NERVOUS TISSUE

There are two basic systems of internal communication and physiological homeostasis in the body: the endocrine system and the nervous system.

The nervous system is derived from embryonic neuroectoderm.

The human nervous system is divided anatomically into:

- **Central Nervous System** (CNS), consisting of the brain and spinal cord.
- **Peripheral Nervous System** (PNS), consisting of nerve fibers, aggregates of nerve cells and glia and ganglia.

It is estimated that the human nervous system consists of at least 10 billion neurons.

Nervous tissue consists of two groups of cell types:

- Nerve cells (Neurons)
- Neuroglia.

Central Nervous System (CNS)

The Central Nervous System consists of the brain and spinal cord.
The nerve cell bodies (perikarya) of the CNS are often found in groups ("nuclei").

The brain and spinal cord are composed of **gray matter** and **white matter**.

Gray matter contains

- nerve cell bodies (perikarya)
- neuroglia
- neuropil (a complicated network of cell processes)

White matter lacks nerve cell bodies (perikarya), but has many processes of neurons. The white appearance is the result of the myelin that envelops many of the neuronal processes. Neuroglia are also found in the white matter and the nuclei seen in white matter belong to neuroglia.

Perikarya in the Peripheral Nervous System (PNS), are found only in ganglia (apart from in some sensory regions such as the retina and olfactory mucosa).

Neurons

Neurons are post-mitotic structures that shortly after birth lose the ability to divide. Further changes involve only reduced number of neurons (neuronal death), or changes in volume or in neuronal connections.

Neurons have two special properties:

- **Irritability** (the ability to respond to a stimulus)
- **Propagation of impulses** (the ability to conduct impulses).

The neuron is the morphofunctional unit of the nervous system. Similar to the Cell Theory, which stipulates the cell as the basic building block of the body, the Neuron Theory describes the neuron as the basic building block of the nervous system, and that the nervous system functions through transmission of information through networks of neurons.

Most neurons have three main parts:

- **Dendrites**
- **Perikarya** (cell bodies)
- **Axon**

The **dendrites** are receptive to stimuli and bring stimuli from the environment (sensory epithelial cells or other neurons) to the cell body. There are usually several dendrites per neuron.

The **perikaryon** (cell body) is also receptive to stimuli, but also serves as the trophic or synthesizing center for the whole nerve.

The **axon** is a long process emerging from the cell body. There is only a single axon for each neuron. The axon transmits impulses to other neurons, or to effectors: muscle or gland cells. The distal portion of the axon is usually branched (terminal arborization).

Neurons and their processes are very variable in form and size. Some neurons are very large (with perikarya of up to 150μm), whereas others are very small (perikarya of only 4-5μm).

Morphological classification of neurons

Neurons are classified according to the size, number and shape of their processes.

- **Unipolar neurons** (pseudounipolar) have a single process (axon). These are found in sensory ganglia of dorsal roots of spinal nerves.
- **Bipolar neurons** have two processes (one dendrite and one axon). These are very rare and have a limited distribution in the body. They are present in special sensory structures including the retina, olfactory epithelium, and vestibular and cochlear nerves).
- **Multipolar neurons** possess several processes (several dendrites and a single axon). Most neurons belong to this category.

Physiological classification of neurons

Neurons may also be classified according to their function.

- **Sensory neurons**. These receive sensory stimuli from the environment (from receptors) and from within the body (e.g. unipolar neurons).
- **Motor neurons**. These control the effector organs (muscles, exocrine glands, endocrine glands)
- **Interneurons** (Intermediate neurons). These are typically found in the CNS and connect between other neurons (often between sensory and motor neurons).
- **Neurosecretory neurons**. These are specialized neurons that synthesize and secrete hormones.

Each neuron has 3 physiological parts or segments:

- **Receptive segment** (dendrites and perikaryon). The perikaryon also has an additional trophic and synthesizing role.
- **Conductive segment** (axon)
- **Transmissive segment** (synapse).

Reflex arcs

The functional roles of various neurons are best illustrated by simple reflex arcs in which peripheral receptors are connected to peripheral effectors in a neuronal network.

- Stimulation of the **receptor** (in skin or skeletal muscle spindle)
- Propagation of an impulse via **afferent sensory nerve** (unipolar neuron), which enters the gray matter of the spinal cord.
- **Interneurons** connect with cell body of motor neuron in the ventral horn.
- **Motor neuron** transmits the efferent impulse to an effector.
- The **effector** e.g. motor end plate of skeletal muscle responds to the impulse.

(An analogy can be made to a cable system of telephone wires. The phone message is sent to a central exchange, that directs the message to the correct connection, resulting in a specific response by the recipient).

MORPHOLOGY OF NEURONS

(1) **Dendrites**

Most nerve cells have several dendrites. These increase the receptive area of the neuron. Dendrites do not maintain a constant diameter (unlike axons) and transmit impulses to the cell body decrementally (unlike axons. The regions of the dendrites closest to the perikaryon are usually larger, than those farther away. Typically dendrites have large numbers of thorny spines, which are now known to be areas of synaptic contact.

(2) Perikaryon

The perikaryon (neuronal cell body or soma) consists of the nucleus and surrounding cytoplasm. (The term perikaryon implies the area surrounding the nucleus, but the term is used freely today to describe the whole cell body including the nucleus). The perikaryon is the trophic center of the neuron involved in protein synthesis. The surface of the perikaryon receives nerve impulses and is the site of many synapses, bringing excitatory or inhibitory stimuli.

Nucleus

The nuclei of perikarya are large, regular, round or oval, typically situated fairly centrally. The nuclei are euchromatic (pale staining with dispersed chromatin). Such large regular nuclei are typical of cells involved in intense synthetic activities. Sex chromatin (**Barr's body**) is commonly seen in the nuclei of females.

Rough Endoplasmic Reticulum (RER) - Nissl bodies

RER is abundant in the cytoplasm and is associated with the protein synthetic activities of the neurons. The RER is basophilic as seen in regular (H&E) staining by light microscopy. This RER is also stained with cresyl violet in the Nissl staining technique (**Nissl bodies**). In the event of injury to axons, Nissl bodies, are displaced to the periphery of the perikaryon.

Golgi bodies

Large well developed Golgi bodies are present in the perikarya.

Mitochondria

Many large mitochondria are found throughout the perikaryon.

Neurofibrils

Neurofibrils are seen in perikarya (and also in the nerve processes) after silver impregnation techniques. At the electron microscope level these are seen to consist of clumped neurofilaments and neurotubules.

Lipofuscin

Lipofuscin is a brown pigment that is common in perikarya of aged neurons. It is now known to be common to post-mitotic cells and to consist of large secondary lysosomes.

(3) Axons

Each neuron has a single axon. The diameter of the axon is fairly constant. The length of axons is fairly variable, and some reach up to 100 cm (the axons innervating the toes have their cell bodies in the spinal cord). All axons originate in a short pyramid-like structure called the **axon hillock**, which lacks Nissl substance. The plasma membrane of the axon is termed the **axolemma**, and the cytoplasm of the axon is termed the **axoplasm**.

In myelinated axons the initial portion, between the axon hillock and the start of the myelin sheath, is called the **initial segment**.
Axons sometimes have right-angled branches known as **axon collaterals**.
The nerve impulse travels down the axon non-decrementally.

Myelinated fibers

Nerve fibers consist of axons enveloped by special sheaths. In peripheral nerves the sheath cell is the **Schwann cell**, whereas in the CNS, the sheath-forming cells are the **oligodendrocytes**.

The axons of small diameter are usually non-myelinated fibers, whereas the thicker axons have concentric wrappings of the enveloping cell to form the myelinated sheath. The fibers with myelinated sheaths are called **myelinated fibers**. Myelinated nerves, composed mainly of myelinated axons, appear white in the fresh state. The sheath of myelinated fibers is formed by concentric layers of membranes of the Schwann cell (or oligodendrocyte in the CNS) around the axon, which unite to form a lipoprotein complex. This stains black with osmium tetroxide. The whorled structure of the myelin sheathe when examined by transmission electron microscopy is seen as a repeating dark line (**major dense line**) and and a thinner repeating **intraperiod line**. The major dense line is formed by the fusion of two of the inner layers of sheath cell membrane, whereas the intraperiod line is formed by the fusion of the outer layers of sheath cell membrane when they come in contact as a result of the concentric arrangement. The myelin sheath is essentially an accumulation of closely packed whorls of lipoprotein rich membranes surrounding the axon.

If a single fiber of a myelinated peripheral nerve is teased, stained with osmium tetroxide and examined by light microscopy, the myelin sheath surrounding the axon is seen as a series of myelinated **internodes** (0.08-1.00 mm) separated by **nodes of Ranvier**. (The myelinated axon is somewhat similar to a long string of sausages). The myelin of each internode is formed by a single Schwann cell, whose nucleus is seen at the periphery. Tangential non-stained areas (similar to arrow heads) are seen in the myelin of the internodes (**Schmidt-Lantermann clefts**). These are areas of cytoplasm of the Schwann cells, where the membranes are not closely apposed. An **endoneurial connective tissue sheath** surrounds each fiber.

In wax sections stained with H & E, the lipid of the myelin is dissolved by the xylene or chloroform during processing and the site of the myelin sheath appears empty apart from a fine network stained by the eosin. This is known as **neurokeratin**.

Myelinated axons of the CNS have myelin sheaths, similar to those of the peripheral nerves. However, a single oligodendrocyte produces the myelin sheaths of several axons. No endoneurial connective tissue sheath is present. The nodes of Ranvier are larger and exposed to the extracellular space.

Nodes of Ranvier

The nodes of Ranvier have several important features:

- sites of axon collaterals

- large concentrations of mitochondria in the axon at these sites (high localmetabolic activity)
- site of saltatoryconduction (non-decremental)
- sites of paranodal loops (important in the saltatory conduction).

Axonal transport

Transport of molecules along the axon (**axonal transport**) is in two directions: anterograde (from the cell body to the terminal synapse) or retrograde (in the direction of the cell body). The axonal transport involves neurotubules and neurofilaments.

Two different systems of axonal transport occur:

- **Slow axonal transport** system, from the cell body in a single direction at a rate of about 1mm per day. This system conveys components needed for growth and regeneratioof the axon.
- **Fast axonal transport** system, which occurs in both directions, at a rate of about 100-200 mm per day. This system involves transport of enzymes needed for synthesis of neurotransmitters within the terminal synapse.

NEUROGLIA

Glia or **neuroglia** get their name from the Greek word for "glue". There is very little connective tissue in the CNS, and the structural support for neurons comes from neuroglia and their processes.

It is estimated that for every neuron there are at least 10 neuroglia, however, as the neuroglia are much smaller than the neurons they only occupy about 50% of the total volume of nerve tissue. Neurons cannot exist or develop without neuroglia.

There are **4 basic types of neuroglia**, based on morphological and functional features.

- **Astrocytes (Astroglia)**
- **Oligodendrocytes (Oligodendroglia)**
- **Microglia**
- **Ependymal cells**

The astrocytes and oligodendroglia are large cells and are collectively known as **Macroglia**.

Neuroglia differ from neurons:

- Neuroglia have **no action potentials** and cannot transmit nerve impulses
- Neuroglia **are able to divide** (and are the source of tumors of the nervous system)
- Neuroglia **do not form synapses**
- Neuroglia **form the myelin sheathes** of axons.

Astrocytes (Astroglia)

These are present only in the CNS and are the largest of the neuroglia. They have many long processes, which often terminate in "**pedicels**" on blood capillaries and contribute to the **blood-brain-barrier**.

There are two categories of astrocytes:

- **Protoplasmic astrocytes**. These are present in the gray matter of the brain and spinal cord. Their processes are relatively thick.
- **Fibrous astrocytes**. These are present in the white matter of the CNS. Their processes are much thinner than those of the protoplasmic astrocytes.

Because of their number and their long processes, the astrocytes appear to be the most important supporting elements in the CNS.

Oligodendrocytes

These are smaller than the astrocytes, with fewer and shorter processes. They are found in both the gray and white matter of the CNS and are responsible for the formation of the myelin sheath surrounding axons. The **Schwann cells** of the PNS belong to the oligodendrocytes and form the myelin sheath around peripheral axons.

Microglia

These are small cells, with elongated bodies, elongated nuclei with dense chromatin and relatively few processes. They are found in both the gray and white matter of the CNS and are thought to function as macrophages. There is some evidence that they are in fact of mesenchymal origin and derived from blood-borne monocytes.

Ependymal cells

The ependyma is composed of neuroglia that line the internal cavities (ventricles) of the brain and spinal cord (central canal). They are similar in appearance to a stratified columnar epithelium. The ependymal cells are bathed in **cerebrospinal fluid** (CSF). Modified ependymal cells of the **choroid plexuses** of the brain ventricles are the main source of the CSF.

FUNCTIONS OF NEUROGLIA

- Structural support (especially the astrocytes in the CNS)
- Participation in the blood-brain-barrier (astrocytes)
- Formation of the myelin sheath of axons (oligodendrocytes)
- Isolation of junctional surfaces of synapses
- Repair processes following damage or injury to nerves.

NERVE STAINING TECHNIQUES

- **Silver impregnation**

These techniques (developed in particular by the Italian ***Camillo Golgi*** and the Spaniard ***Ramon y Cajal***) stain whole neurons, but selected ones only).

- **Nissl staining**

Cresyl violet is used in the Nissl staining technique to demonstrate the Nissl bodies (RER) of the perikarya. The processes are not stained.

- **Myelin stains**

In these techniques the lipid of the myelin of myelinated fibers is stained.

Connective Tissue of Peripheral Nerves

Examination of a peripheral nerve shows a thin connective tissue layer surrounding each individual fiber. This is the **endoneurium** (also known as the sheath of Key and Retzius).

Fibers are grouped in bundles, which are also surrounded by a connective tissue layer, known as the **perineurium**.

The **epineurium** is a more extensive connective tissue layer between the bundles and extending to the most peripheral parts of the nerve.

Nerves possessing only sensory fibers are called **sensory nerves**, whereas nerves possessing only motor fibers are called **motor nerves**. Most nerves are **mixed nerves** in that they possess both sensory and motor fibers.

SYNAPSES

Synapses are specialized areas of contact between neurons. Various categories of synapses are found including:

- **axo-dendritic**
- **axo-somatic**
- **dendro-dendritic**
- **axo-axonic**

Morphologically the axon terminal is seen as a club-shaped bulb (terminal buttons or "***boutons terminaux***"). If the synapse is not at the end of the axon, but at a site along the length of the axon, it is known as a "***bouton en passage***". Many of the synapses occur on swellings of the dendrite (**dendritic spines**).

The synapses in the human body are chemical synapses. They involve the release of **neurotransmitters**, which combine with receptors on the post-synaptic membrane and result in the transmission of the impulse.

Synapses examined by transmission electron microscopy the terminal bulb are seen to contain membrane-bound **synaptic vesicles** (25-65μm), which store **neurotransmitters**. Mitochondria are also common in this **presynaptic region**. When the impulse reaches the presynaptic area, the synaptic vesicles migrate and fuse with the **presynaptic membrane** and release their contents into the **synaptic cleft** (20nm). The neurotransmitters combine with specific **receptors** on the postsynaptic membrane leading to the transmission of the impulse. Specific enzymes act on the receptors. For example, the neurotransmitter acetycholine (of cholinergic nerves), when it combines with the postsynaptic receptor is affected by the enzyme, acetylcholinesterase.

Some synapses are **excitatory**, whereas others are **inhibitory**.

MOTOR END PLATES

Motor end plates (**neuromuscular junctions**) are specialized structures at the ends of motor axons and are the sites of innervation of skeletal muscle fibers. In order to contract each individual muscle fiber needs to receive an impulse from a motor nerve. A single motor nerve may innervate a single fiber or may have several neuromuscular junctions. A single motor nerve and all the muscle fibers it innervates is called a **motor unit**.

Motor nerves and the fibers they innervate can be demonstrated by silver impregnation techniques. At the ultrastructural level the axon terminal has several features similar to those of synapses. Neurotransmitters are present in synaptic vesicles and mitochondria are common. There is also a synaptic cleft. The **postsynaptic membrane** is modified sarcolemma of the muscle fiber. This has many **folds** (to increase the surface area). When the nerve impulse reaches the motor end plate, the synaptic vesicles release acetylcholine into the cleft. These bind to specific receptors on the postsynaptic membrane. This results in the transfer of the impulse to the sarcolemma and on to the T-tubules.

NERVE GANGLIA

Ganglia are groups of nerve cell bodies (perikarya) outside the CNS. Two types of nerve ganglia can be distinguished based on their morphology and function:

- **Sensory ganglia** (Dorsal root ganglia)
- **Autonomic ganglia**

Spinal ganglia are found in the dorsal roots of spinal nerves and carry afferent sensory impulses. The ganglia are surrounded by a fairly thick connective tissue capsule. The perikarya belong to the unipolar (pseudounipolar) neurons. Each perikaryon has a T-shaped process continuous with the afferent axon. The cell bodies have a purely trophic function and are not involved with the nerve transmission. Each perikaryon is surrounded by a layer of glial cells (satellite cells). The perikarya are not evenly distributed in the ganglia, but are found in groups, mainly fairly close to the periphery.

Autonomic ganglia are associated with nerves of the autonomic nervous system. They are found as dilatations of autonomic nerves and may be encapsulated. In many cases the ganglia are seen in the walls of organs (intramural) and lack a capsule. They differ from spinal ganglia in that the neurons are multipolar. The perikarya are smaller,have fewer satellite cells and are more evenly distributed.

NON-MYELINATED NERVE FIBERS

Non-myelinated nerves are found in both the CNS and PNS. Postganglionic fibers of the autonomic nervous system are non-myelinated. The axons are enclosed in simple clefts of oligodendrocytes or Schwann cells. Each Schwann cell may enclose several non-myelinated axons.

At areas of transmission, the axon lies in a "naked" groove on the surface of the Schwann cell. This is the autonomic neuromuscular junction and is the site of innervation of smooth muscle bundles. The release of neurotransmitter (acetylcholine in cholinergic fibers, nor-epinephrine in nor-adrenergic fibers) causes depolarization of the sarcolemma of the muscle fiber and contraction. The impulse can be transferred to other adjacent smooth muscle cells via the gap junctions in the sheaths. As a result only one muscle fiber needs to be innervated, though the message to contract is rapidly spread to the adjacent fibers, so that they can contract in unison.

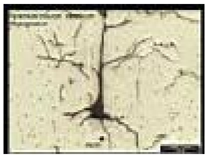
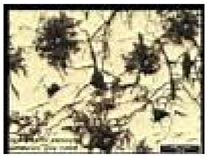
DEGENERATION AND REGENERATION OF NERVE FIBERS

Neurons do not divide, though neuroglia can divide. Tumors of the nervous system result from uncontrolled growth of glia. If neurons are damaged in the CNS, there is permanent loss and no regeneration. If, for example the optic nerve is severed, permanent blindness results. In contrast peripheral nerves if crushed or even severed may regenerate provided the perikaryon is not injured.

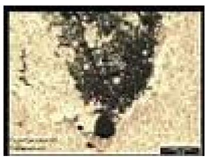
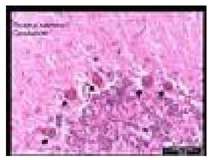
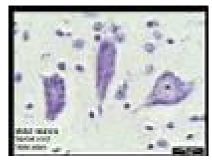
If a peripheral nerve is severed, the distal segment degenerates. Axonal injury causes morphological changes in the perikaryon including:

- chromatolysis (loss of Nissl bodies) with the remaining Nissl moving to the periphery of the perikaryon
- swelling of the perikaryon
- movement of the nucleus from its central position to the periphery.

Regeneration is possible if the proximal segment of the axon grows, sends out "sprouts" and these penetrate the correct column of Schwann cells.

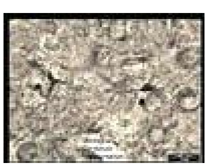
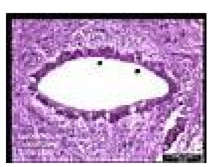
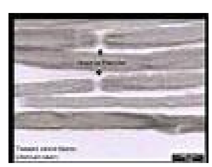
Pyramidal neuron   Fibrous Astrocytes   Fibrous Astrocytes   Protoplasmic astrocytes

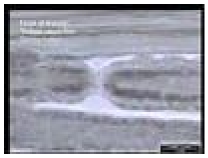
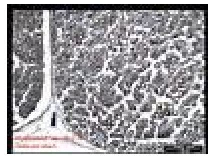
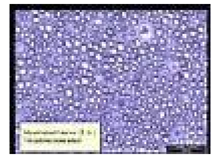
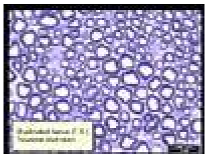
Purkinje neuron   Purkinje neurons - Cerebellum   Motor Neurons   Motor Neurons

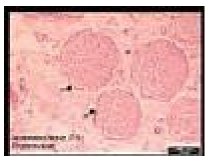
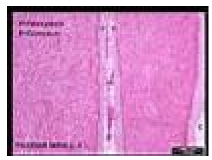
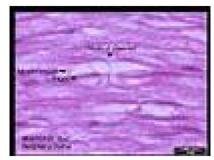
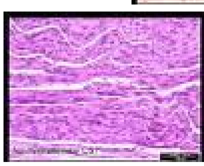
Motor Neurons   Motor Neuron - neuropil   Fibrous astrocytes   Microglia - Cerebrum

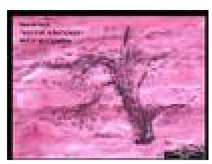
Microglia - Cerebrum Ependyma - Central Canal Teased nerve fibers Schmidt-Lantermann Clefts

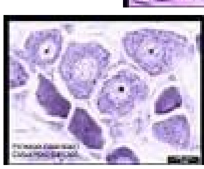





Node of Ranvie Myelinated Nerve Myelinated Nerve Myelinated Nerve

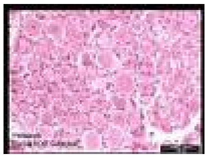
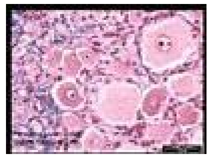
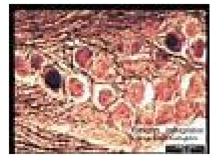





Myelinated Nerve Peripheral Nerve Myelinated fiber Non-myelinated nerve

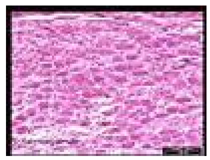
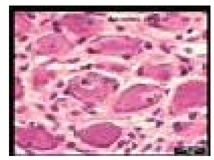





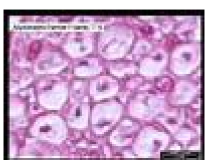
Non-myelinated nerve Motor Unit Motor end plates Perikarya (Nissl stain)

Perikarya- Dorsal Root Ganglion Perikarya (Azan stain) Perikarya - Impregnation Myenteric Plexus

Myenteric Plexus Autonomic Ganglion Autonomic Ganglion Myelinated nerve



Myelinated Nerve Fibers

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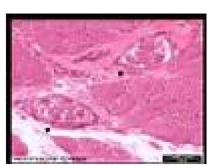
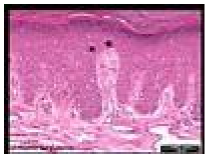
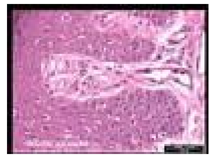
  

Neuromuscular Spindle Neuromuscular Spindles Pacinian corpuscle Pacinian corpuscle

Meissner corpuscles Meissner corpuscles

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