (nerve growth factor), was found to be abundant in male mouse salivary glands. This productive collaboration led Cohen to declare: "Rita, you and I are good, but together, we are wonderful."

Beyond identifying a crucial source for purifying NGF for *in vitro* and *in vivo* biological studies and for chemical characterization, the mouse provided an essential model for understanding NGF biology. Injection of mice from birth with NGF produced hypertrophied sympathetic nervous systems. Production of antisera to NGF soon followed. Injection of antiserum into newborn mice as they developed led to suppression of the sympathetic nervous system. This was the first biological knockout mouse experiment.

The sheer beauty of the semiquantitative NGF bioassay almost made the work seem a fantasy. The novelty of the hypotheses and observations were so surprising to some scientists that it took time for the field to become established. This skepticism can explain the sensitivity that Rita felt to criticism and competition.

Cohen observed that the mice injected with NGF preparations opened their eyes several days early. This led to his discovery of epidermal growth factor (EGF) in the salivary gland, and to the beginning of this field of study. Rita continued working on the mechanism of action of NGF with a variety of collaborators, including Pietro Angeletti, Pietro Calissano, and Luigi Aloe, among others. She supported my work on the chemical determination of the primary and secondary structure of mouse and snake venom NGFs, together with Ralph Bradshaw. The productive work continued in her laboratory in St. Louis as she gradually returned to Italy to work.

The opportunity for Rita to return to Italy presented itself when she met Pietro Angeletti while he was working at the Washington University Medical School. He had a position in the Department of Biological Chemistry at the Istituto Superiore di Sanità (ISS) in Rome and suggested that she could transition her work there. Rita requested only a microscope, microtome, knives, and slides from the director of the ISS. Rita spent a few months a year in the lab in Rome and wrote research proposals to the CNR to support NGF work in the guest location at the ISS. Eventually, she settled into Rome again full time. With her colleagues, she submitted research proposals each year to the CNR. It sometimes took 9 months before the funds arrived for those not working directly for the ISS. Scientific staff would receive their back pay, regular paychecks for a few months, and then the process would begin again. The devotion of these scientists to Rita and to NGF research was inspiring. This situation was untenable in the long term, so Rita worked with colleagues to establish the Laboratorio di Biologia Cellulare (LBC) of the CNR and, eventually, to create the European Brain Research Institute (EBRI). This provided stability to the scientists. Notwithstanding, this unusual time of financial instability was also one of the most productive and exciting periods of her work. In the labs in Rome, she became *la professoressa*, no longer “doc.”

When Rita settled in Rome, she lived with her twin sister Paola, an artist whose studio was in the adjacent apartment. She called Paola “Gioia” (Joy) in their everyday conversations. There was no longer a need to write daily letters to her, nor to anxiously await her letters. There were many dinner parties at their home, for friends, colleagues, and fellow scientists who came to visit Rita in Rome. Rita no longer cooked; in fact, no one believed that she was indeed an exceptional

cook. Entering the pathway to her home in Viale di Villa Massimo, the scent of jasmine along the walkway in the summer was an invitation—and the signal of pleasant hours ahead.

Rita herself expressed her attitude toward her research: “It was not work.” She felt “a joyous state of mind in every moment of her days.” Describing the research leading to the discovery of NGF, she said that “I seem to be a truffle dog. In this moment, I sense the odor of the truffle and rapidly dig in the direction of the smell. It isn’t anything special. However, the solution to a problem that has absorbed me for some time, and that the others have overlooked” lay ahead.

When alone, Rita thought about present and future experiments incessantly. She took great joy and inspiration in planning experiments and discussing results with her close colleagues. Discussions took place not just in her office, but in the laboratory, with all working intently at the bench while listening. When her guests at dinner were her daily colleagues and/or other scientists, art and social issues would be discussed, but the conversation returned to science periodically. If a colleague had dinner together with other friends at her home, she would telephone right before bedtime to plan experiments for the coming days and weeks. Of course, she also telephoned first thing in the morning. Luigi Aloe described Rita as a “hurricane” entering his life.

A first international symposium on NGF took place in April 1986 in Monterey, California. It was organized to honor Rita on the occasion of her 75th birthday, although the festivities finally occurred on her 76th birthday. The meeting celebrated the birth of the new fields of NGF, growth factors, and neurotrophic factors. In the past, Rita had tensions with scientific colleagues and perceived competitors over the fast pace of developments in this area. Through the scientific presentations and joyful social interactions at this first symposium, she realized how valued she was for her groundbreaking work in establishing a completely new area of research. Fences were mended with colleagues; old and new friendships flourished. The sense of being threatened by so many new colleagues entering this research field was replaced by the respect and esteem they gave to her. Later, all were happy to have honored Rita before her recognition by the Nobel Committee. This event was a genuine expression that she profoundly appreciated.

In 1986, Rita Levi-Montalcini and Stanley Cohen were awarded the Nobel Prize in Physiology or Medicine. This type of honor is life-changing, even for someone as well-known as Rita. She experienced the perils and rewards of even greater fame. An immediate result was a deluge of well wishes. Every day, mailbags of correspondence arrived at her home and office. Rita was a prolific letter writer.

However, in the face of the extravagant amount of good wishes proffered, she became depressed at her inability to answer each letter personally, as was her habit.

There is a cultural difference in appreciation of science and scientists between Italy and the United States (at least). After the Nobel, Rita became a celebrity in Italy, not just with scientists and students, but with hairdressers, shopkeepers and most citizens. After a seminar at the CNR laboratory outside Rome, her driver drove Rita, Pietro Calissano, and the speaker to a lovely garden restaurant, which was almost empty in mid-afternoon. She included her driver at the luncheon table. Rita ordered rice with a little olive oil, and the others ordered their preferred dishes. Not long after ordering, a procession of food emerged from the kitchen, with portions of each dish ordered for all. The cook and owner entered at the end of the parade to greet her. Food was presented as love for Rita.

An unpleasant aspect of the Nobel award was the furor created by supporters of Viktor Hamburger, her mentor and colleague, who had not been included in the award with Rita and Stanley Cohen. Viktor Hamburger and Rita were close personal friends as well as colleagues. While it is understandable that a great scholar and gentleman such as Hamburger should be so admired (including by this author, who was an undergraduate student in Hamburger's department when he was chair), the Nobel Prize was clearly stated as an award for the discovery of growth factors, not of NGF itself. There is an extensive literature dissecting the development of the NGF story, beginning with the work of Schenkein and Bueker, to determine who was the most meritorious and seminal in the NGF discovery. However, Viktor Hamburger gave Rita wings to follow the project that she had started on her own and with him. Stanley Cohen joined with her, and together they launched this field.

Even as late as the occasion of Viktor Hamburger's 100th birthday celebration, there was bitter protest against Rita. During the dinner, among those standing to make laudatory comments were too many complaining about the 1986 Nobel Prize. The next day, I called Hamburger, who immediately invited me to his home to visit. Just before I arrived, Rita had called him to tell him of the death of her twin sister Paola, with whom he also had a close relationship. This underscores the love and respect in this friendship, belying the furor raised by so-called Hamburger advocates.

Rita's consuming passion for her work did not blind her to social inequities. This was exhibited in both large and small ways. She was appalled by segregation in America, and kept a poster of Martin Luther King, Jr. on the wall behind her desk at work. When she was asked, she

said that she had marched with him. After winning the Nobel Prize, she established a foundation first for Italian students, which later became a foundation in support of Ethiopian women. In 2005, she established the Rita Levi-Montalcini Foundation first for support/encouragement for Italian young people, and finally for education of young African women at all levels. The website still exists, but activities have been temporarily suspended. She wrote books for both causes. She called for “educational resources for the survival of mankind” and a “life of commitment.” Also in 2005, she founded the European Brain Research Institute (EBRI). Although it still exists, funds and leadership are required for carrying it into the future as she wished. On August 1, 2011, the President of the Republic of Italy designated Rita as Senator for Life, an honor bestowed upon citizens for extraordinary social, scientific, artistic, or literary contributions. She was among those who took her obligations seriously. Rita wanted to inspire and leave gifts for the future.

While Rita’s dedication to important causes is well-known, it was not as well-known that she helped many individuals. More important, she treated everyone she worked with and everyone she met with dignity and as equals. She would include her driver at guest lunches with seminar speakers. Those who worked with Paola on her artistic creations were treated as family. Indeed, Rita left a portion of her estate to some of her “family” who had worked with her and Paola for many years.

I was privileged to be a guest in Rita’s life, both scientifically and personally, and I learned from both. I worked with her in St. Louis and Rome—first in the lab in the basement of the Istituto Superiore di Sanità, and for a few years in the temporary location of the Laboratorio di Biologia Cellulare near Piazzale Flaminio. On the occasion of Rita’s 100th birthday, celebrations were held by the ISS and by the government of Italy at the Campidoglio. The day at the Campidoglio was highlighted by a symposium of scientific colleagues. Rita gave opening introductions. She listened intently to each speaker without taking notes. She asked questions of each, and at the end, she gave a succinct summary of the highlights of each talk. We must listen, stay alert, contribute.

After a dinner in the countryside outside Rome, Rita found time to spend a few minutes with individual guests. To me, she asked: “Do you still have the same passion for your work as always?” Then, “how old are you?” After the response, she said: “you still have 35 good years to contribute.” Yes, we are not supposed to stop trying to make the world a better place. And, indeed, she did write a book about it. Old age should be the “most serene [time of life] and no less productive than

earlier stages.” The use of the brain does not cause it to deteriorate as other organs or muscles do, but instead, reinforces and develops qualities that remain undeveloped earlier in one’s travels through life.

At the time of Rita’s 100th birthday, the outpouring of emotion and respect for her was stunning. The bookstalls in Piazza Navona had all of her books. The rest stops on the Autostrada del Sole featured her books. When she died, thousands in Turin turned out to honor her.

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