Introduction
Peripheral neuropathy is common in clinical practice but its prevalence is still uncertain. Problems involving the peripheral nerves or root represent at least 30% of new patients in a general neurology outpatient clinic in the UK. Worldwide, the most common cause of peripheral nerve disease is diabetes and the commonest treatable cause is leprosy. Diabetes as well as alcoholic neuropathies are commonest in the USA. Many physicians have a pessimistic approach to the diagnosis and management of patients with peripheral nerve disease, but the advent of new treatments and a greater understanding of pathogenesis is beginning to change opinion.

Peripheral neuropathies are caused by deranged function and structure of peripheral motor, sensory, and autonomic neurons. The main causes of neuropathy are entrapment, leprosy, diabetes, and other systemic diseases; inherited disorders; inflammatory demyelinating, ischemic, paraneoplastic conditions; deficiency states; and toxins. A logical systematic diagnostic approach consists of a careful history, physical examination, and electrophysiological studies, which not only confirm the presence of a peripheral nerve disorder but also may shorten the list of diagnostic possibilities. Further laboratory studies are often performed based on the outcome of the initial evaluation to arrive at a specific diagnosis. It is possible to establish a specific diagnosis in up to 75% of patients evaluated in tertiary referral centers by experts in neuromuscular disorders.

Arrangement of peripheral nervous system
The peripheral nervous system includes all neuronal structures lying outside the pial membrane of the spinal cord and brain stem with the exception of optic nerves and olfactory bulbs, which are but special expansion of the brain.

Structure of peripheral nerve
Axon thicker than one micron in the CNS and peripheral nervous system (PNS) are myelinated. Myelin is a spiral sheet of plasma membrane wrapped around axon. In the CNS, myelin is produced by oligodendroglial cells & in the PNS by schwann cells. Each oligodendrocyte makes multiple segments of myelin that wrap many axons. Each schwann cell makes one segment of myelin. This is one reason why peripheral myelin regenerates more efficiently. Nodes of Ranvier are points of discontinuity between adjacent myelin sheath in which axon is not covered by myelin. The structure of central and peripheral myelin is the same. Myelin is composed of 70% lipid & 30% protein. There are some important differences in myelin proteins between CNS and PNS. This differences explain why an allergic reaction against PNS myelin does not cause central demyelination and vice versa; and inherited metabolic disorders of myelin protein that affects peripheral nerves do not damage central myelin. On the other hand lipid are similar between CNS and PNS myelin. For this reason, metabolic disorders of lipid, such as metachromatic leukodystrophy, affect both, the central white matter and peripheral nerves.

A typical spinal nerve contains motor, sensory and autonomic fibres

Types of Nerve Fibre:
Type A - Myelinated, Diameter -2-20m,
NCV 10-70 m/sec  
Function - motor, vibration & proprioception  

Type B - thinly myelinated, Diameter - 3m,  
NCV 5-7 m/sec  
Function - preganglionic auto, pain & temp.  

Type C - Unmyelinated, Diameter - <1m, NCV <2 m/sec  
Function - pain & temperature.  

Pathological Pattern of Neuropathy  
Damage may occur to –  
• Axon  
• Myelin sheath  
• Cell body  
• Supportive connective tissue & Nutrient blood supply to nerves  

The pathology of peripheral neuropathy follows 3 basic patterns  
• Wallerian Degeneration  
• Distal Axonopathy  
• Segmental Demyelination  

Wallerian degeneration  
The neuronal cell body maintains the axon through the axoplasmic flow. When the axon is transected, its distal part, including its myelin sheath, undergoes a series of changes leading to its complete structural disintegration and chemical degradation. This process is called Wallerian degeneration. The neuronal body of the transected axon enlarges. Nissl granules disperse, and the nucleus is displaced peripherally. This cellular change which is called central chromatolysis reflects activation of protein synthesis in order to regenerate the axon. Cytoskeletal proteins and other materials flow down the axon. The proximal stump elongates@1-3 mm/day. Schwann cells distal to the transection also proliferate. The degree of regeneration and recovery depends on how well the cut ends are put together and the extent of soft tissue injury and scarring around the area of transaction. Wallerian degeneration was initially described in experimental anatomy. Neuropathies characterized by trauma, cooling, infarction of peripheral nerve (diabetic mononeuropathy, vasculitis) and neoplastic infiltration are of this type.  

Distal axonopathy  
When the neuronal body is injured from whatever cause, pathology develops first in the most distal parts of the axon and, the abnormality persists, the axon "dies back". This causes a characteristic distal ("stocking-gloves") sensory loss and weakness. Neurofilaments and organelles accumulate in the degenerating axon (probably due to stagnation of axoplasmic flow). Eventually the axon become atrophic and breakdown. Severe distal axonopathy resembles Wallerian degeneration. At the advanced stage, there is loss of myelinated axons. Distal axonopathy involves more severely large axons that have the highest metabolic and nutritional demands. Many clinically important neuropathies caused by drugs, and industrial poisons such as pesticides, acrylamide, organic phosphates, and industrial solvents are characterized by distal axonopathy.  

Segmental demyelination  
Initially described in experimental lead poisoning, is breakdown and loss of myelin over a few segments. The axon remains intact and there is no change in neuronal body. Segmental demyelination causes loss of saltatory conduction. Recovery, due to remyelination, is faster and more complete than Wallerian degeneration. Remyelinating axons have thin myelin sheath. Neuropathies characterized by segmental demyelination include Guillain-Barre syndrome (GBS), Chronic inflammatory demyelinating polyneuropathy (CIDP), diphtheritic neuropathy, metachromatic leukodystrophy and Charcot-Marie-Tooth disease. "Onion-bulb" formations are concentric layers of Schwann cell processes and collagen around an axon. This proliferation is caused by repetitive segmental demyelination and regeneration of myelin and cause gross thickening of peripheral nerves (hypertrophic neuropathy). The central axon is often demyelinated or has thin layer of myelin. Onion-bulb formations are the
histological hallmark of Charcot-Marie-Tooth disease, but also seen in other hereditary neuropathies (Dejerine-Sottas disease, Refsum disease), Diabetic neuropathy and in CIDP.

Neuropathies can be classified on the basis of their pathological changes into
I. Axonal (Wallerian degeneration & distal axonopathy),
II. Demyelinating and
III. Mixed.

Clinical Types of Peripheral Neuropathies
1. Radiculopathy
2. Plexopathy
3. Mononeuropathy
4. Mononeuritis multiplex
5. Polyneuropathy

1. Causes of Radiculopathies
• Traumatic
• Disc degeneration & spondylosis
• Diabetic polyradiculopathy
• Neoplastic polyradiculopathy
• HIV polyradiculopathy
• Tabes dorsalis
• Lyme radiculopathy
• Herpes Zoster
• GBS
• CIDP

2. Causes of Plexopathy
I. Brachial plexopathy-
• Traumatic
• Neurogenic TOS
• Metastatic
• Radiation
• Idiopathic

II. Lumbosacral plexopathy-
• Hematoma
• Abscess
• Aneurysm
• Trauma
• Pregnancy
• Neoplasm
• Radiation
• Vasculitis
• Idiopathic

3. Causes of Mononeuropathy
• Entrapment neuropathy & pressure palsy
• Leprosy
• Diabetes Mellitus
• Trauma

4. Causes of Mononeuritis Multiplex
(Vasculopathy of vasa nervosum or infiltration of nerves)
• Diabetes Mellitus
• Leprosy
• Polyarteritis nodosa
• Rheumatoid arthritis

5. Causes of Polyneuropathy
2. Chronic
• Hereditary- Hereditary motor sensory polyneuropathy (HMSN) type I and III, Mitochondrial leucodystrophy
• Paraproteinaemia-Myeloma, Waldenstrom's macroglobulinaemia
• Drugs- Amiodarone, Perhexiline
• CIDP

b. Causes of axonal neuropathy-
1. Acute- Toxins, Porphyria, Vasculitic disease (e.g. SLE, PAN)
2. Chronic
• Metabolic- Diabetes, Uraemia
• Deficiencies- B12, Thiamine, Vit. E, Nicotinamide
• Toxic-Alcohol, Drug
• Paraneoplastic- Lymphoma, Ca lung, Paraproteinaemias
• Autoimmune diseases
• Hereditary- HMSN type II, Giant axonal neuropathy, Hereditary ataxias
• Miscellaneous- Chronic obstructive airways disease, Primary
• Amyloid, Sarcoid
• Leprosy
• Undetermined

Causes of polyneuropathy according to clinical type-
Predominantly sensory-
Approach for the Investigation of peripheral Neuropathy
The goal of the investigation of peripheral neuropathy is to
1. Establish the diagnosis of peripheral neuropathy,
2. Determine if it is axonal or demyelinative process, and
3. Find its cause.

Clinically, Neuropathy cause weakness and atrophy of muscles, loss of sensation or altered sensation (paraesthesia) and weak or absent tendon reflexes. NCV can distinguish demyelinative neuropathy (slowing velocity & conduction block) from axonal neuropathy (low action potential amplitudes). EMG can distinguish denervation atrophy from primary muscle disease. Careful history taking with attention to family history, environmental exposure, and systemic illness, combined with neurological examination and laboratory studies can determine the etiology in most of the cases. When diagnosis is in doubt, sural nerve biopsy studies by light microscopy, electron microscopy, morphometry, and teased fibre preparations can give more definitive information. Nerve biopsy should be the last resort 10.

Management of neuropathy
The most appropriate management of neuropathy is to reverse the aetiological factor leading to that neuropathy. This gives the best chance of recovery, but may be impossible. If specific treatment is impossible (e.g. vitamin B12 replacement, immunosuppressive agents) management is aimed at preventing decline in function. Occupational therapy is useful in maintaining full use of weak muscles, and physiotherapy helps to stimulate recovery and maximum gain of function. Genetically inherited disorders are often associated with foot deformity, requiring attention to footwear and appropriate orthotic aids. Sensory neuropathies, which lead to loss of sensation in the feet, also require attention to footwear to avoid further nerve damage and disability 10.

Prognosis
Recovery from peripheral neuropathy is usually slow. Depending on aetiology patient may fully, partially recovered or patient may develop chronic muscular atrophy if severely affected.

Rehabilitation
Rehabilitation is required for chronic disabled patients. The patient should be rehabilitated in his occupatin, in his family, and in the society. Social and government active co-operation is needed for training and providing a suitable job so that they can

Some Important Neuropathies:
1. Bell's Palsy
The diagnosis of idiopathic facial nerve palsy (Bell's palsy) is not difficult in a setting of lower motor neuron type of facial palsy in one side. Randomized controlled trials have shown that aciclovir alone is not as effective as corticosteroids in the treatment of Bell's palsy, but the combination of aciclovir and prednisolone appears to be more effective than steroids alone 11,12.

2. Carpal Tunnel Syndrome
Commonest of all entrapment neuropathies. Supportive therapy i.e. control of precipitating factors and if needed decompression of carpal tunnel gives excellent result if done in time.
3. Diabetic Neuropathy

- Commonest of all neuropathy
- 7.5% of all diabetics at diagnosis.
- Common etiologic mechanism based on chronic hyperglycemia.
- Pathophysiologic basis leading to peripheral neuropathy is not fully understood.

Multiple hypothesis have been advanced.

- Metabolic theory
- Vascular theory
- Altered neurotropic support theory
- Laminin theory
- Autoimmune theory

Metabolic theory
This theory proposes that hyperglycemia causes increased level of intracellular glucose in nerves, leading to saturation of the normally used glycolytic pathway. The extra glucose is shunted into the Polyol pathway and converted to sorbitol & fructose by the enzyme aldose reductase and sorbitol dehydrogenase. Accumulation of sorbitol and fructose leads to reduced nerve myoinositol, decreased membrane Na⁺/K⁺ ATPase and impaired axonal transport and structural breakdown of the nerve, causing slowing of conduction velocities. This describes how aldose reductase inhibitor seems to work to improve nerve conduction.

Vascular (ischemic-hypoxic) theory
According to this theory, endoneurial ischemia develops because of endoerarial vascular resistance to hyperglycemic blood. Various metabolic factor, including formation of advanced glycoylation end products. Also have been implicated, leading to capillary damage, inhibition of axonal transport, Na⁺/K⁺ ATPase activity, and finally to axonal degeneration.

Altered neurotropic support theory
Neurotropic factors are important in the maintenance. Development and regeneration of responsive elements of the nervous system. Nerve growth factor (NGF) is the best studied. This protein promotes survival of sympathetic, and small fibre neural crest-derived factors in the PNS. Antioxidants are used to enhance the effect of NGF.

Laminin theory
Laminin is a large glycoprotein composed of a large alpha chain and 2 smaller beta chains, beta 1 and beta 2. Laminin promotes neurite extension by cultured neurons. Lack of normal expression of laminin beta 2 gene may contribute to the pathogenesis of diabetic neuropathy.

Autoimmune theory
Autoimmune neuropathy can emerge from immunogenic alteration of the endothelial capillary cells. This also hold true on the basis of reported success of using IVIG to treat diabetic neuropathy.

4. Guillain-barre syndrome
This acute postinfectious polyneuropathy characteristically occurs 1-3 weeks after a viral or other infections or immunization. Its incidence is 2/100000 population/yr. Peripheral nerve myelins are involved by both antibody and cell mediated reactions. Segmental demyelination results with secondary axonal damage if the process is severe. CSF protein is elevated and NCV shows slowing of motor conduction, conduction block and prolonged distal latencies. Both NCV and CSF protein may be normal early in the illness until second week. Steroid is not effective but plasmaphresis or, IVIG are equally effective.

5. Chronic inflammatory demyelinating polyneuropathy (CIDP)
3% of all neuropathies. Similar to GBS with a progressive to fluctuating course over weeks to months and rarely involving cranial nerves and respiratory muscles. Segmental demyelination with remyelination (onion bulb formation) and sparse mononuclear cells infiltration occurs in nerves. Conduction velocity diminished to 70% of normal with conduction block and prolonged distal latencies. CSF protein is also elevated. Immunosuppressive therapy, plasmapheresis or, IVIG are effective.
6. Multifocal motor neuropathy with conduction block
This presents with asymmetric LMN weakness and may be mistaken for MND. NCV shows conduction block at sites distant from possible entrapment. Antibodies to gangliosides (Anti GM1) are found in serum. Immunosuppressive therapy or IVIG when indicated results in clinical improvement.3,5

7. Hereditary motor sensory polyneuropathy (HMSN/CMT disease)
A hetarogenous group of disorders with a prevalence of 1: 2500-the largest category of genetic neurological disease. The characteristic appearance is that of distal wasting. The lower limb have an inverted with bottle appearance. The demonstraton of genetic markers and the application of nerve conduction studies allows early and correct diagnosis. Nerve biopsy is of no diagnostic value. Treatment is symptomatic with provision appropriate footwear, splints or orthopaedics to maintain mobility. In adult onset disease the rate of progression is exceedingly slow.7,9

Conclusion
Peripheral neuropathy is a common neurological problem. 1/3rd of neurology out patient department are of this type as reported from a developed country like UK. So awareness should be created among the general physicians and public for its early diagnosis and treatment to prevent long term neurological complications.

References