INTRODUCTION

Peripheral nerve injury is a serious health concern for society, affecting 2.8% of trauma patients, many of whom acquire long-term disability, and the related socioeconomic costs are relatively expensive. Although recovery of nerve function occurs in many mild injuries, outcomes are often unsatisfactory following severe trauma ***(Wang et al., 2011)***.

Seddon classified nerve injuries into three categories: neuroapraxia, axonotmesis and neurotmesis. After complete axonal transection, the neuron undergoes a number of degenerative processes, followed by attempts at regeneration. A distal growth cone seeks out connections with the degenerated distal fiber to re-innervate its territory whether muscle or skin ***(Lee et al., 2000 and Susan and Novak, 2001)***.

Early primary repair with epineural microsutures is performed when a tension free coaptation in a well vascularized bed can be achieved. Other repairs include group fascicular and fascicular repair requiring intra-neural dissection and direct matching and suturing of fascicular groups. Despite its anatomical attractiveness, overall group fascicular repair is no better than epineural repair in functional outcomes ***(Grinsell et al., 2014).***

Peripheral nerve injuries with neuronal gaps larger than 1-2 cm usually require bridging strategies for repair. Various

methods exist to reconstruct nerve lesions with a significant gap: nerve grafts as autologous non-vascularised nerves, vascularised nerve grafts, allograft and interposition of natural or synthetic conduits ***(Fabrizio et al., 2012)***. The autologous nerve graft is currently considered the gold standard to overcome a neuronal gap ***(Jonathan et al., 2014).***

In the past several years, regenerative medicine has oriented itself toward decellularized autologous tissue grafts in order to overcome the disadvantages of autologous nerves. The biological tissues that have received the most attention other than blood vessels are skeletal muscles, and tendons ***(Belanger et al., 2016).***

Designed scaffolds with natural and synthetic materials are now widely used in the reconstruction of damaged tissues. Utilization of absorbable and non-absorbable synthetic and natural polymers with unique characteristics can be an appropriate solution to repair damaged nerve tissues ***(Arslantunali et al., 2014).***

Polymeric nanofibrous scaffolds with properties similar to neural structure can be more effective in the reconstruction process. Better cell adhesion and migration, more guiding of axons and structural features such as porosity provide clearer role of nanofibers for the restoration of neural tissues. Methods to improve the performance of tubes like orientation, nanotechnology applications for nerve reconstruction, fiber and

nanofibers, electro spinning methods and their application in the peripheral nerve reconstruction ***(Biazar et al., 2010).***

Although the autogenous nerve graft is still the first choice to replace a nerve tissue loss, the evolving technologies provide a promising outcome to compete with the nerve graft.

AIM OF THE WORK

The aim of this work is to elicit and highlight recent modalities for guided nerve regeneration for peripheral nerve repair after injuries.

ANATOMY OF PERIPHERAL NERVES

Peripheral nerves are formed by axonal extensions of neurons in the dorsal root ganglia of spinal cord (spinal nerves), brain stem (cranial nerves), or sympathetic and parasympathetic ganglia (autonomic nerves) that connect the central nervous system (brain and spinal cord) with the rest of the body to maintain homeostasis, mediate sensation, movement, and coordination. The 43 pairs of sensory and motor nerves in the human body are composed of bundles of axons embedded in a collagenous matrix (endoneurium), ensheathed by connective tissue (perineurium), and wrapped by an external connective layer (epineurium). The cellular components of peripheral nerves include Schwann cells, fibroblasts, endothelial-like cells, and macrophages ***(Stewart, 2003).***

Histology of the peripheral nerves (figure 1)

The typical neuron consist of a cell body which has many radiating processes called dendrites, which are specialized to receive signals from other neurons, and a single long process the axon, which is capable of generating nerve impulse and conducting it ***(Angevine, 1997)***.

The axon

The axon arises from a conical extension of the cell body, the axon hillock. It is a cylindrical process that varies in length and diameter according to type of neuron unlike the

dendrites which diminish in diameter as they branch; the axon has essentially the same caliber throughout its length.The axon contains the axoplasm which is a viscous fluid enclosed in a surface membrane, the axolemma, The axolemma is composed of a phospholipid bilayer into which are inserted protein molecule that have a central channels or pores which can open or close in response to changes in membrane voltage.

The axoplasm lacks Nissel bodies, Rough endoplasmic reticulum but contains short segment of smooth endoplasmic reticulum and long, slender mitochondria. Microtubules are also numerous but less uniformly distributed than the neurofilaments. Both neurofilaments and microtubules are essential to axoplasmic flow ***(Angevine, 1997).***

Histologically, peripheral nerve fibres may be divided into myelinated and unmyelinated varieties on the basis of absence or presence of myelin sheath ***(Angevine, 1997)***.

Most axons in adult nerve tissue are ensheathed by single or multiple folds of sheath cell. In peripheral nerve fibers, the sheath cell is the Schwann cell, or neurolemma sheath. Axons of small diameter are usually un-myelinated nerve fibers; thicker axons are generally ensheathed by myelin sheath ***(Junqueira and Carneiro, 1980)***.

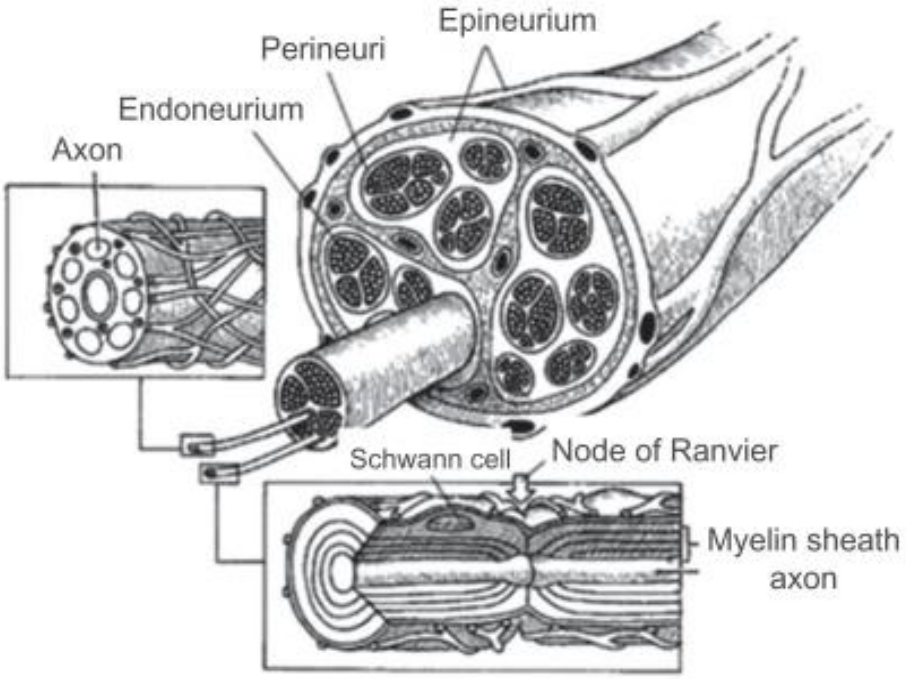

Figure (1): Cross-sectional anatomy of the peripheral nerve. Inset at left shows an unmyelinated fiber. Inset at bottom shows a myelinated fiber ***(Lundborg, 1988).***

The myelin sheath is a highly refractile layer. The lipids that make up the bulk of this layer (cholesterol, phospholipid and glycolipids) are extracted in a specimen preparation for light microscopy ***(Angevine, 1997)***.

At intervals along the axon, there are short gaps in the myelin sheath, called the nodes of Ranvier. These are spaces between the successive Schwann cells of the sheath ***(Angevine, 1997).***

The myelin sheath of peripheral nerves begins a short distance from the cell body. The port of the axon between the

axon hillock and the beginning of the sheath is called its initial segment.The presence of the myelin sheath greatly influences the ability of an axon to conduit on impulse. It acts as an insulator with the axon exposed to the extracellular space at the nodes of Ranvier. The inter-nodal segment of the myelin sheath prevent the inter change of ions necessary to generate an action potential. However the action potential is regenerated at each node of Ranvier. This is called saltatory conduction and is very much faster than in axons lacking myelin sheath ***(Angevine, 1997)***.

The Schwann cells

Schwann cells are satellite cells of the peripheral nervous system; all peripheral axons are ensheathed by them.They participate in the supply of metabolites and trophic factors to the axons and in the maintenance of ionic state of the periaxonal space ***(Williams's et al., 1992)***.

The close interrelation of axons and Schwann cells is confirmed by their mutual reactions to injury. Crushing or cutting of the nerve fiber produces wallerian degeneration. In this reaction, axons distal to the site of injury degenerate and an intense proliferation of schwann cells follows in which myelin and axonal debris are phagocytosed. This will leave a tube consists of Schwann cells ***(Williams et al., 1992)***.

Dendrites

Structurally, dendrites are very similar to perikaryons, however they are devoid of golgi bodies. Nissel bodies and mitochondria are present except in very thin dendrites. Neurofilaments and microtibules are more numerous in dendrites then in axons ***(Angevine, 1997)***.

The Perikaryon or Soma

It is part of the neuron that contains the nucleus. It is the primarily trophic factors producing center, and also has a receptive function. The perikaryon of most neurons receives a great number of nerve endings that convey excitatory or inhibitory stimuli generated in other nerve cells ***(Junqueira and Carneiro, 1980)***.

The contents of the soma include

The nucleus:

Most nerve cells show a spherical, unusually large, euchromatic (pale staining) with a prominent nucleolus.The nucleus is centrally located and the chromatin is finally dispersed reflecting the intense synthetic activity of these cells ***(Junqueira and Carneiro, 1980)***.

Granular (Rough) endoplasmic reticulum

Such endoplasmic reticulum synthesizes bothstructural protein and protein for transport. Granular endoplasmic

reticulum and free ribosomes are called Nissel bodies they are abundant on large nerve cells as motor neuron.

Axonal or neuronal exhaustion resulting from strong or prolonged stimuli causes a reduction in the number of Nissel bodies.This alteration is called chromatolysis and occurs simultaneously with nuclear migration to the periphery of the perikaryon ***(Junqueira and Carneiro, 1980)***.

Golgi apparatus

It is located only in the perikaryon around the nucleus.There are also a number of small spherical vesicles that likely represent both transfer and secretory vesicle ***(Junqueira and Carneiro, 1980)***.

Mitochondria

Found in neurons and are abundant in axon terminal.

Neurofilament and microtubules

Three kinds of filamentous structure are found: neurofilaments, microfilament, and microtubules. The microtubules of the axon are of greater functional significance, in that they serve as conveyor lines along which vesicles are transported from the Golgi body to the nerve endings ***(Angevine, 1997)***.

The synapse (figure 2)

The synapse is a specialized region of contact where neurotransmitter is released from an axon to stimulate another cell. A common neurotransmitter is acetylcholine, but a growing number of other compounds serving this function have been identified to date, including certain monoamines, the catecholamine noradrenaline and dopamine ***(Angevine, 1997)***.

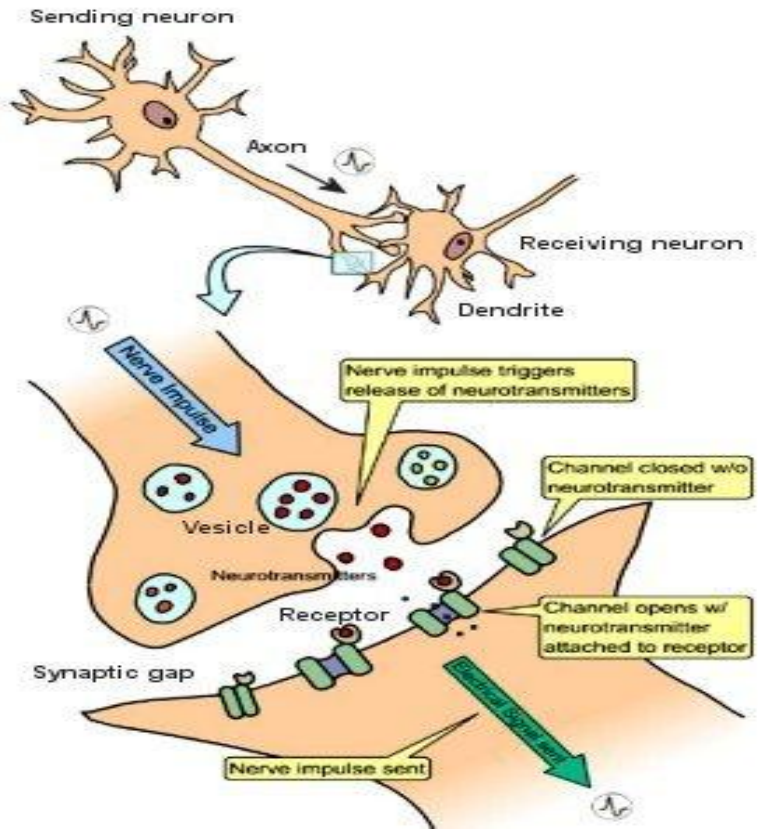

Figure (2): The Synapse ***(Angevine, 1997).***

At a synapse the most conspicuous constituent are numerous small synaptic vesicles, 20-40 nm in diameter, clustered near the presynaptic membrane. When an action

potential travelling down the axon reaches its terminal, voltage-gated channels are opened permitting Calcium ions to enter and this trigger the release of neurotransmitter ***(Angevine, 1997)***.

The connective tissue elements

The peripheral nerve trunk consist of both neural (nerve fibre) and non-neural (connective tissue) elements (figure 3)

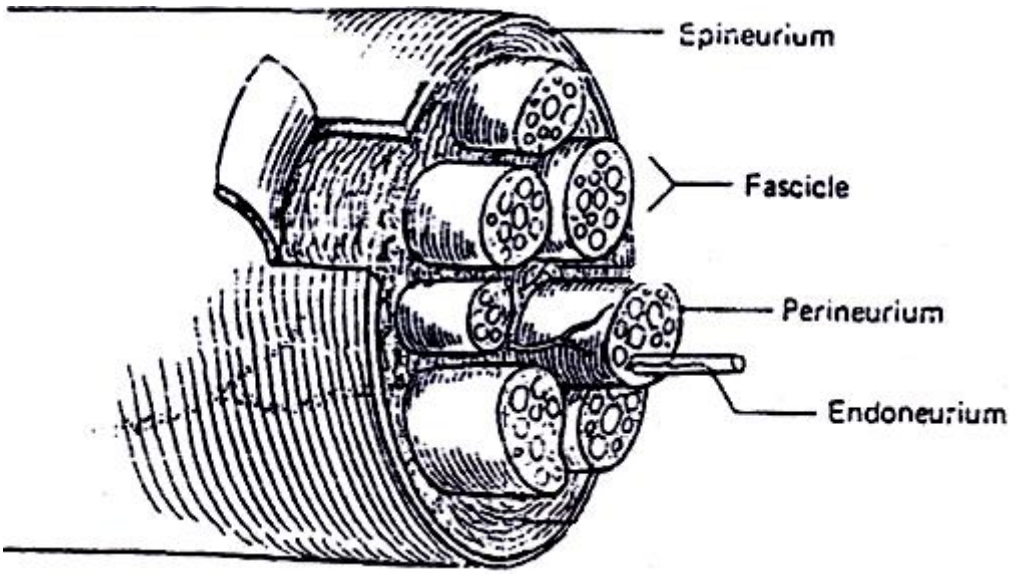

Figure (3): The surgical anatomy of a peripheral nerve ***(Mc Gillicuddy, 1996)***.

The epineurium: It is the outer most connective tissue layer which surrounds the trunk and separates it from the surrounding structures. It is composed mainly of longitudinally disposed collagen fibers, fibrocytes and some elastic fibres.

The perineurium: It is a circulatory arranged tissue that surrounds a number of axons to form the fascicle. The perineurium forms a dense mechanically strong sheath,

surrounding each fascicle and acting as a mechanical barrier to external trauma. It also serves as a diffusion barrier for preservation of the specific internal environment of the fascicle.

The endoneurium: It is the inner most layer of connective tissue structure surrounds the nerve fiber and is composed of connective tissue, small capillaries and extracellular fluid ***(Lundborg, 1988).***

The nerve fascicle

The fascicle is the smallest segment of the nerve that is generally visible by the operating microscope it is formed by a number of axons that are grouped together and surrounded by the perineurium. The fascicles are grouped together to form a peripheral nerve trunk which is covered by the epifascicular epineurium ***(Worth, 1996).***

Fasciculi vary in different nerves and at different levels along their paths, their number increase and their size decrease some distance to a point of branching. Similarly when nerves are passing deep to a retinaclum fasciculi increase in number but decrease in size and the associated connective tissue and vascularity also increase ***(Williams et al., 1992)***.

Fascicular Composition

According to ***Sunderland (1945)*** there is significant plexus formation between the fascicles. In his study on the musculocutaneous nerve, the maximum length with fixed

fascicular pattern was 1.5 cm. He concluded that fibers were diffusely scattered across the different fascicles and follow a tortuous course of plexus formation until they organize into specific motor or sensory groups distally as shown in **Figure 4A** ***(Sunderland, 1978; Amr, 2008; Gad, 2014).***

Sunderland (1978) suggested that the plexiform configuration enhances the tensile strength of the nerve trunk and helps to protect against mechanical deformation. The constantly changing position of individual fibers within the nerve also reduces the likelihood that a focal injury might damage a large number of fibers destined to innervate a specific muscle group or sensory distribution. ***(Amr, 2008; Gad, 2014)***

Jabaley et al. (1980) contradict the work of Sunderland. They found the plexus formation located only in the proximal parts of the nerves. In the distal part, the weaving and plexus formation become less extensive. The internal topography of the peripheral nerve becomes more organized as it extends distally **(Figure 5).** The recurrent motor branch of the median nerve can be dissected retrograde without plexus formation for seven centimeters. Fibers destined for specific territory are organized into distinct groups proximally within the nerve as shown in **Figure 4B** ***(William and Jabaley, 1986; Gad, 2014).***

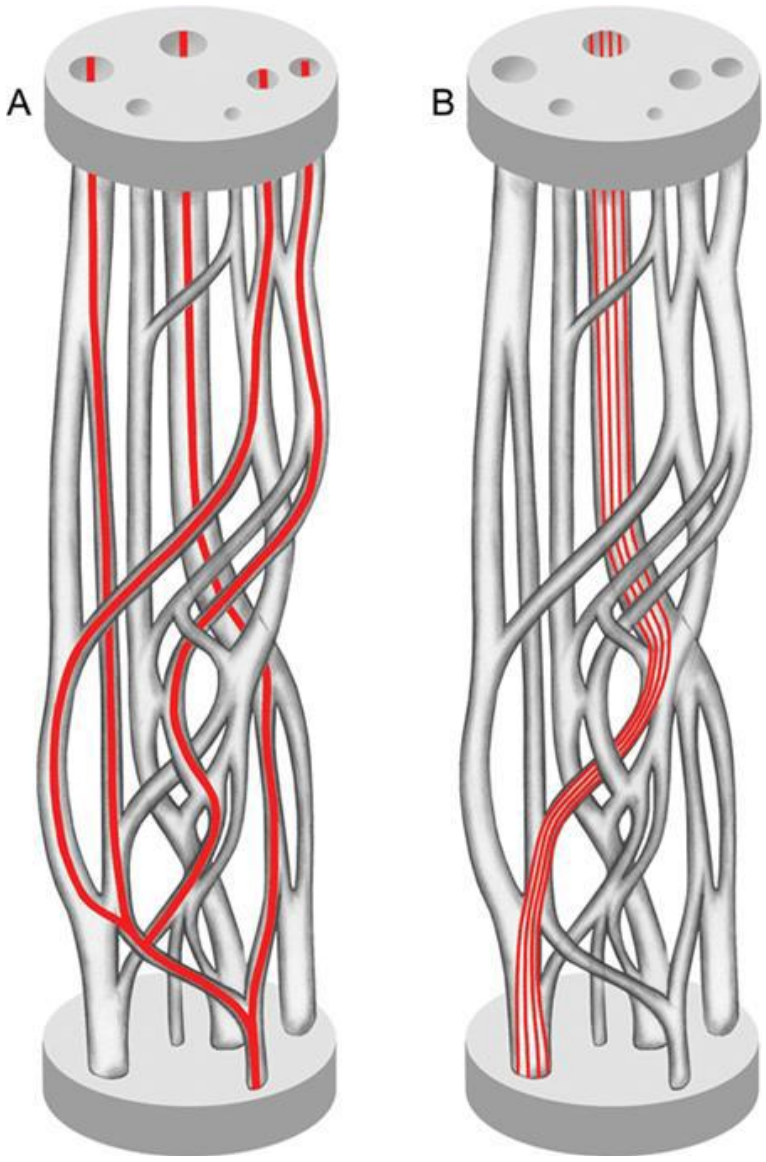

Figure (4): A, show the concept concluded by ***Sunderland (1978)*** for the diffusely scattered fibers along the course of the nerve. **B,** The concept suggested by ***Williams and Jabaley (1986)*** where the fibers are organized in distinct group in the proximal aspect of the nerve ***(Gad, 2014).***