Archives Italiennes de Biologie, 141: 85-88, 2003.

THE NERVE GROWTH FACTOR AND THE NEUROSCIENCE CHESS BOARD

R. LEVI-MONTALCINI

Institute of Neurobiology and Molecular Medicine, CNR, Viale Marx 15, 00137, Roma, Italy

The date of 10 December 1986 marked the end of the errant life of the Nerve Growth Factor and its official recognition by the scientific community.

The ceremony held in Stockholm on the occasion of its presentation to the Swedish royal family brought it to the attention of both biologists and non scientists. Its solemn recognition as the firstborn of a constantly growing group of endogenous specific growth factors and as a precursor of the oncogens brought it to the attention also of researchers working in other scientific sectors, in particular in biochemistry, molecular biology, genetics and immunology. One constant feature of the long and tortuous path followed by NGF ever since, half a century earlier, it had appeared on the biological scene, was the fairytale and adventurous nature of the path it followed. NGF was to open up increasingly broad vistas and horizons as we strove to find a place for it in the framework of the neurosciences.

When, in the winter of 1951 the effects obtained by grafting a malignant tumour on to chick embryos were reported for the first time at a neuroembryology congress, the results aroused more perplexity than interest.

The discovery that nerve fibres could cross barriers, such as vein tunics, that normally barred them access, penetrate the circulatory system, and at the same time ramify chaotically in embryonic organs, was considered to be an abnormal phenomenon. This was because it reflected and extended to nervous tissue components a property typical of neoplastic cells from which derived the hitherto unidentified substance synthesized and released by the cells themselves.

The use of in vitro culture techniques led to the discovery that the submaxillary gland of the adult male rate synthesizes and releases into circulation a protein molecule that is exactly the same as the one produced by tumours that is ten thousand times more active than that identified.

The discovery that NGF plays an essential role in promoting the differentiation of nerve cells receptive to its action suggested that other similar factors might exert a proliferative or differentiating action on both neuronal and non neuronal populations.

The demonstration that NGF specific antibodies caused the death of the nerve cells receptive to its action represented undeniable proof of the essential role played by this molecule. Many years later its action mechanism was to be interpreted differently, that is, that the activation of the programmed death gene is normally inhibited by the action of the NGF gene.

Studies carried out in 1971 revealed the sequence of amino acids contained in NGF, that is, its primary structure. This demonstration then led to the discovery of the NGF gene.

The discovery that a neoplastic cell known as PC12, derived in vitro from a rat pheocromocytoma, responded to NGF by a mitotic arrest, taking on the phenotypic property of an adrenergic nerve cell, allowed the NGF action mechanism to be studied at the sub-cellular and molecular level.

In the 1970s and 1980s it was discovered that the role played by NGF is likewise essential for primary or secondary cells of the immune system (mastocytes, T and B lymphocytes, macrophages and others) and endocrine system cells (hypophysis, thyroid and endocrine glands).

At the same time it was discovered that the activity of the NGF molecule was not restricted to peripheral nervous system cells but extended also to cholinergic type central nervous system cells involved in cognitive (neocortical system) and emotional and affective (limbic system) activities. All the neuronal and non neuronal cells receptive to NGF action in the above systems are subjected to programmed death if deprived of the NGF molecule.

In the nineties a low affinity receptor for NGF, p75, was identified, and of high activity a tyrosine kinase, TrKA. This opened up the possibility of identifying populations belonging to different cell lines in both normal and diseased conditions.

Research using animal models and clinical trials revealed the important role performed by the NGF and NGF-like molecules in certain forms of disorder of a neurodegenerative, inflammatory and autoimmune nature.

What position is occupied by the NGF molecule in the field of the neurosciences today?

In 1975, on the occasion of an MIT conference, I said that despite all its extraordinary exploits, NGF had still not found its proper place on the neuroscience chess board (1). Today, nearly half a century after its discovery, the role of this molecule may be likened to that of a "pawn" on a real chess board.

In the arrangement of the various pieces on the neuroscience chess board, genes are placed hierarchically. During early embryonic development, the genes known as homoeotipic direct the formation and activity of individual body parts: among these of particular interest, from an anthropocentric point of view, are the activator genes in the neocortical and limbic system (like the King and Queen on a real chess board). Next on the hierarchical scale are the genes involved in the activity of the sub cortical system (thalamus, hypothalamus, cerebellum and medulla oblongata) comparable to the Bishops, Rooks and Knights in the game of chess. Lastly, in the neuroscience chess board the genes involved in functions which were considered in the past of second order such as that of the "Pawns" of the real chess board, program the release of chemical substances (cytokines, endorphins, hormone factors, growth factors, neurotransmitters, etc.) which intervene in the complicated nervous and non nervous functions of all vertebrates, from the lowest to the highest phylogenetic level.

One of these is the NGF factor which has not only found its rightful place on the neuroscience chess board but, at the same time, also led to the recognition of the role played by the other factors.

A deregulation of the role of "pawns" in the chess board of the brain can be harmful. Their function can vary from defensive to offensive not on a topographical basis

(that is, by proximity or remoteness) but according to the environmental conditions and to the complex of factors at work in the processes in which they are involved. When over-activated, they can have a harmful effect on the "pieces" they are subject to or serve.

Another difference in the role displayed by the pawns in the real chess board and in the neuroscience chess board resides in the fact that "cerebral pawns" differ in their activity one from another and that their strength depends on them interacting together continuously. Their activity has a strong modulating effect on the activity performed by all the "pieces" on the board. One particularly important activity is that exerted on the nervous components having cognitive and emotive functions. The "pawns" have the merit of having incorporated the nervous system in the body complex from which it had been previously excluded and of providing a more correct definition of the tasks assigned to them.

This reappraisal of Pawns in the real chess game was introduced more than two centuries ago, as Philidor claims, and was recently confirmed by the great Russian chess player: "... the Pawn has another virtue compared with the pieces, and that is that it is a born defender, we discover little by little that on all 64 squares a Pawn deserves all our respect .... Who protects its own piece most securely? The Pawn. And who works at the lowest cost? Again the Pawn, since the pieces do not possess its capacity for work ..."(2).

Likewise on the neuroscience chess board, the discovery of the working capacity of "pawns" opened up a new chapter in our knowledge of the mechanisms underlying not only homeodynamic functions but also the processes involving the whole organism.

The nervous system, the endocrine and the immune system, autonomously operating units, are no longer considered as elements of continuous interchange, but integrated through morphological and functional relations: they are parts of a single network regulated by mutual communication among the systems, and not through independent cell complexes as was believed in the past.

The evidence that NGF circulates without any limitation of organ or structure, nor of system boundaries, assigns to this molecule a key role in the body's global homeostasis.

The results achieved in recent decades have allowed great leaps forward in the process of our understanding of the physiological mechanisms underlying the health of man. These results were attained by combining the analytical method with a holistic approach in which individual parts are investigated in order to obtain an overall view. You cannot appreciate a mosaic by concentrating on individual tesserae; the most detailed analysis of the parts cannot in fact tell us anything about the overall view.

This basic philosophy gave rise to a new experimental approach designed to connect, combine and associate, just as the systems at work to maintain the body's equilibrium are connected, combined and associated.

These roughly outlined stages of development must not be considered as a "list of independent facts" but as a logical sequence of events linked together by the thread

of the need to elucidate properties or functions that gradually come to our knowledge.

The NGF provides confirmation of the difficulty of predicting at the outset of the research what the later developments will be and the contribution it will make to the field of investigation and neighbouring fields. The studies that were to lead to the discovery of the NGF were originally aimed at investigating the role played by peripheral tissues and organs on the nervous centers innervated by them in the spinal cord. This was an emerging problem that was viewed at the time in the vast field of the neurosciences as "peripheral" in both meanings of the term. First because the active cells have a peripheral location and function. Second because these cells have tasks that are relatively insignificant compared with those of the central nervous system, which are involved in cognitive functions: thinking, memory, creativity and in the complex of psycho-emotional functions.

The research forming the subject of the present conference opens up new chapters having a huge potential for further development of the study of the neuroendocrinoimmunitary circuits involved in the homeostatic equilibrium of living beings.

The NGF saga, presented as a paradigm of the stages in the gradual development of scientific research, followed a winding and imperfect itinerary. This is further evidence that it is imperfection and not perfection that lie at the basis of human endeavour.

REFERENCES

1. Levi Montalcini, R. An uncharted route. In: Worden, F.G., Swazey, J.P., Adelman, G., (Eds.), *The Neurosciences Paths of Discovery*. Cambridge, (Mass.), pp. 245-265, 1975.
2. Nimzowitsch, A. *Il mio Sistema*, Collana "I giochi", Mursia, Milano, 1989.