CHAPTER 1
INTRODUCTIONS

Cellular degeneration can occur via necrosis or apoptosis, a distinction based initially on morphological differences and later on other apparent differences between the two. [1,2] Apoptosis is a Greek term referring to the naturally occurring seasonal loss or falling of flowers, and has been used to describe all forms of spontaneous cell death that exhibit certain morphological characteristic. [1,3] Cell dying by apoptosis shrinks in size, the nuclear chromatin becomes pyknotic and condenses against the nuclear membrane, and cytoplasmic organelles remain intact. Eventually, the DNA is rapidly broken down and degradates and is rapidly phagocytosed by macrophages or by neighboring cells. Apoptosis is most characteristic of normal tissue turnover, embryonic cell death, and metamorphosis. Necrosis by contrast, involves an initial swelling of the cell with early loss of plasma membrane integrity and major changes to the organelles and the nucleus tends to swell. Necrotic cell death elicits an inflammatory response; macrophages derived from the immune system attack and phagocytic cellular debris. [4,5]

Apoptosis is an important physiological process for maintaining a steady state number of cells in a tissue.[6] Abnormal regulation of apoptosis may contribute to disease such as neurodegenerative disease. Neuronal apoptosis is a prominent feature in the developing nervous system where between 50 to 80 percent of all neurons generated are lost. [7,8] The central tenet of this theory is that neurons die because they are unable to access sufficient amounts of neurotrophic factors ,which are release in limited amounts by their target tissues (Figure 1). In fact, considerable evidence indicates that neurons in embryo, postnatal and adult animals continue to be dependent upon their targets for both their survival and the maintenance of normal morphology and biosynthetic events. It should be stressed that the axon, through its terminal synaptic ramifications, plays a key role in the retrograde transport of survival signals from target tissues. It is therefore not surprising that axonal transection, or axotomy, particularly during development causes rapid neuronal death. [9]

Cutting an axon, by sectioning a peripheral nerve, divides it into two segments. The part of the axon that is connected to the cell body is called the proximal segment and the part isolated from the rest of the cell is called the distal segment. Immediately after injury, axoplasm seeps out of the cut ends of both segments until the severed ends of each segment seal by fusion of the axonal membrane. The proximal and distal segments also retract from one another and begin to swell because material that is normally carried with the axons, either by fast axonal transport or slow axoplasmic flow, now accumulates in the axonal stump. Both segments swell because axonal transport carries components both away from and toward the cell body. [10]

In the injured neuron, degeneration occurs at the nerve terminals and Wallerian degeneration occurs at the distal segment of the axon; myelinating cells withdraw leaving myelin debris; phagocytic cells infiltrate the site of the lesion; and the cell body undergoes chromatolysis. Degenerative change may eventually occur in cells that had synaptic contacts with an injured neuron. In the presynaptic neuron terminals retract from the dendrites of the injured neuron and the cell body can undergo retrograde transneuronal degeneration. In the postsynaptic neuron anterograde transneuronal degeneration can occur (Figure 2).

Neurons are able to regenerate and eventually restore functional connection of their peripheral axons. Division of Schwann cells is the first step in the regeneration of a severed or crushed peripheral nerve. The Schwann cells then bridge the scar. As the second step in regeneration, large numbers of new nerve processes (neurite) sprout from the proximal stump. The Schwann cell bridges then serve as guides for the regenerating axons to grow across the scar, thus maintaining the normal pathways of the growing axons. Although many of the new nerve processes degenerate their large number increase the probability of reestablishing sensory and motor connections. After crossing the scar, neurites enter the surviving Schwann tubes in the distal stump. These tubes will then guide the neurites to their destination as well as provide the microenvironment for continued growth.[11]

Some of the molecules involved in the survival of neurons after injury may be the same, as those needed by immature neurons as they develop. All neurotrophic factors that prevent neuronal death appear to have other important biological activities, including effects on development, maintenance, and function of the nervous system. Two major families of neurotrophic factors, which block axotomised neurons from apoptotic death, are the neurotrophins and neuropoietic cytokines.

The neuropoietic cytokines such as Leukemia inhibitory factor (LIF) act via the gp130 and LIFRβ complex. LIF is a multifunctional polypeptide, which acts on a number of tissues including the nervous system. LIF is expressed in neuronal targets during embryogenesis and shares many characteristic neurotrophic factors, including its retrograde transport to sensory DRG neurons after injection into the footpad and neurotrophic factor binds to these neurons in tissue culture. [12,13]

Several experiments have demonstrated that the application of Leukemia inhibitory factor to the proximal nerve stump prevents the degeneration of axotomized sensory neurons in the dorsal root ganglia and motor neuron in spinal cord of neonatal animals. The present study was undertaken to determine the time course of sensory and motor neuron loss after axotomy only, compared with axotomy with ligation, and it investigated the ability of LIF to prevent the loss of sensory and motor neuron after median and ulnar nerve axotomy in young adult rats.

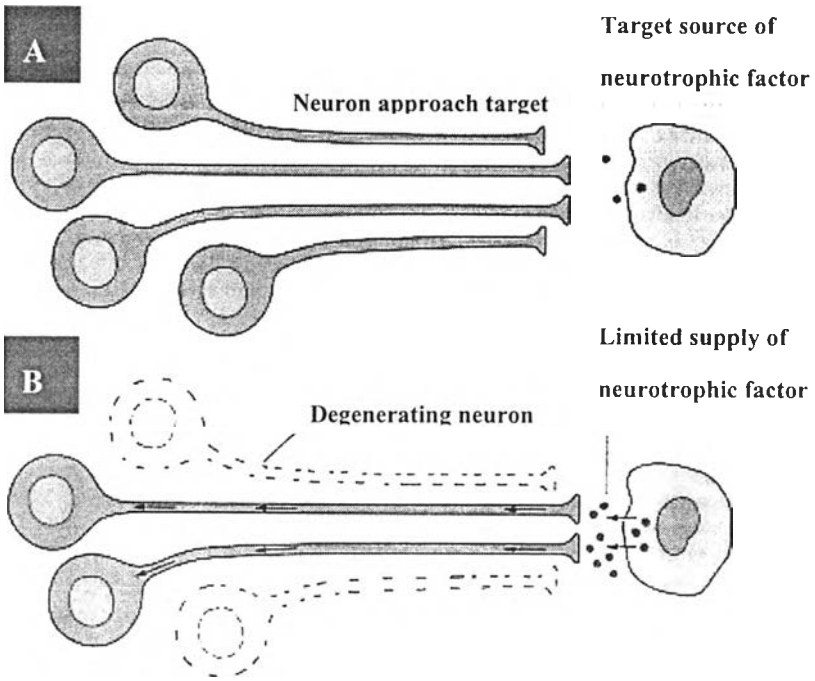

Figure 1 The neurotrophic factor hypothesis.[14] *(A)*, Neurons extend axons to the vicinity of target cells and, *(B)*, The target cells secrete limited amounts of neurotrophic factors. The neurotrophic factors bind to specific cell surface receptors. Neurons that do not receive adequate amounts of neurotrophic factor die by apoptosis with fragmented nuclei.

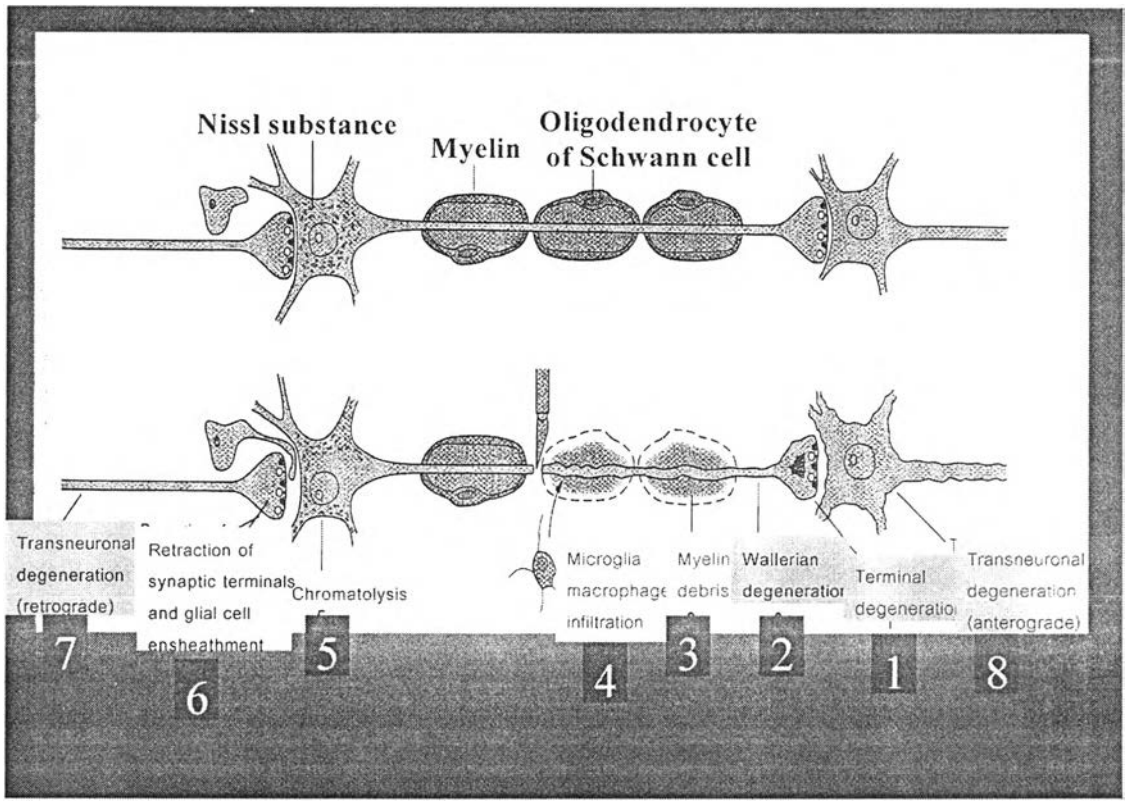

Figure 2 Axotomy affects not only the injured neuron but also its synaptic partners and neighboring cells.[10] *(A)*, A normal neuron with an intact functional axon. *(B)*, (1) After axotomy the nerve terminals of the injured neuron fail rapidly. (2) The distal stump, separated from the cell body, undergoes Wallerian degeneration. (3) Myelin degenerates and (4) Phagocytic cells invade. (5) The cell body undergoes chromatolysis, in which the nucleus moves to an eccentric position. (6) Presynaptic terminals on the chromatolytic neuron withdraw and are enwrapped by glial processes. (7,8) The inputs to and targets of the injured neuron can atrophy and even degenerate.