

RITA LEVI-MONTALCINI AND THE DISCOVERY OF NERVE GROWTH FACTOR: PAST AND PRESENT STUDIES

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Levi-Montalcini received her medical degree and her specialization in neurology and psychiatry from the Faculty of Medicine at the University of Turin, Italy, in 1936. In the early postgraduate years, first at the University of Turin with Prof. Giuseppe Levi and then at home in spite of severe personal restrictions and difficulties due to racial discrimination during World War II, she carried out studies on the neurogenesis of the cervical and thoracic ganglia of chick that takes place during prenatal development. The results of these studies came to the attention of V. Hamburger, a leading scientist at Washington University of St. Louis USA, who invited her to St. Louis to continue these studies and to characterize the effect of wing or limb extirpation on the development of motor and sensory neurons of chick embryos. This invitation marked the beginning of a long and fruitful scientific collaboration between Levi-Montalcini and Hamburger that led to the discovery of the nerve growth factor (NGF). In the following years, she studied the mechanisms of cell migration and neuronal differentiation in the central nervous system of developing birds. The results she obtained on transitional morphology and on cell survival or death occurring during nervous system development most probably represent the first and best documented contribution to the knowledge in the field of experimental neuroembryology of what is now more correctly termed "apoptosis" or "programmed cell death".

The NGF story started in 1949 when V. Hamburger showed Levi-Montalcini the results of one of his postgraduate students, Elmer Bueker. Bueker had observed that after the implantation of a small fragment of a malignant mouse tumor tissue into the body-wall of 3-day chick embryos, sensory fibres invaded the mouse, and that the ganglia which contributed fibers to the neoplastic tissue were somewhat larger than the contralateral ganglia innervating the limb. Bueker hypothesized that this effect was due to the fact that the rapidly expanding tumor offered the possibility to sensory fibers to branch in a much larger field than the embryonic tissues replaced by the neoplastic cells. This hypothesis did not convince Rita Levi-Montalcini. The results of her reinvestigation led Levi-Montalcini to the hypothesis that the mouse sarcoma tissues 180 and 37, when transplanted into a chick embryo, produced and released a diffusible agent that stimulated growth and the differentiation of developing nerve cells. Using a variety of *in vitro* methodologies, she then demonstrated that these tumor tissues produced and released a molecule that was able to stimulate neurite outgrowth from sensory and sympathetic nerve cells. In 1952 she gave to this substance the name of NGF. In the following years she worked on the characterization of the biochemical nature of NGF, and in collaboration with Stanley Cohen, co-winner of the Nobel Prize in 1986, she identified in a protein fraction, the agent

released by the tumor that promoted the effect on embryonic sensory and sympathetic ganglia. Together, they discovered that NGF was stored in snake venom and in the submaxillary salivary gland of mouse and that this gland produced the largest available source of NGF. This latter finding not only made a better biochemical characterization of NGF possible, but also that of its biological activities on neonatal and adult mammals and its purification. The description of the two classical studies published in 1952 and 1954 showing that chick embryos bearing transplants of mouse tumor 180 or 37 into the body cavity promote growth and differentiation of neurons of the prevertebral ganglia was a clear example, as the Nobel Committee recognized, of "how a skilled observer can create a concept out of apparent chaos".

In the early fifties, Levi-Montalcini, Professor at the Department of Zoology at the Washington University of St. Louis, intensified *in vivo* and *in vitro* studies of NGF on small rodents, while first S. Cohen and later P. U. Angeletti investigated the chemical and biochemical properties of NGF and both devised a methodology of purifying large quantities of NGF from snake venom and from mouse salivary gland. The availability of large amounts of NGF in the mouse salivary gland provided an additional opportunity to carry out numerous and collaborative *in vivo* studies and to investigate the structural, biochemical pharmacological action of NGF on sympathetic and sensory nerve cells. The large amounts of purified NGF also led to the possibility of producing anti-NGF antibodies and to characterize the effects of NGF on the development of the peripheral nervous system by injecting this antibody into new-born rodents. The immunodeprivation of NGF through exogenous administration of NGF-antibodies to these rodents and the observation that inhibition of circulating NGF levels results in death of NGF-target cells described in the late sixties, became known as immunosympathectomy.

In 1961, Levi-Montalcini established a small neurobiological unit in Rome, first at the Superior Health Institute and in 1970 a larger group at the National Research Council (CNR), where she became director of the newly formed Institute of Cell Biology. In 1986 she founded the Institute of Neurobiology.

From 1968, she decided to spend three months a year in Italy and the rest of the year at the Washington University of St. Louis.

In 1968 Levi-Montalcini decided to take a sabbatical leave from the NGF studies and was looking for a suitable invertebrate animal model to identify potential growth factors in insect nervous system. Among the numerous insects available, she selected the *Periplaneta Americana* cockroach. Levi-Montalcini working on the development of the peripheral and central nervous system of cockroaches she identify a molecule endowed with neurite-growth promoting activity on isolated nerve cells of the same or other insects. Unfortunately, the quantity of tissue storing this molecule was very small and recombinant methods were not yet available and Levi-Montalcini decided to give up to idea of isolating and purifying this unknown invertebrate neurotrophic factor.

After 1972, Levi Montalcini returned to NGF studies. The first approach to the renewed interest in this factor was the study of NGF on chemical and surgical axotomized peripheral neurons. Eugene Gene Johnson, a young pharmacologist work-

ing at Washington University Medical School in St. Louis, USA, joined her group and to the NGF field. These collaborative studies produced the first consistent evidence that NGF can prevent injury or even death of peripheral neurons exposed to sympatholytic drugs. During these same years numerous other groups working in the USA and in Europe showed great scientific interest in NGF studies. The increased attention to this molecule brought to light original findings regarding its spectrum of action on both the developing and the adult central nervous system (CNS) as well as on cells of the endocrine and immune system. Meanwhile, other investigations led to the identification of NGF receptors, protein sequences, gene localization and to the discovery of a new class of neurotrophins belonging to the NGF families. NGF

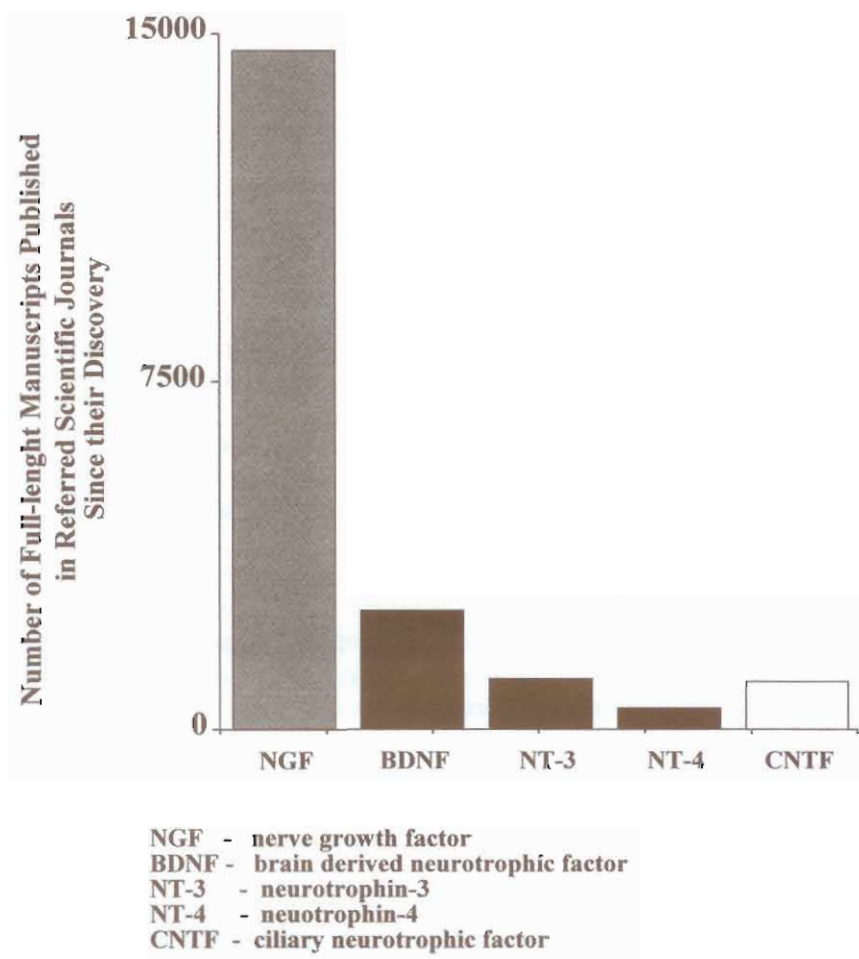


Fig. 1. - Number of original articles on the neurotrophins indicated since their discovery.

is the first discovered and the most studied member of a family (Figure 1) of neurotrophic factors, collectively called neurotrophins.

The purification of NGF isolated, first from the submaxillary gland and more recently obtained through the human recombinant methodologies (hrNGF), lead to the identification of a wide spectrum of NGF action and to the biochemical and molecular characterization of NGF and of its target cells. These first observations have stimulated an interest in NGF as a potential therapeutic agent for the treatment of nerve injury and neurodegenerative diseases.

More recently, molecular studies revealed that NGF codes for a much larger precursor, though the biologically active NGF contains 118 amino acids defined as 7S NGF. The 7S complex consists of three different molecular species, the alpha subunit, whose function is largely unknown, the gamma subunit, endowed with protease activity, and the beta subunit, which is biologically active NGF. The human gene for NGF is located on the proximal short arm of chromosome 1 and NGF protein is a highly conserved molecule that shares a great homology within different species. Two structurally unrelated receptors for the NGF family are known: A low affinity ($K_d = 1 \text{ nM}$) to the so-called p75 NGF receptor. The second NGF binding protein is a member of the trk family of tyrosine kinase receptors, gp 140^{trkA}. The receptor gp 140^{trkA} has many of the properties of a high-affinity receptor class (K_d between 10^{-11} and 10^{-9} M), and its interaction with NGF appears to be responsible for mediating neuron survival and differentiation.

In 1977, Rita Levi-Montalcini and Luigi Aloe published the first indication that NGF acts on cells of non-neuronal origin. Subsequently, other investigators confirmed and extended this observation and provided additional evidence that other cells of the immune system are receptive to the action of NGF. More recent studies carried out by Levi-Montalcini's group demonstrated that NGF is also involved in the regulation of memory B cells and that NGF plays an equally important role in the neuronal cell population of the CNS controlling the activation of the neuroendocrine axis. In the following years other studies carried out in this same Institute showed that NGF is also involved in neuroendocrine responses, as revealed by findings that the circulating and brain NGF levels undergoes significant changes following aggressive behavior and in states of emotional anxiety. These studies lead to the hypothesis that NGF might be implicated in homeostatic interaction and in the pathogenesis of autoimmune inflammatory disorders. In the last ten years murine and recombinant NGF received clinical attention from neurologists who began to utilize NGF and other neurotrophins to stimulate recovery from neuropathies of the central and peripheral nervous system.

The presence of large quantities of NGF in the mouse salivary gland gave the possibility not only to study the spectrum of action and the mechanisms which regulate many important physiopathological processes in different cell types, but also to identify new target cells of NGF in the immune, and endocrine systems. NGF has been shown to improve cognitive abilities, and to promote recovery of certain neuropathies of the CNS. NGF has been administered to patients affected by Alzheimer or Parkinson's diseases by Swedish scientists, who found clinical improvement of



Fig. 2. - Dr. L. Aloe and Prof. R. Levi-Montalcini.

the patients. More recently, human recombinant NGF was tested on peripheral diabetic neuropathy.

A clinical positive effect in the absence of adverse effect was recently demonstrated by our Group demonstrating that NGF displays a marked healing action on damaged human corneal ulcerated without causing undesired side-effects.

Levi-Montalcini may also be appreciated as a writer. She recently wrote five books. The first, "*In Praise of Imperfection*" is a very inspiring autobiographic work where she tells of her success, but also of the delays and distractions and potential mistakes researchers can make and their tendency to underestimate difficulties (Levi-Montalcini, R. *In Praise of Imperfection*. Basic Book, Inc. Publisher, New York, 1988). A second one entitled "*Il tuo futuro*" is dedicated to young people who during their early lives often face the need to make vital choices (Levi-Montalcini, R.. *Il Tuo Futuro*. Garzanti Editor, Milano, Italia, 1993). In the third book entitled "*Senza Olio e contro Vento*", she tells 10 true stories of well known or unknown people, united by the courage and honesty they showed in very difficult moments of their lives (Levi-Montalcini R. *L'Asso nella Manica a Brandelli*. Baldini and Castaldi Editor, Roma, Italia, 1996). In the most recent book "*L'asso nella manica a brandelli*" she discusses the capacity and creativity of famous elderly people and how to maintain or improve cognitive abilities in later life (Levi-Montalcini R. *Senza*

Olio e Contro Vento Baldini and Castaldi Editor, Roma, Italia, 1998) and more recently, “*La Galassia Mente*” (Levi-Montalcini R. *La Galassia Mente*. Baldini and Castaldi Editor, Milano, Italia 1999) and “*Un Universo Inquieto*” (Levi-Montalcini R. *Un Universo Inquieto*. Baldini and Castaldi Editor, Milano, Italia 2001). From a scientific point of view the most important book is perhaps the “*The NGF Saga*” (Levi-Montalcini R. *The Saga of the Nerve Growth Factor*. World Scientific Series in 20th century Biology, Vol 3. World Scient. Publish. Singapore 1997). This is a scientific autobiographic book reporting her experience as a medical scientist during her early postgraduate years, and subsequent and later studies leading to the NGF discovery and more recent findings presented at the 7th International NGF Conference in Modena.

For her scientific achievement Rita Levi-Montalcini was recently nominated Senator in the Parliament of the Italian Republic.

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RITA LEVI-MONTALCINI'S SCIENTIFIC ACHIEVEMENTS AND MEMBERSHIPS

1936. Degree in Medicine, Summa cum Laude, University of Turin.
- 1936-38. Assistant, Clinic of Neurobiology and Psychiatry, University of Turin.
- 1944-45. Aids Italian refugees as Volunteer Physician with Allied Forces in Florence.
- 1945-47. Assistant Professor of Anatomy, University of Turin.
- 1947-56. Research Associate, Institute of Zoology, Washington University, St. Louis, Missouri, USA.
- 1956-58. Associate Professor, Institute of Zoology, Washington University, St. Louis, Missouri, USA.
- 1958-77. Professor of Neurobiology, Institute of Biology, Washington University, St. Louis, Missouri, USA.
- 1961-69. Director of the Neurobiology Research Center, National Research Council (CNR), Rome, Italy.
1962. Max Weinstein Award from the Cerebral Palsy Foundation for "outstanding scientific contribution" in the field of neurology, USA.
1963. Elected member of the scientific society Sigma Xi and Phi-Beta-Kappa.
1963. Nominated one of the ten most "outstanding women scientists" in the United States.
1964. The Gateway Arch Award, from the city of St. Louis, for scientific merit.
1965. Elected member of the Harvey Society, and invited to deliver a Harvey Lecture in New York.
1965. Gold Medal from the Lombard-Milan Medical Academy.
1966. Appointment by the Cultural Academy of Rome.
1966. Claude Bernard Medal and invitation to conduct a series of conferences as "Claude Bernard Professor" at the Institute of Experimental Medicine in Montreal, Canada.
1966. Elected member of the American Academy of Arts and Sciences, USA.
1968. Elected member of the National Academy of Sciences, USA.
1969. "Feltrinelli" International Prize in Medicine. Award money donated to create the Giuseppe Levi Foundation, through the National Academy "dei Lincei". Foundation offers scholarships to young and deserving students from Calabria (southern Italy).
1970. The Golden Plate Award, from the American Academy of Achievement, Dallas, Texas, USA.
1970. "Ibico-Reggino" Award in Biological Sciences, Reggio Calabria, Italy.
1971. Silver Cup from Washington University for scientific and didactic merit.
1971. Elected member of the Alpha-Omega-Alpha Medical Society, USA.
1972. "Ambrogino d'Oro" Award, Milan, Italy.
1974. William Thompson Wakeman Award for Basic Neuroscience Research toward a cure for paraplegia, Washington D.C..
1974. Elected member of the Pontifical Academy.
1975. "Vittoria Alata" Award, Brescia, Italy.
1976. National Academy "dei Lincei". Elected foreign member of the Class of Physical, Mathematical and Natural Sciences, Italy.
1977. Laurea ad Honorem, University of Uppsala, Sweden.
1978. Nominated Fogarty Scholar, Washington D.C..
1978. Laurea ad Honorem, Weizmann Institute, Rehovot, Israel.
1979. Elected foreign member of the Royal Academy of Medicine, Belgium.

1979. International "St. Vincent" Award.
1979. "Knights of Humanity" Award, International Philanthropic Society.
- 1979-89. Full-time Researcher as Guest Professor, Cellular Biology Laboratory, CNR, Rome.
1980. Laurea ad Honorem, St. Mary's & Notre Dame's College, USA (presented in Rome, Italy).
1980. Member of the "Accademia delle Scienze dei Quaranta", Rome.
1980. Elected member of the European Academy of Sciences, Arts and Humanities, Paris, France.
1980. Foreign Correspondent of the Royal Academy of Medicine, Brussels, Belgium.
1981. Member of the European Academy of Sciences, Arts and Letters, Paris, France.
1981. Award from the cities of Turin and Florence for outstanding contributions in science.
1982. Lewis S. Rosenstiel Award for distinguished work in Basic Medical Research, Brandeis University, Boston, Mass., USA.
1982. Member of the St. Claire Academy, Genova, Italy.
1982. Laurea ad Honorem, Washington University Medical School, St. Louis, Missouri, USA.
1983. "Immagine Italia" Award, Milan, Italy.
1983. Louisa Gross Horwitz Award, Columbia Univ., New York, USA.
1983. "Fregene" Award in Science, Rome, Italy.
1983. International Trophy "I Guerrieri di Riace", conferred by the International Cultural Association, "I Templari", Rome.
1984. Gold Medal in Neurosciences, Rome, Italy.
1985. "Matilde di Canossa" Award, Reggio Emilia, Italy.
1985. Ralph Gerard Award, Neuroscience Symposium, Dallas, USA.
1985. Columbus Award, "Palazzo Vecchio", Florence, Italy.
1986. Member of the American Philosophical Society, Philadelphia, USA.
1986. Gold Medal for Science, bestowed by the "Nuova Accademia delle Scienze", Rome, Italy.
1986. First Annual Conference of the "Rita Levi-Montalcini Award Lectures", Fidia Georgetown University, Institute for the Neurosciences, Washington D.C., USA.
1986. Seal of the City of Turin Award, Italy.
1986. "Premio Universo", Potenza, Italy.
1986. Lasker Award, New York, USA.
1986. Nobel Prize in Medicine or Physiology, Stockholm, Sweden.
1987. Honorary Membership, American Society of Zoologists, USA.
1987. Thudicum Award and Lecture, Leichester, England.
1987. United States National Medal of Science, USA.
1987. Honorary Citizenship, cities of Rome, Asti, Quattro Castelli (Romagna), Torino, Italy.
1987. Laurea ad Honorem, University of London, England.
1987. Laurea ad Honorem, University of Buenos Aires, Argentina.
1987. Laurea ad Honorem, Loyola University of Chicago in Rome.
1987. Laurea ad Honorem, Biophysic Institute of the University of Brazil in Rio de Janeiro.
1987. Approximately 40 Gold Medals from different cities throughout Italy and Europe.
1988. Honorary Citizenship, cities of Viterbo, Maratea, Susa, Casal Monferrato.

1988. Honorary Member, Tissue Culture Association, USA.
1988. Special Literary Awards: "Premio Comisso" Treviso, Italy; "Ape d'Oro" Imola, Italy.
1988. Series of lectures and Awards, Geneva and Zurich, Switzerland.
1988. Principality of Monaco, Lecture and Award.
1988. First Ramon y Cajal Award, Madrid, Spain.
1988. Gold Medal, Ministry of Public Health, Montecitorio, Rome.
1989. Honorary Member Medical Women's Association, USA.
1989. Elected Honorary Member, "Academie des Sciences", Paris, France.
1989. Honorary citizenship, city of Vercelli, Italy.
1989. Laurea ad Honorem, Harvard University, Cambridge, Massachusetts, USA.
1989. July Guest Professor, Institute of Neurobiology, CNR, Rome.
1990. Gold Medal of the Consejo Superior de Investigaciones, Madrid, Spain.
1990. San Martino Award 1989, City of Noceto, Parma, Italy.
1990. International Academy for Biomedical and Drug Research, International Scientific Advisory Board Member, Brussels, Belgium.
1990. Laurea ad Honorem, University of Urbino, Italy.
- 1990-Jan.'95. Member, National Committee for Bioethics, Italy (Hon. President).
1990. Member, National Commission UNESCO, Italy.
1991. Laurea ad Honorem, University of Lecce, Italy.
1991. "Premio Dodici Apostoli", Verona, Italy.
1991. Honorary Citizenship, cities of Sassari and Bari, Italy.
1991. Laurea ad Honorem, University of Trieste, Italy.
1991. Laurea ad Honorem, University of Siena, Italy.
1992. Laurea ad Honorem, Constantinian University, Rhode Island, USA.
1992. Associate Member, Third World Academy of Sciences, Italy.
1992. Wyeth Research Visiting Professorship, London, UK.
1992. Honorary Citizenship, city of Montalcino, Italy.
1993. President of the Enciclopedia Italiana - Treccani.
1993. President of the Italian National Commission of United World Colleges.
1993. Member of the United Nations High Level Advisory Board on Sustainable Development.
1993. Honorary Member of the International Academy of the History of Science, France.
1993. President, Institute of the Italian Encyclopedia, Treccani.
1993. Honorary Citizenship, city of Catanzaro, Italy.
1993. Laurea ad Honorem, University of Palermo, Italy.
1994. Honorary Member, Accademia Nazionale di Medicina, Italy.
1994. Member, Technical Scientific Committee, Ministry of Public Health, Italy.
1995. Foreign member, Royal Society of London, England.
1995. Member, UNESCO-CNR AIDS Committee.
1996. Guest Professor, Institute of Neurobiology, CNR, Rome.
2000. Nominated Senator.