Acta Orthop. Scand. *58*, 91–92, 1987

Editorial

Neurotropism and nerve growth
The evolution of a concept

In 1898, John Forssman, a 30-year-old bacteriologist at Lund University, presented a thesis on the mechanism of nerve growth: *Über die Ursachen, welche die Wachstumsrichtung der peripheren Nervenfasern bei der Regeneration bestimmen.* He reported on observations that axons growing out from nerves of experimental animals tended to grow towards the distal nerve segment rather than towards other tissues, a phenomenon that he observed to occur even if the distal nerve segment was placed out of alignment. In these experiments, Forssman introduced animal nerves into tubes and chambers of various shapes made of straw. In the interspace inside the straws, the axons, on their way to the distal nerve segment, organized themselves into well-differentiated nerve structures.

The apparent attraction exerted by the distal nerve segment on nerve fibers was named *neurotropism* or *chemotropism*. At the beginning of this century, the Spanish neurobiologist Ramon y Cajal suggested that cells in the distal degenerating nerve segment produced diffusible substances that, by setting up a concentration gradient in the tissues, helped to attract the growing axons.

However, the original concepts of Forssman and Cajal were strongly opposed by Paul Weiss 40 years later. In a series of experiments, Weiss systematically tried to prove that the apparent directed axonal growth was nothing more than the end result of randomized growth: if fibers grew out in all directions, some of them would perchance reach the distal nerve segment. According to Weiss, the contact with the distal nerve tissue induced these fibers to mature, whereas misdirected axons disappeared. Weiss felt that mechanical guidelines, constituted by already established fibers, as well as polarized tissue structures - like, for instance, oriented strands in a fibrin clot - were determining factors. Weiss's ideas were widely accepted and have, indeed, by emphasizing the significance of mechanical alignment of nerve structures, been the basis for the modern microsurgical approach to nerve injuries.

Today, 80 years after Forssman's observations and 40 years after Weiss's studies, the concepts have again changed in favor of Forssman. Forssman's experiments are being repeated in numerous laboratories throughout the world, although the straws have been replaced by modern biomaterials and the methods for analysis of axonal regeneration are more refined. Probably this trend is the result of a general disappointment of the poor results of peripheral nerve surgery, but it also reflects a worldwide, increasing interest in growth factors that are involved in the regulation of the growth, development, and differentiation of tissues. The choice of the 1986 Nobel Prize laureates should be seen as an expression of this trend. Nerve growth factor (NGF), originally described by Rita Levi-

Montalcini, has for decades served as a model substance for so-called neurotrophic factors – which are probably synthesized by target organs and Schwann cells, are transported intraaxonally by retrograde exonal transport, and which serve to maintain the viability of the nerve cell body. We are in the beginning of a period characterized by an increasing understanding of the significance of "neurotrophic factors" – as well as of macromolecules that are bound to the surfaces of cells and other tissue structures – for the growth and directionality of axons.

In an historic perspective, the circle is closed. The review of nerve regeneration and repair by Göran Lundborg in this issue of *Acta Orthopaedica Scandinavica* shows that current neurobiologic concepts originated in thoughts presented by the great pioneers almost a century ago. Recent work from Lundborg's laboratory, as well as from laboratories in the United States and Japan, has shown that under ideal conditions there is axonal growth specificity not only with respect to the type of distal tissue, but also with respect to topographic components of the nerve tissue; for instance, it appears that tibial nerve axons prefer growing towards distal tibial nerve components rather than distal peroneal nerve components.

Retrospectively, the evolution of the concept of neurotropism can teach us that, although observations over the years may be identical, the interpretation of these observations may be totally different as a consequence of current methods of analysis, trends, traditions, and the like. Well-established concepts today may be radically different tomorrow. Concerning treatment of nerve injuries, there is increasing evidence that the role of microenvironmental molecular factors, as reflected in the microsurgical approach, is on a parity with purely mechanical considerations. For the future, increased understanding of these mechanisms may be a key in developing better methods for nerve repair.

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