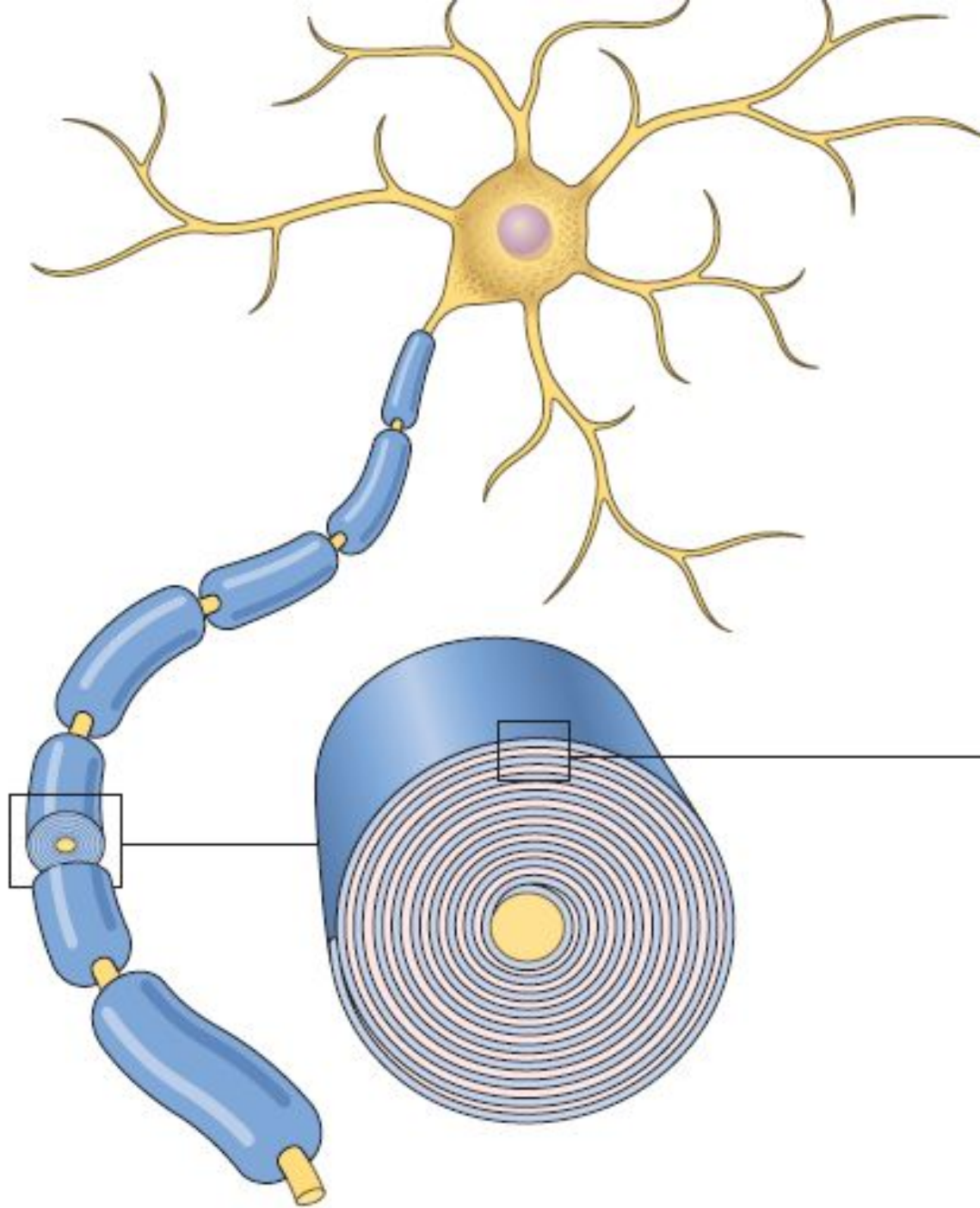
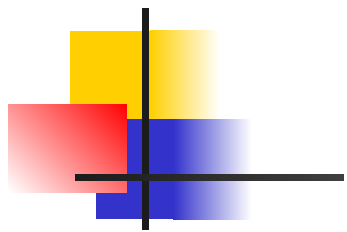
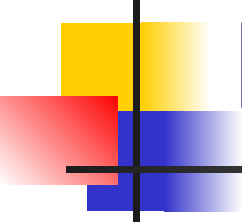


# The CNS

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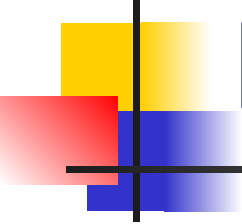




# Demyelinating diseases

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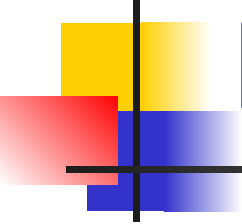
- Acquired, preferential damage to myelin
- Relative preservation of axons
- Initially effect on transmission of impulses along axons
- Determined in part by
  - The limited capacity of the CNS to regenerate the myelin
  - The degree of secondary damage to axons



# Demyelinating diseases

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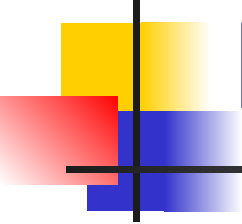
- Etiology
  - Immune mediated destruction (MS)
  - Infection (PML)
  - Inherited (leukodystrophies)
    - Affecting synthesis and turnover of myelin components



# Multiple sclerosis (MS)

---

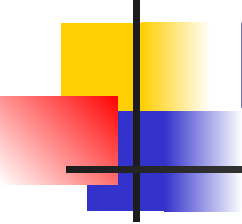
- Autoimmune demyelinating disorder
- Distinct episodes of neurologic deficits
  - Separated in time
  - Attributable to patchy white matter lesions that are separated in space
- The most common demyelinating disorder
  - 1/1000 in the US and EU



# Multiple sclerosis (MS)

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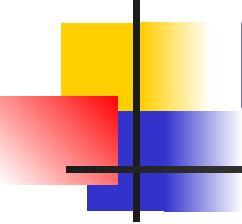
- Any age
  - but rare in childhood and after 50
- W/M = 2/1
- Clinically relapsing and remitting episodes of variable duration
- Neurologic deficits then gradual and partial recovery



# Multiple sclerosis (MS)

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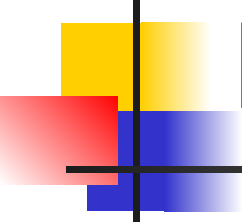
- Relapses frequency tends to decrease over time
- But with steady neurologic deterioration



# Pathogenesis

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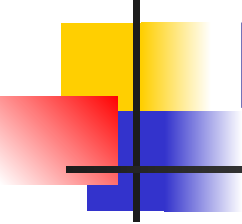
- Autoimmune response against myelin components
- Genetic factors
  - 15 fold in first degree
  - 150 fold in monozygotic twin
  - Strong association with HLA-DR
  - Additional association with IL-2 and IL-7 receptor, CKs/receptors genes



# Pathogenesis

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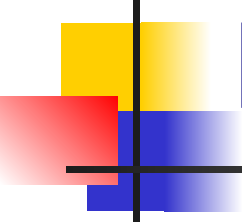
- Environmental factors
  - Geographic variation
    - Equator, sun/vit D??



# Pathogenesis

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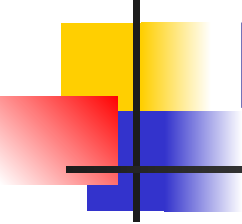
- Immune mechanisms
  - Initiated by Th1 and Th17 cells
  - Reaction against myelin
  - Secrete cytokines
  - Th1 secrete INF- $\gamma$ , activates macrophages
  - Th17; recruitment of leukocytes,
  - Demyelination by these activated leukocytes and their injurious products



# Pathogenesis

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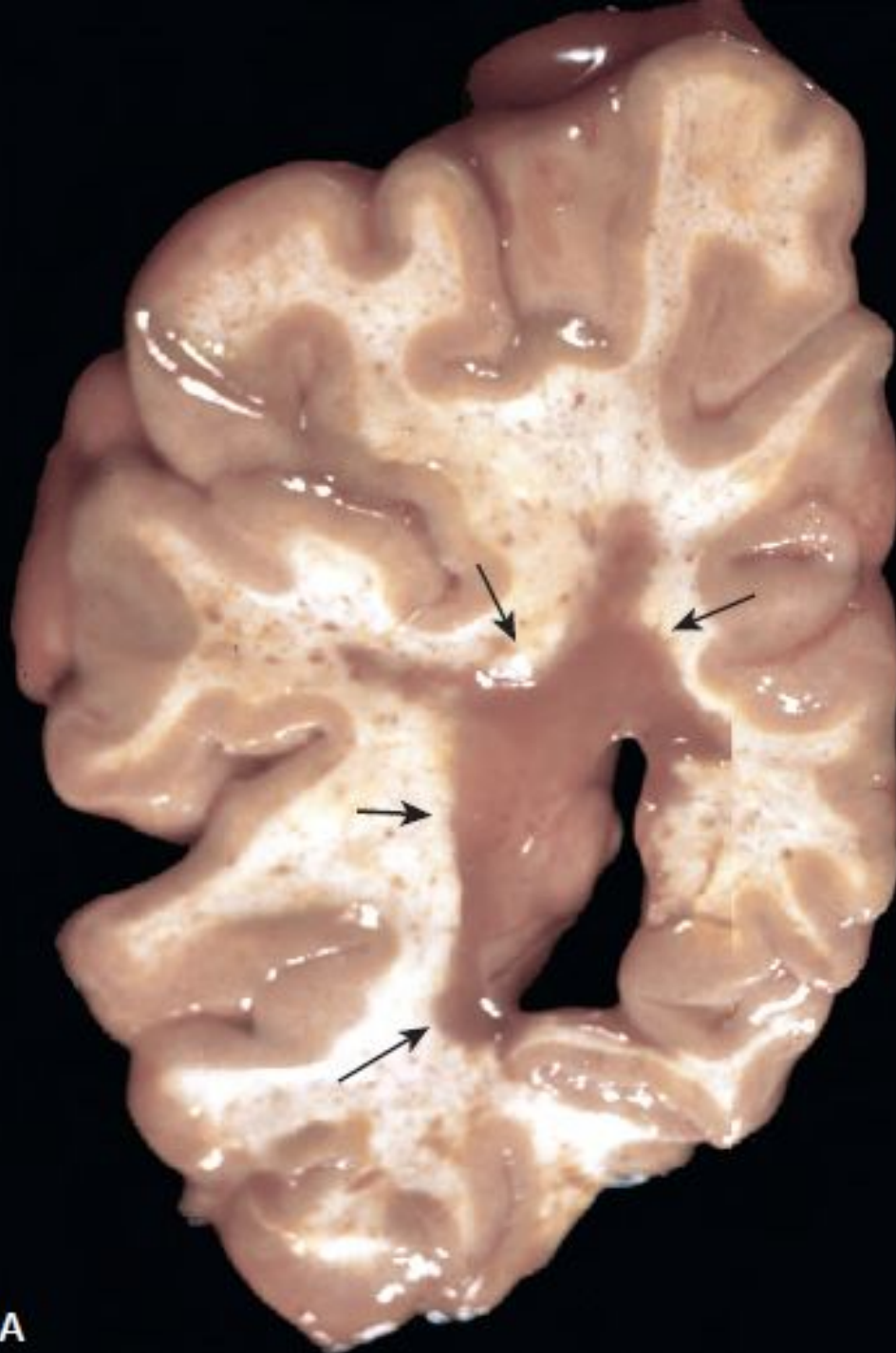
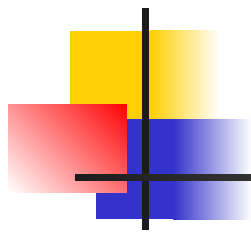
- Immune mechanisms
  - The infiltrate in plaques
    - CD4, CD8 and macrophages
  - How the autoimmune reaction is initiated??
  - Viral infection??
  - Therapy
    - Modulation or inhibition of T-cell responses
    - Blocking of the recruitment of T-cells to the brain
    - Depletion of B-cell Igs ????



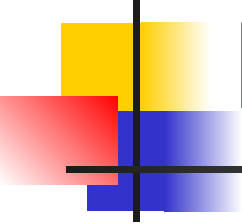
# Morphology

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- A white matter disease
- The lesion
  - is firmer than the surrounding white matter "sclerosis"
  - Well circumscribed
  - Depressed
  - Glassy
  - Irregularly shaped plaques



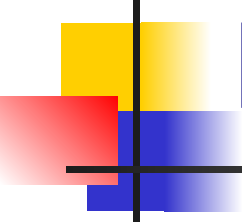
A



# Morphology

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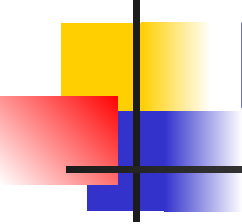
- The area of demyelination
  - Sharply defined borders
- Variable size



# Morphology

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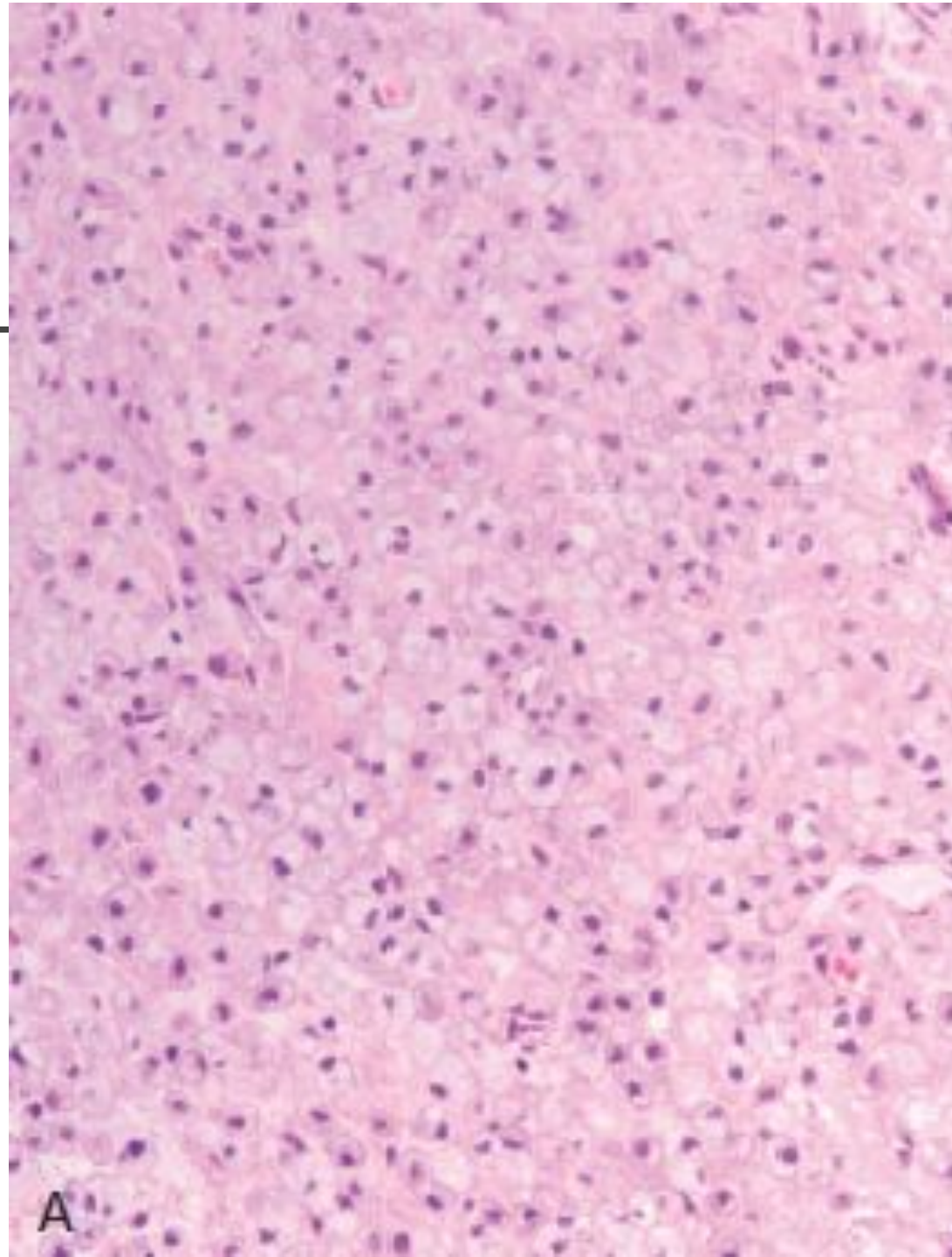
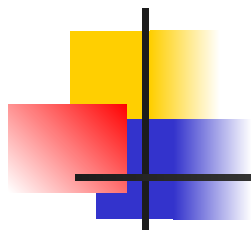
- Localization Commonly
  - Adjacent to the lateral ventricles
  - In the C. callosum
  - Optic nerves and chiasm
  - Brainstem
  - Ascending and descending fiber tracts
  - Cerebellum, and spinal cord
- Plaques can extend into gray matter



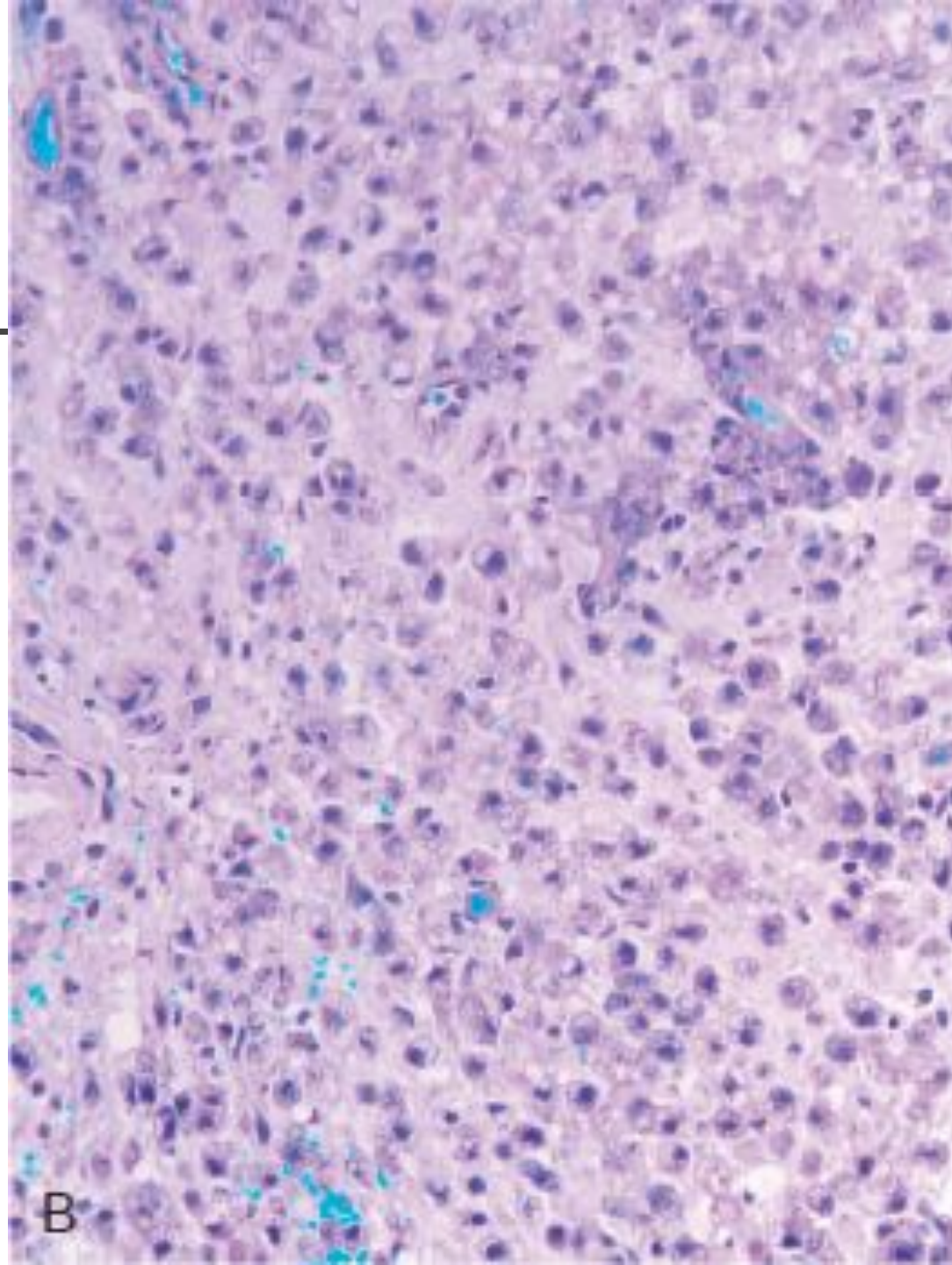
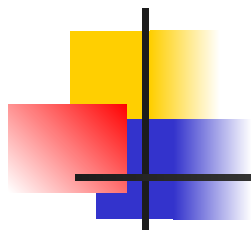
# Morphology

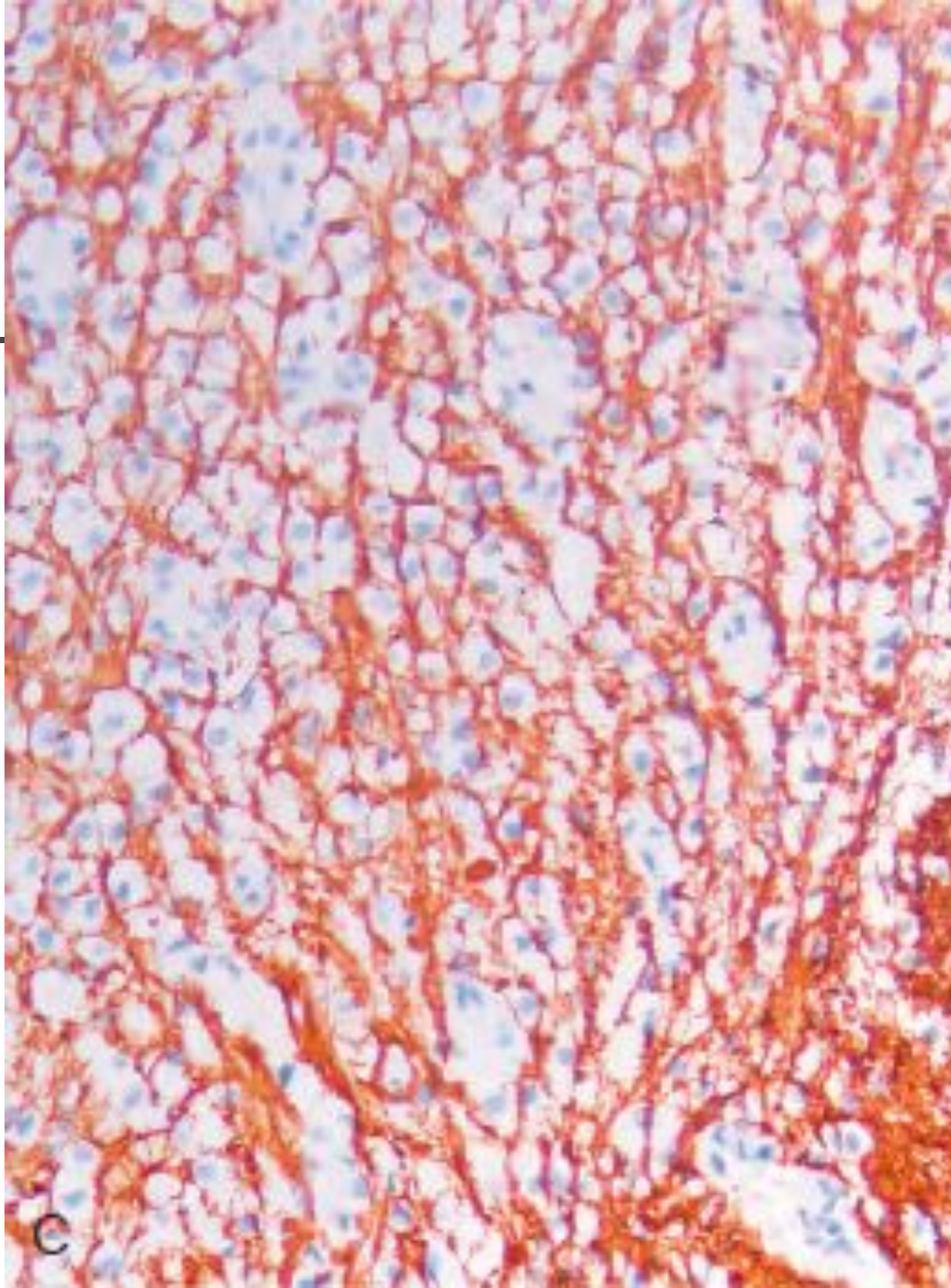
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- Ongoing myelin break-down
- Associated with abundant foamy macrophages
- with lymphocytes as perivascular cuffing at the outer edge of the lesion
- Active lesions are often centered on small veins; myelin is completely absent
- Axons are relatively preserved

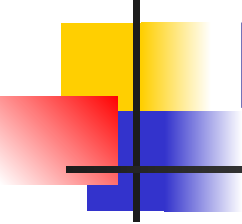


A





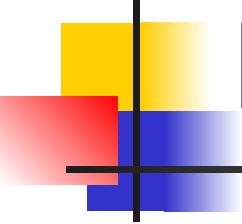
C



# Morphology

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- In time reactive changes of the astrocytes
- As lesion become quiescent; inflammatory cells slowly disappear



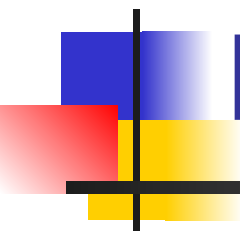
# Morphology

---

- Inactive plaque
  - No macrophages
  - Little to no myelin
  - Reduced oligos
  - Prominent reactive gliosis
  - Greatly diminished axons in old gliotic plaques

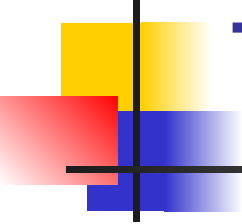


B



# Diseases of peripheral nerves

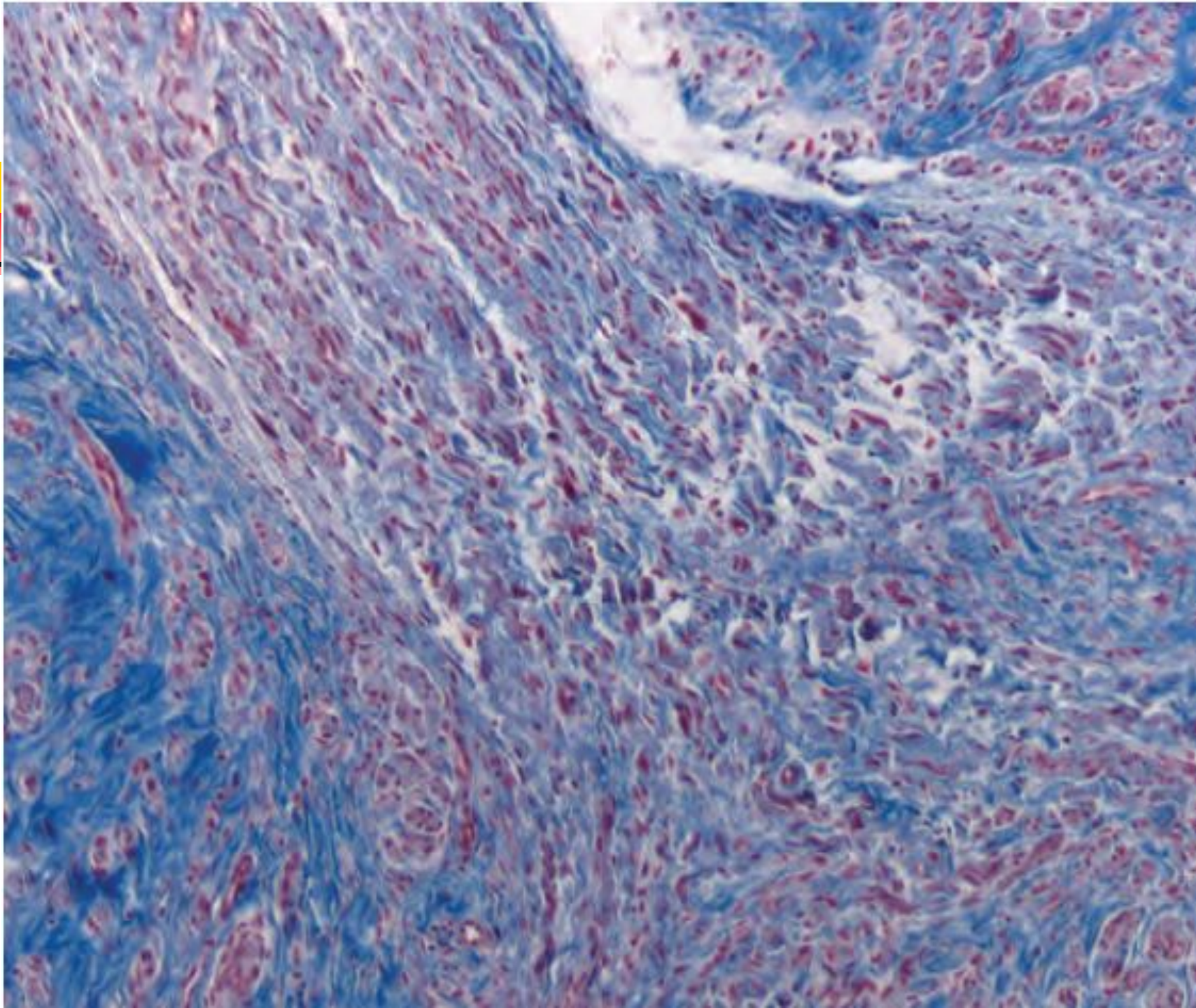
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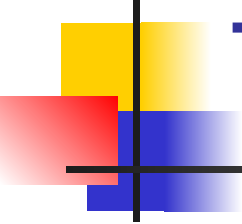


# Types of injury

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- Axonal neuropathy
  - Primary damage of axons
  - Wallerian degeneration
    - Sequence of events
    - Traumatic neuroma

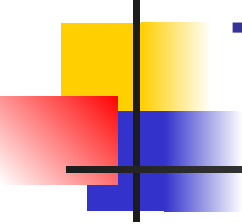




# Types of injury

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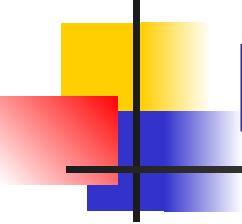
- Demyelinating neuropathy
  - Primary damage targeting myelin and Schwann cells
  - Relatively preserved axons
  - Random degeneration
  - Repair attempts by schwann cells
    - Shorter and thinner than original internodes
  - Electrophysiologic hallmark is slowed nerve conduction velocity due to loss of myelin



# Types of injury

---

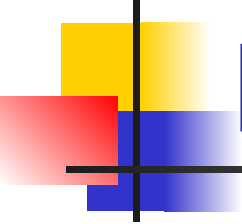
- Neuronopathies
  - Axon degeneration secondary to destruction of neuron
  - H. zoster
  - Platinum compounds



# Anatomic patterns of peripheral neuropathies

---

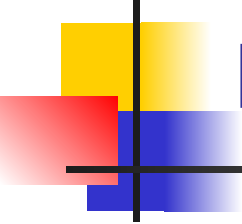
- Mononeuropathies
  - Single nerve and distribution
  - Infection and trauma
- Polyneuropathies
  - Multiple nerves
  - Usually symmetric
  - Axons are affected in length dependent fashion



# Anatomic patterns of peripheral neuropathies

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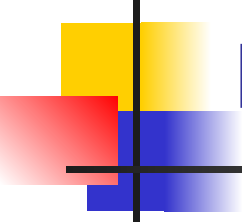
- Mononeuritis multiplex
  - Individual nerves in a haphazard fashion
  - Vasculitis
- Polyradiculoneuropathies
  - Affect nerve roots as well as peripheral nerves
  - Leading to diffuse symmetric symptoms
  - In proximal and distal parts of the body



# Specific peripheral neuropathies

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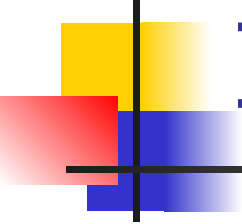
- Clinically
  - Numbness
  - “pins and needles” sensation
  - Weakness; distal



# Specific peripheral neuropathies

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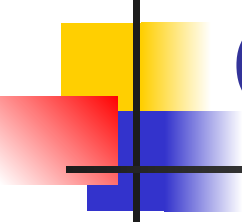
- Types
  - Inflammatory
  - Infectious
  - Metabolic
  - Toxic
  - Trauma
  - Paraneoplastic
  - Genetic



# Inflammatory neuropathies

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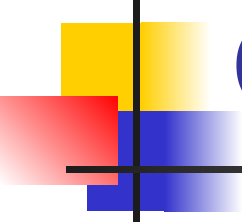
- Guillain-Barré Syndrome (acute inflammatory demyelinating polyneuropathy)



# Guillain-Barrè Syndrome

---

- Immunologically mediated
- Demyelinating peripheral neuropathy
- May lead to respiratory paralysis
- 1/100000/year
- Weakness from distal to proximal limbs  
“ascending paralysis”
- Inflammation and demyelination of  
spinal nerve roots and peripheral nerves  
= radiculoneuropathy

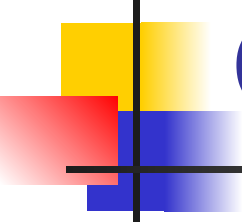


# Guillain-Barrè Syndrome

---

- Pathogenesis

- Acute onset, immune mediated, demyelinating neuropathy
- 2/3 preceded by influenza like illness
- As well as association with
  - C. jejuni, CMV, EBV, and M. pneumonia
  - Vaccination
- No microorganism in the nerves
- Experimentally role of lymphocytes, macrophages and Abs

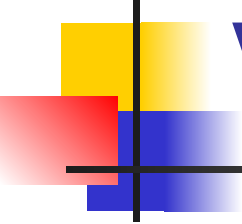


# Guillain-Barré Syndrome

---

- Morphology

- Inflammation of peripheral nerves
- Perivenular & endoneurial infiltration
  - Lymphocytes, macrophages and few plasma cells
- Segmental demyelination
- Damage to axons is also seen (in severe conditions)
- Inflammation is more prominent close to the nerve roots



# Infectious neuropathies:

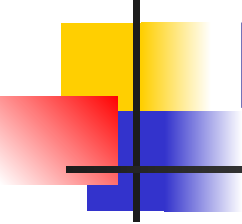
## Varicella-zoster virus

---

- Common
- Latent infection of chickenpox in sensory ganglia
- Reactivation and transport to dermatomes (shingles)
  - Decreased cell mediated immunity??
- Neuronal death with abundant mononuclear infiltrate
- Degeneration of axons



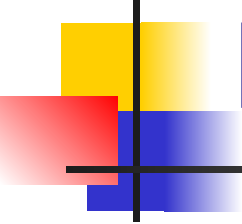




# Metabolic neuropathies: DM

---

- DM is the most common cause of peripheral neuropathy
- Overall 50% of Diabetic patients
- Mostly ascending distal symmetric sensorimotor poly neuropathy

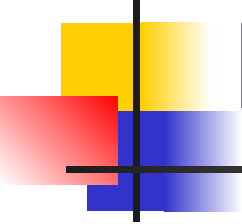


# Metabolic neuropathies: DM

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- Pathogenesis

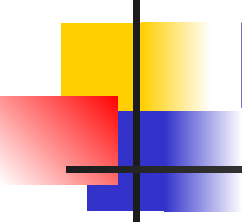
- Complex
- Damage to both axons and Schwann cells
- Non enzymatic glycosylation of proteins, lipids and nucleic acids
- Activation of inflammatory signaling
- Depletion of NADPH
- Injury by free radicals
- Or secondary damage due to vascular ischemia



# Metabolic neuropathies: DM

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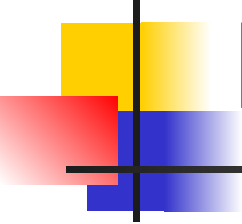
- Morphology
  - Axonal neuropathy
  - Reduced number of axons
  - Degenerating myelin sheaths
  - Regenerative axonal clusters
  - Thickening hyalinization of endoneurial arterioles



# Diseases of the NMJ

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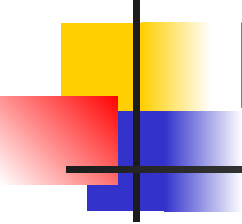
- Physiology
- Painless weakness and fatigue
- autoantibodies



# Myasthenia gravis

---

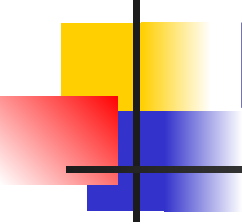
- Ab mediated disease of the NMJ
- Autoimmune
- Auto Abs against ACh receptors
- 150-200/1000000
- Bimodal age distribution



# Myasthenia gravis

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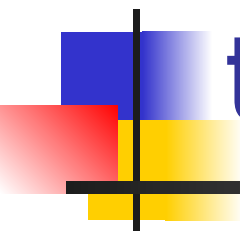
- Pathogenesis
  - ACh Rs autoAbs
    - Pathogenic
    - Passive transfer to animals
    - Improvement by decreasing these Abs
    - Leads to aggregation and destruction of the receptors
    - Damage to postsynaptic membrane through complement fixation
    - No response to ACh



# Myasthenia gravis

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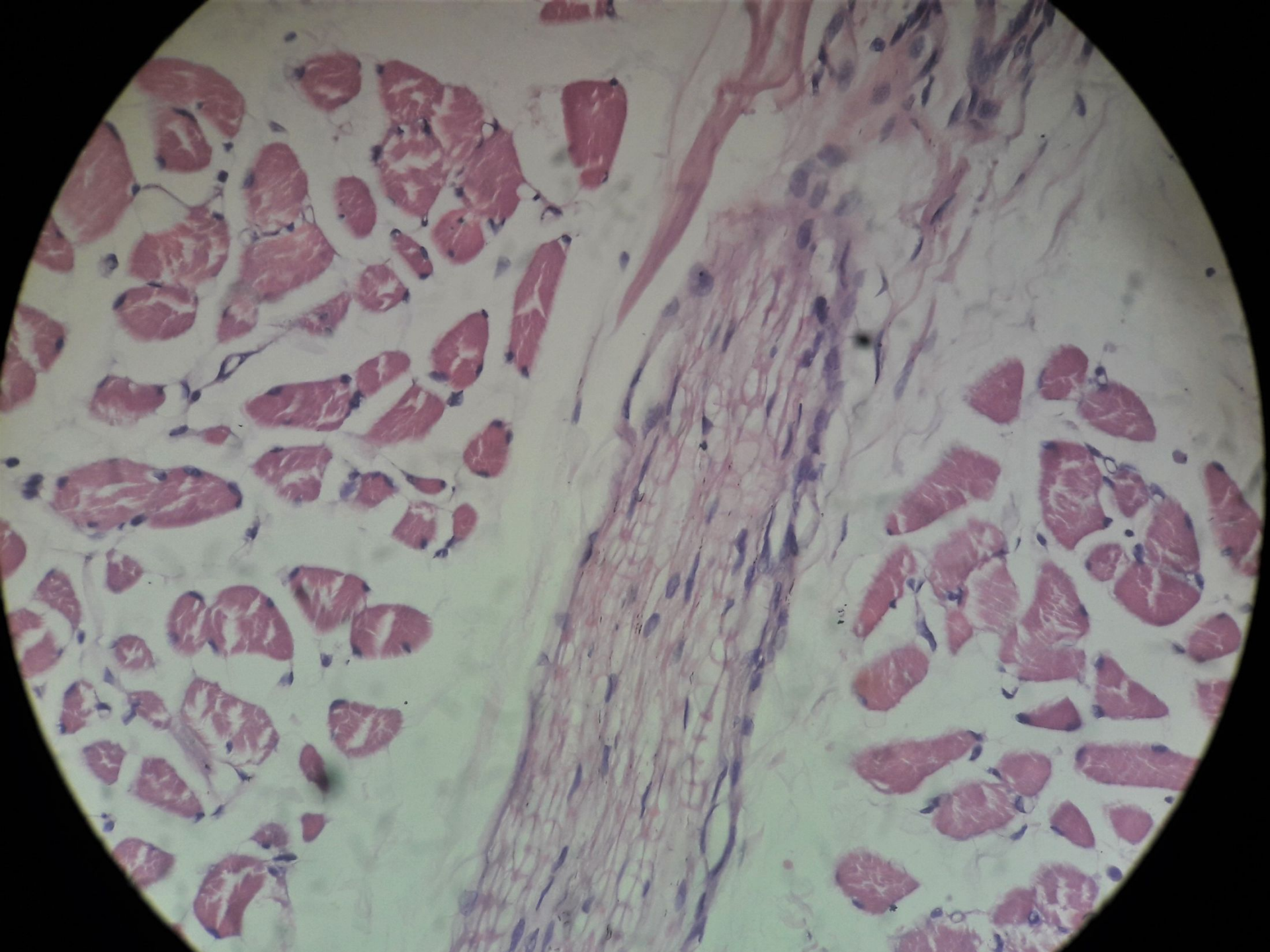
- Pathogenesis
  - Strong association with thymic abnormalities
    - 10% thymoma
    - 30% thymic hyperplasia
    - Promoting autoimmunity

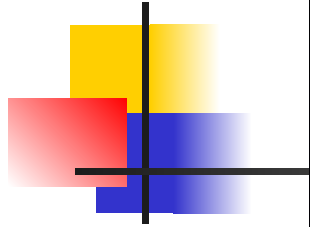
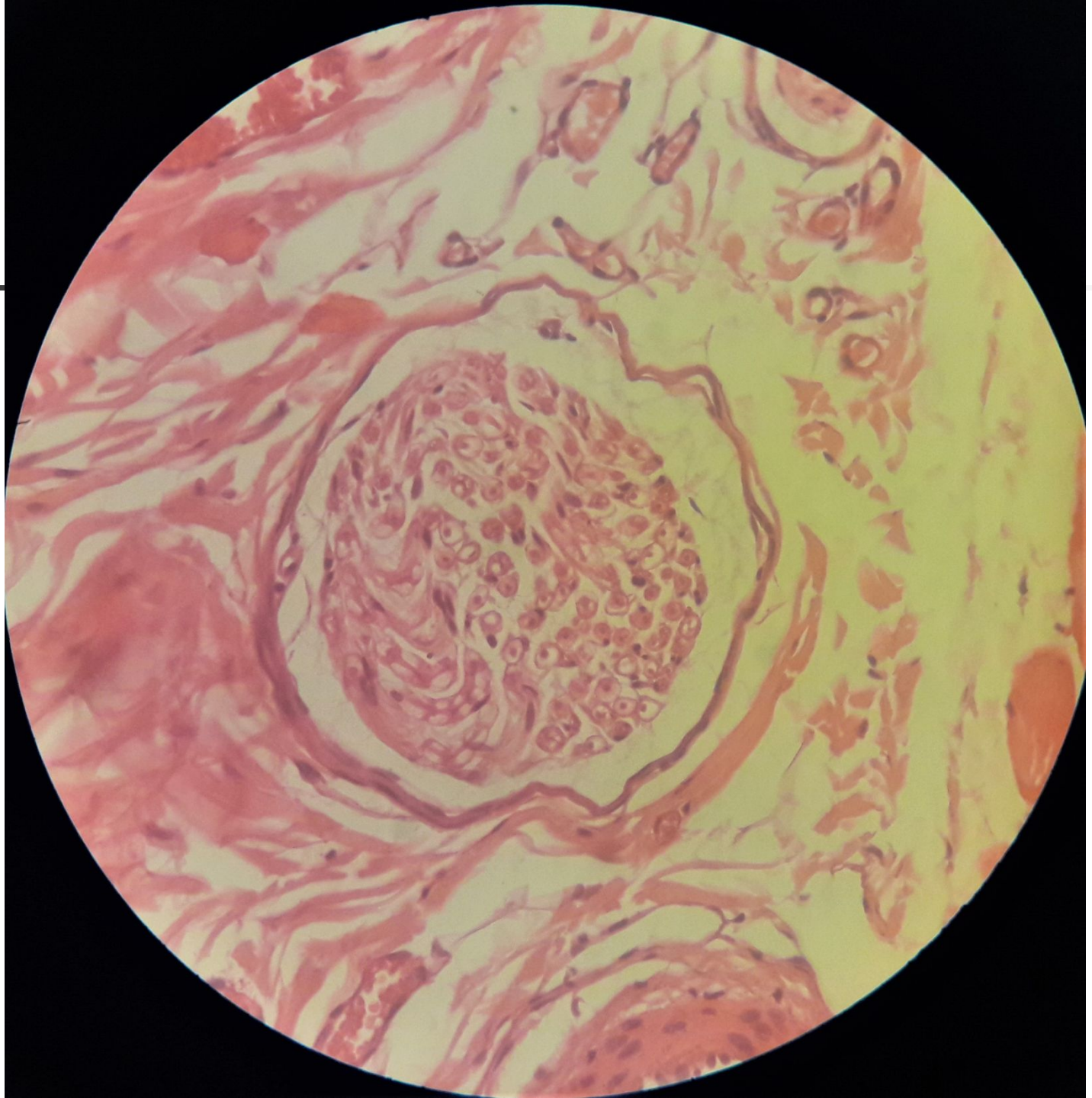


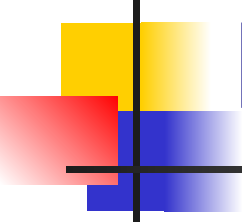
# Peripheral nerve sheath tumors

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PNSTs



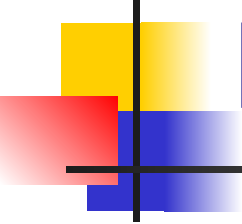




# PNSTs

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- Most reveal Schwann cell differentiation
- Rarely perineurial cell differentiation
- Common types
  - Schwannoma
  - Neurofibroma
  - MPNST
- Abrupt transition between central and peripheral myelin
  - PNSTs may arise within the dura

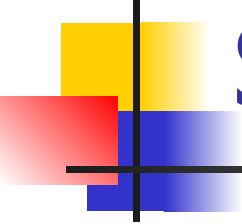


# PNSTs

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- Unique features

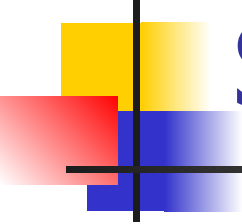
- Association with common familial tumor syndromes
  - NF1
  - NF2
  - Schwannomatosis
- MPNSTs in the context of NF1 are thought to arise through malignant transformation of preexisting neurofibroma (unusual for soft tissue tumor)



# Schwannomas

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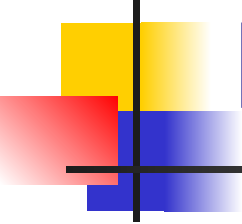
- Arise directly from nerves
- Schwann cell differentiation
- Hereditary
  - A component of NF2



# Schwannomas

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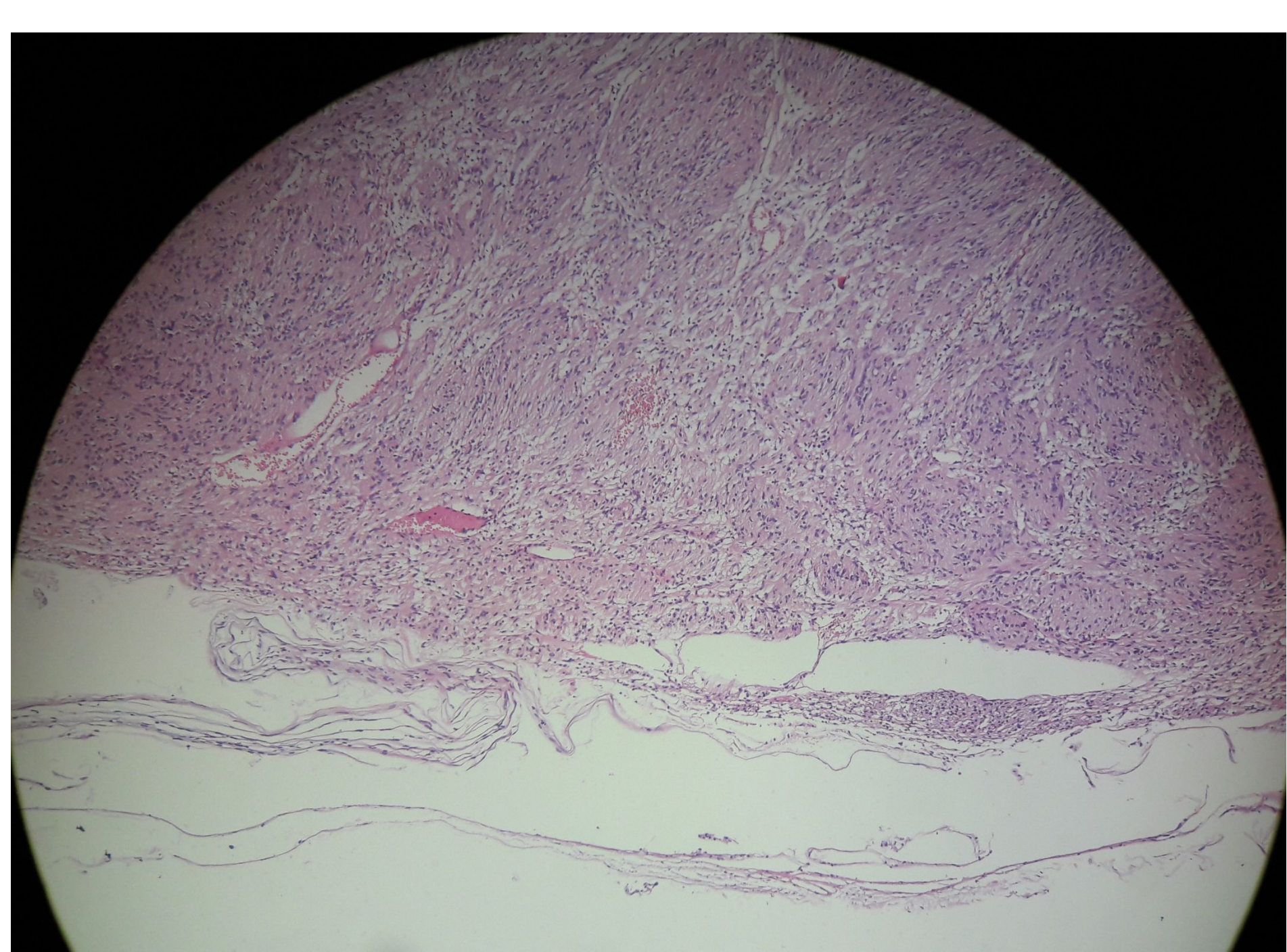
- Sporadic
  - Commonly associated with inactivation of NF2 gene
  - Thus loss of function of merlin
    - A consistent finding of all Schwannoma
    - Participates in control of cell shape, growth and adhesion

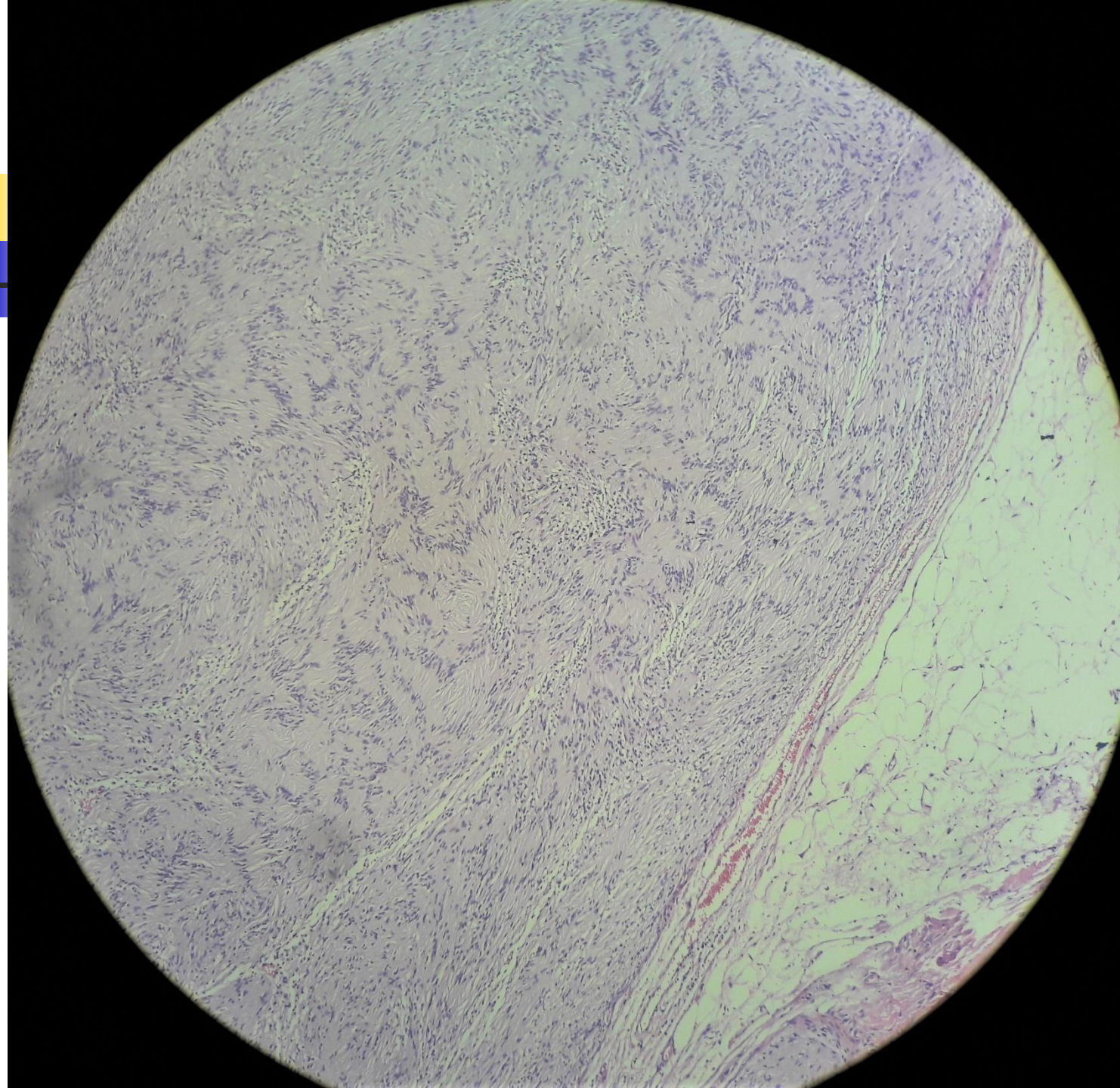


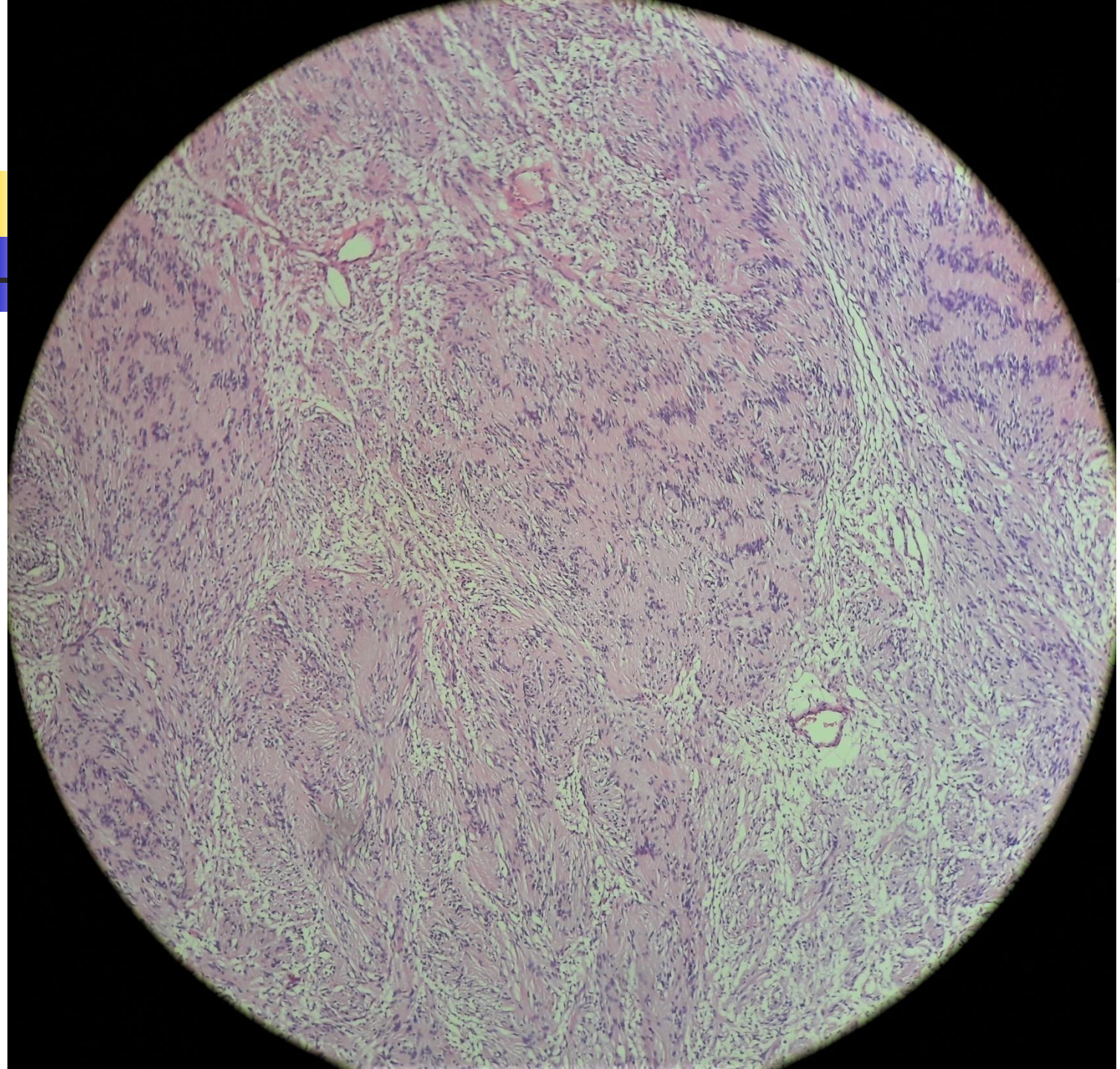
# Morphology

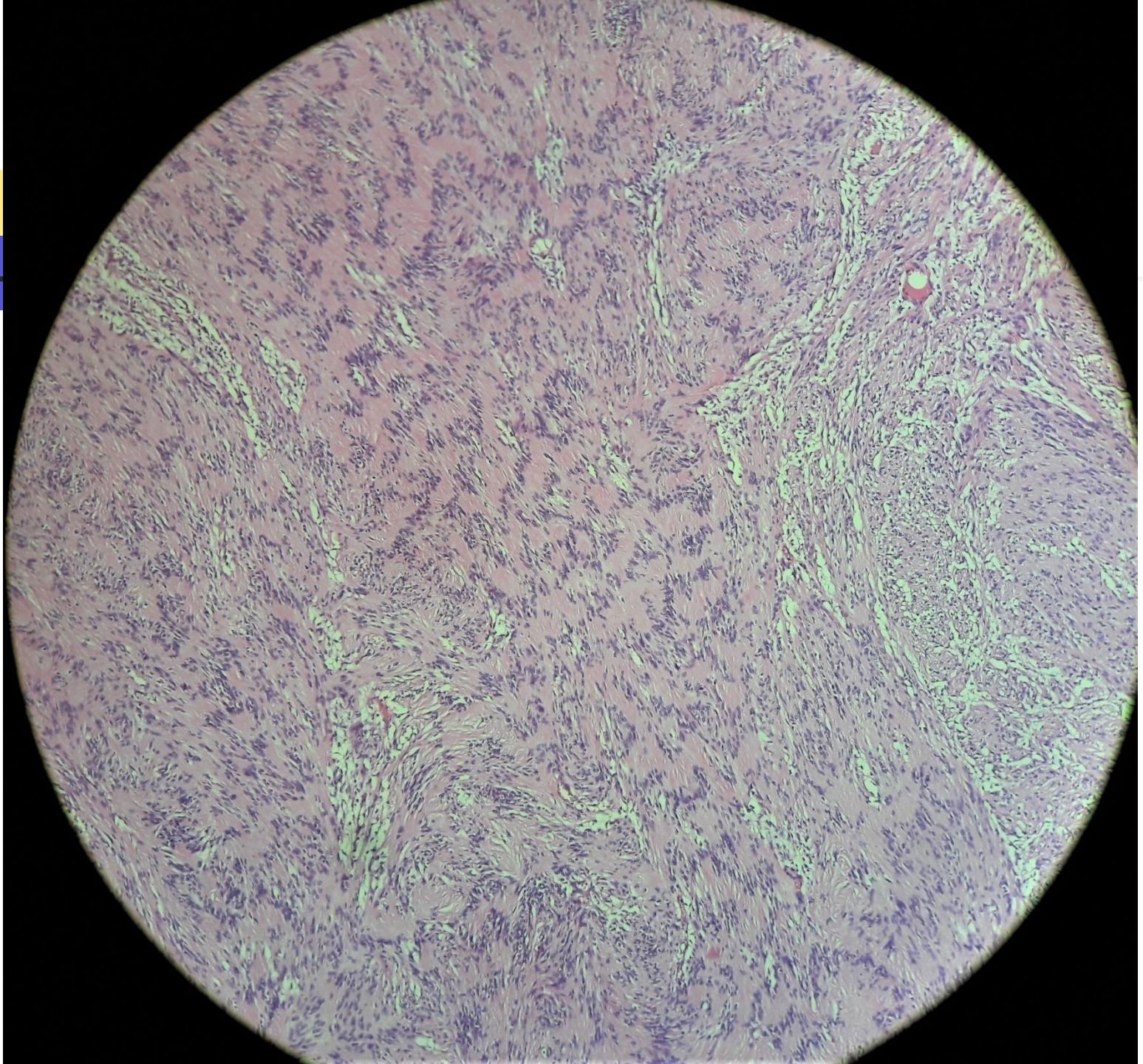
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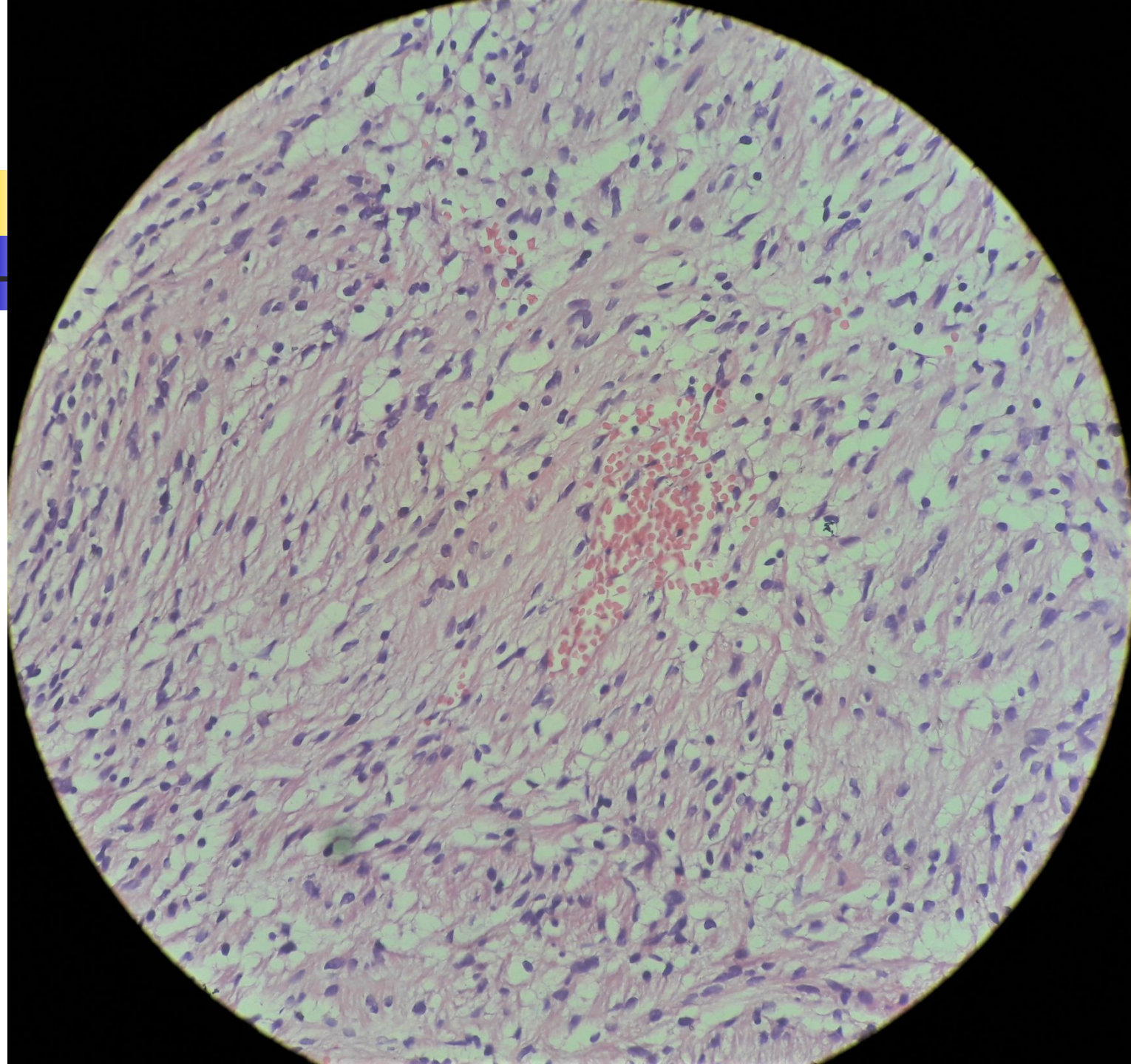
- Gross
- Microscopic
  - Antoni A and B
  - Verocay bodies
  - Morphology of Schwann cell
  - No axons
- EM
- IHC

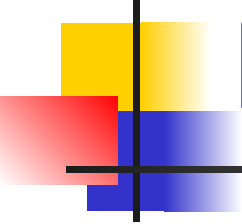








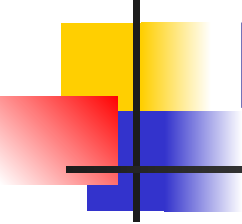




# Morphology

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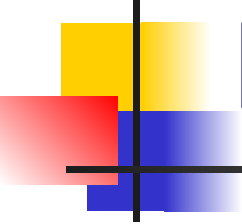
- Degenerative changes
- May recur locally
- Extremely rare malignant transformation



# Localization

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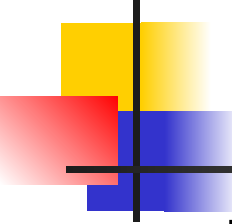
- Acoustic neuroma
- Within the dura, sensory nerves are preferred
  - Trigeminal nerve and dorsal roots
- Extradural
  - Association with large nerve trunks
  - Soft tissue without identifiable nerve



# Neurofibromas

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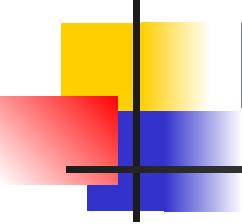
- More heterogenous composition than schwannoma
  - Schwann cells
  - Perineurial like cells
  - Fibroblasts
  - Mast cells
  - CD34+ spindle cells



# Neurofibromas

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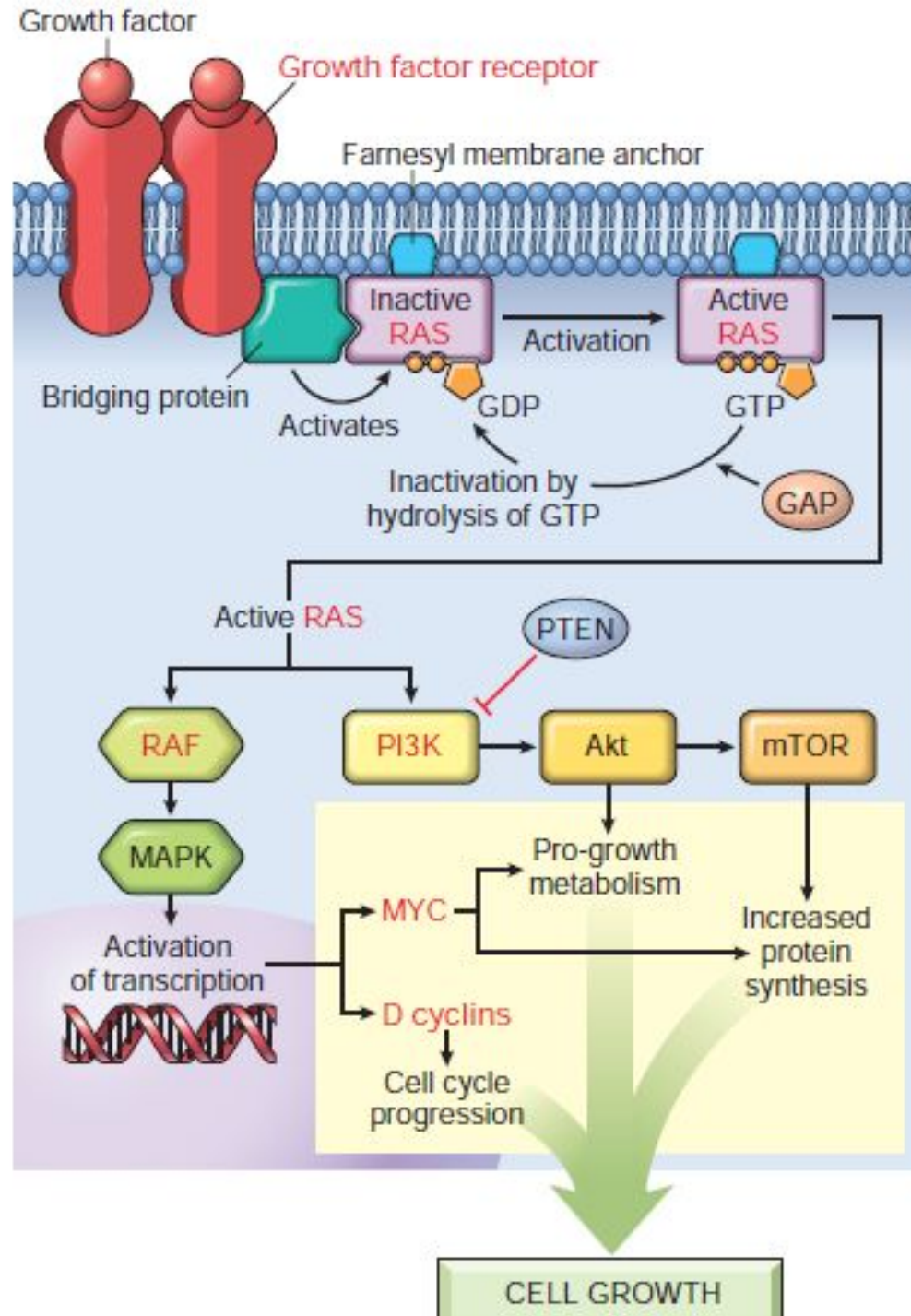
- Presentation
  - Sporadic
  - NF1 associated
- Types of growth pattern
  - Superficial cutaneous neurofibromas
    - Single or multiple
  - Diffuse neurofibromas
    - Plaque like
  - Plexiform neurofibroma

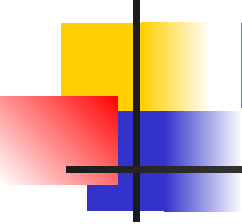


# Pathogenesis

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- Complete loss of NF1 in schwann cells ... neoplastic
- Role in carcinogenesis
- Haploinsufficiency for NF1 in other cells also may contribute to growth
  - Hypersensitive mast cells to KIT ligand produced by schwann cells
    - May be targeted by inhibitors of KIT RTK
  - Secreting factors stimulate schwann cell growth

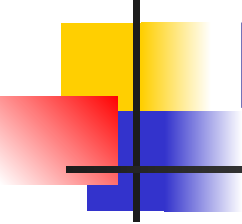




# Pathogenesis

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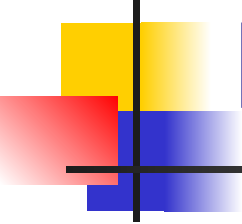
- Plexiform NFs and dermal NFs arise from different neural crest precursors
- Malignant transformation
  - Usually in plexiform NFs
  - Some times in diffuse type
  - The overall incidence of MPNST in NF1 patients 5-10%
  - Higher risk in those with large number of plexiform NFs and large deletions in the NF1 gene



# Morphology

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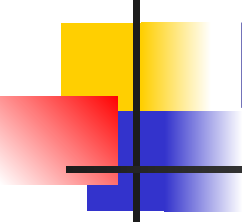
- Localized cutaneous neurofibroma
  - Gross
  - Localization
  - Hypocellular loose collagen
  - Cellular composition
  - Entrapment of adnexae



# Morphology

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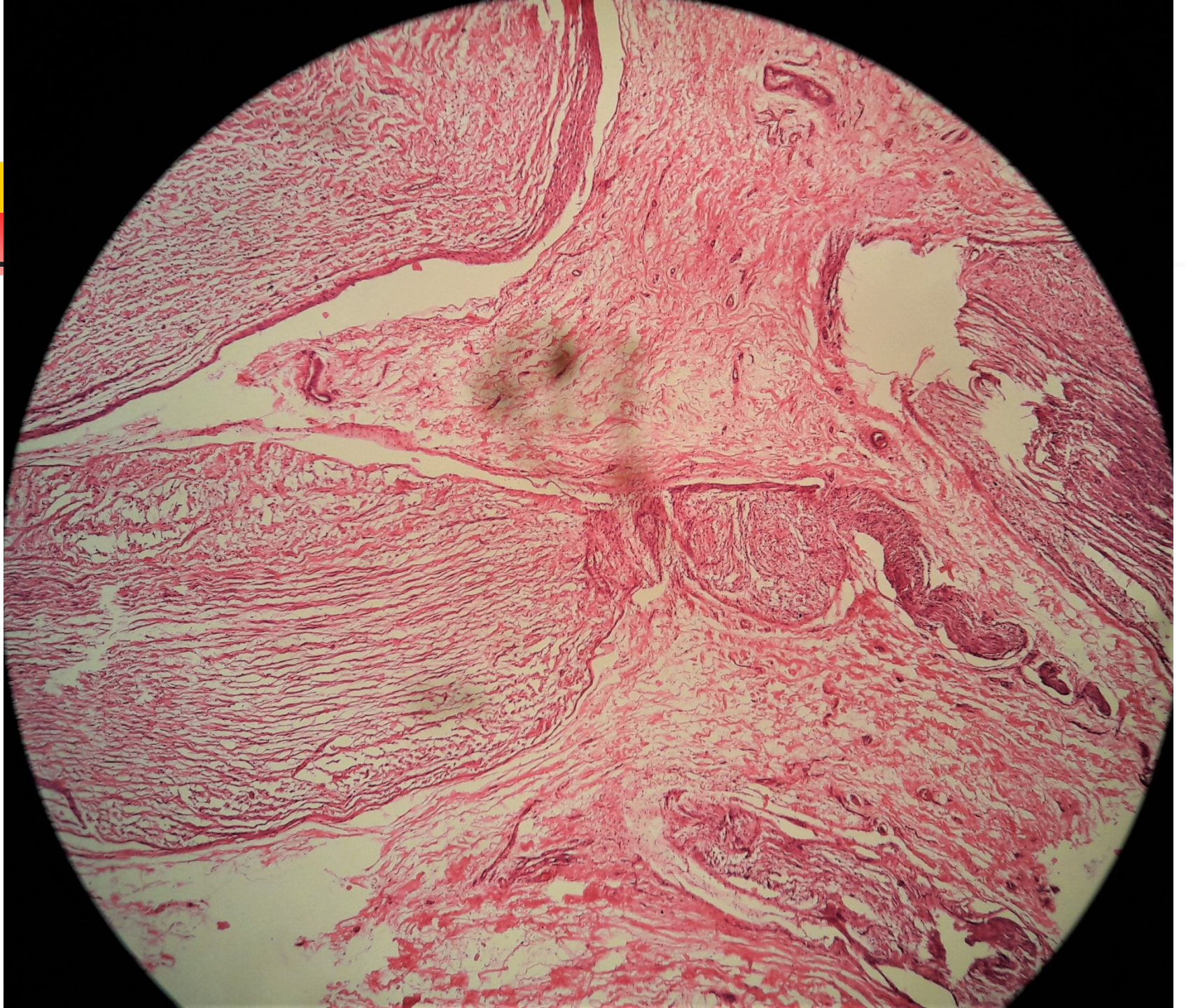
- Diffuse neurofibroma
  - Different pattern
  - Large sizes
  - Meissner corpuscles

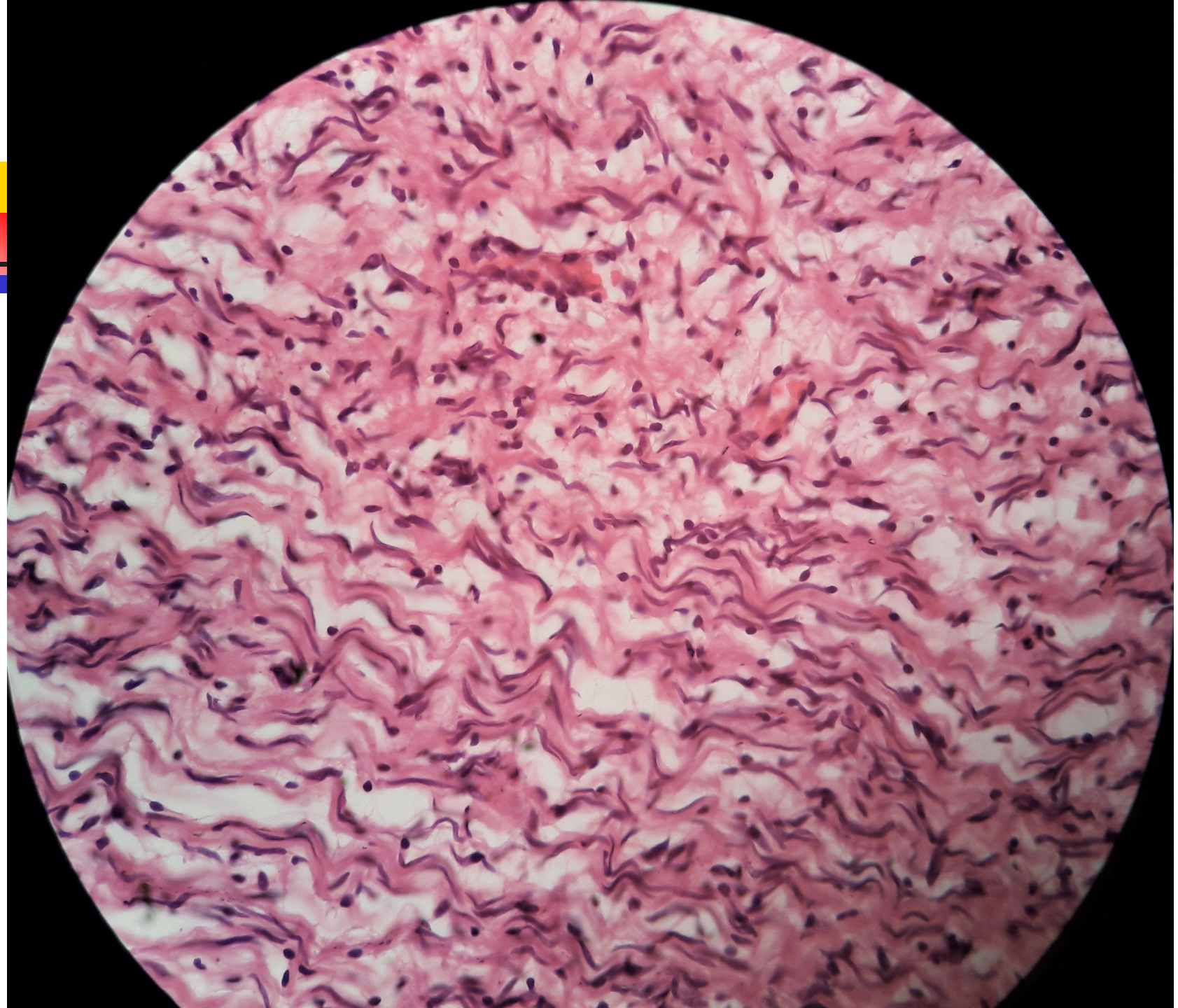


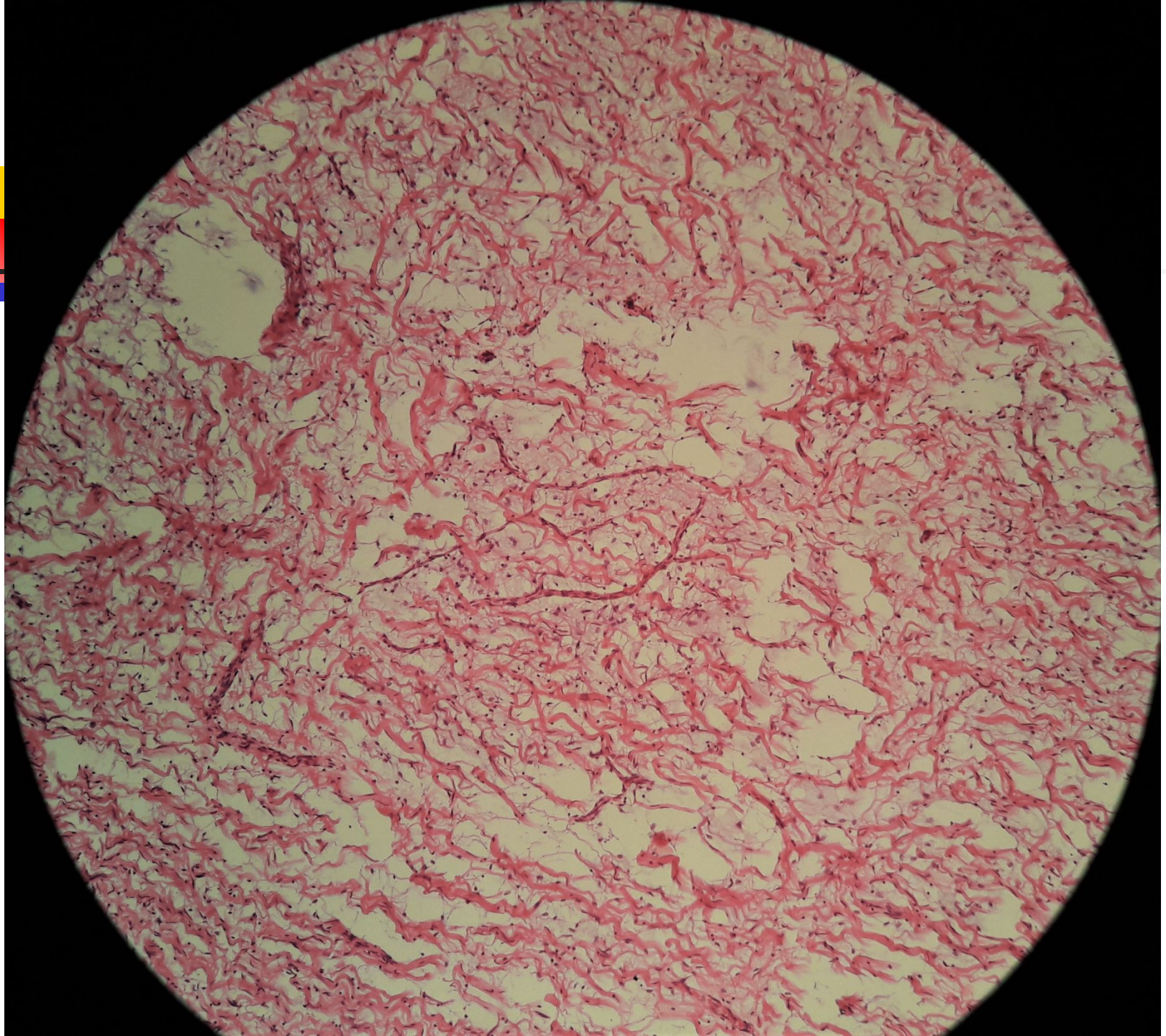
# Morphology

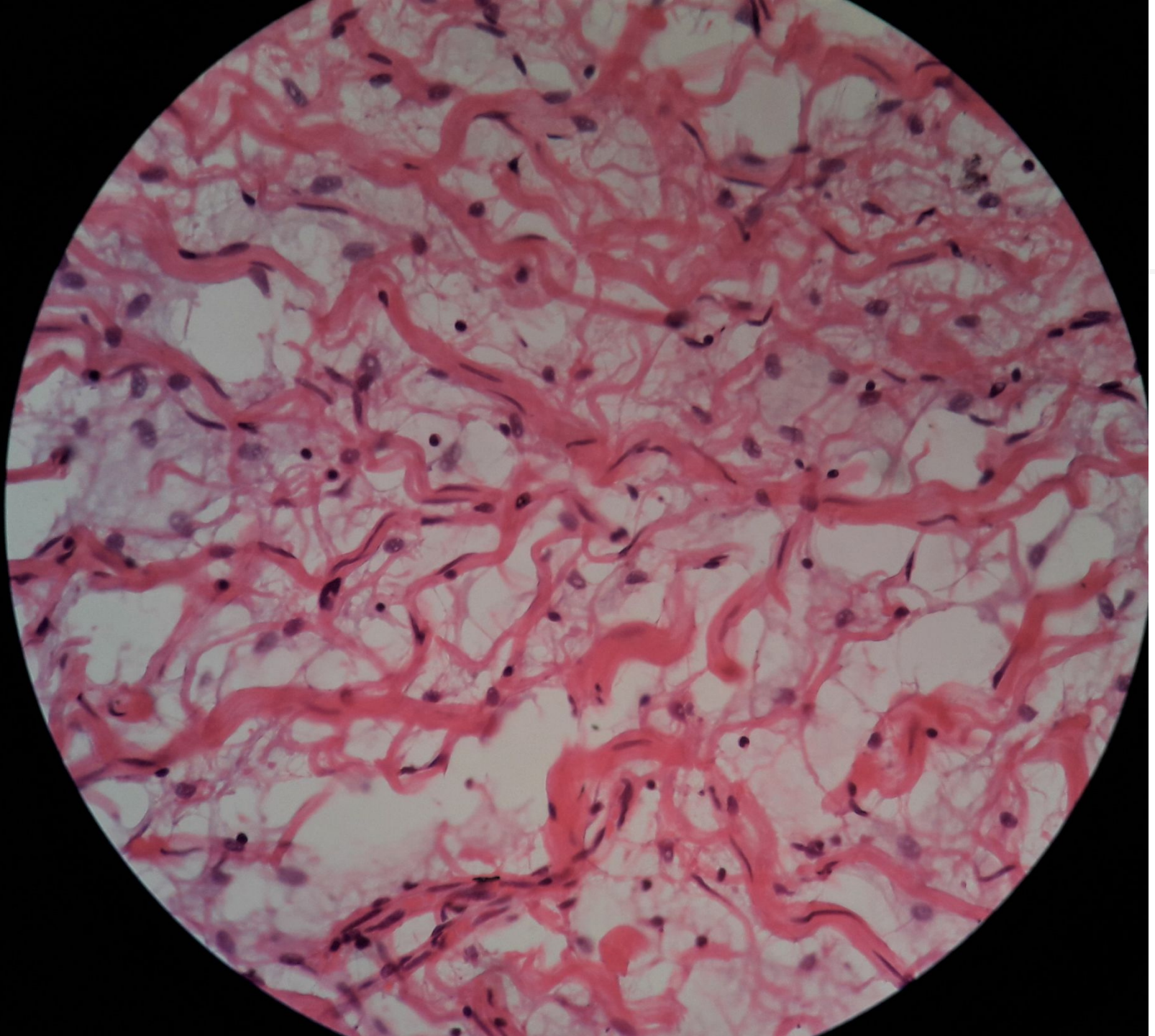
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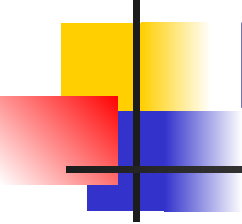
- Plexiform neurofibroma
  - Within and expand the nerve
  - Entrapping associated axons
  - Perineurial layer is preserved
  - Giving encapsulated appearance
  - “bag of worms” appearance
  - Myxoid/fibrous stroma
  - “shredded carrot” like collagen







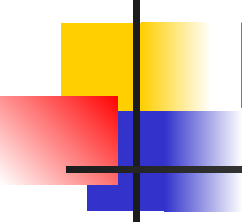




# MPNSTs

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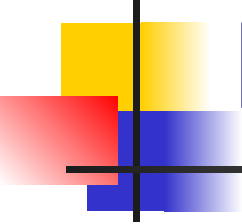
- Mostly 85% are high grade tumors
- 50% arise NF1 patients
  - Transformation from Plexiform NF
- de novo sporadic cases
- Most associated with large nerves in the chest, abdomen, pelvis, .....
- Complex chromosomal aberrations



# MPNSTs, morphology

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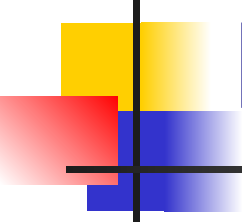
- Invasive, poorly demarcated
- Fascicles of spindle cells
- “Marbleized”, variation in cellularity
- Mitosis, necrosis and anaplasia
- Divergent differentiation
  - “Triton tumor”
- Clues to diagnosis
  - NF1, Relation to nerve, Preexisting neurofibroma



# Neurofibromatosis type I

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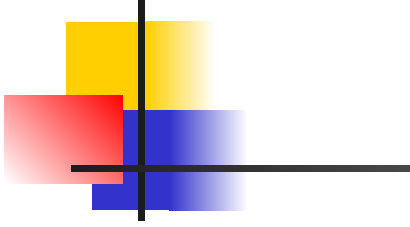
- Autosomal dominant
- 1/3000
- Non neoplastic manifestations
  - Intellectual disability
  - Seizures
  - Skeletal defects
  - Pigmented nodules of the iris "Lisch nodules"
  - "café au lait" spots

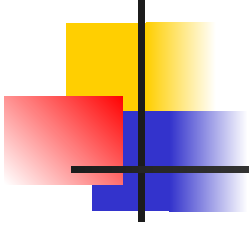


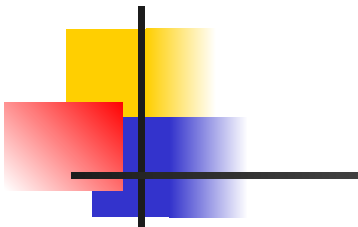
# Neurofibromatosis type 1

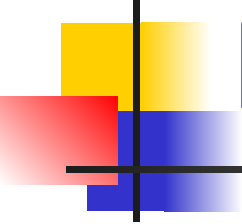
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- Tumors
  - NFs of all types
  - MPNSTs
  - Gliomas of optic nerve
  - Hamartomas
  - Pheo s





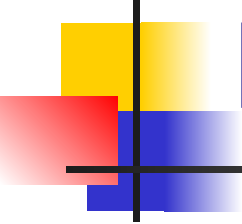




# Neurofibromatosis type 1

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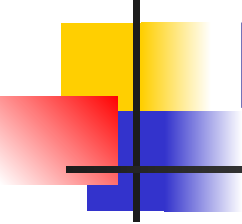
- Loss of function mutation of NF1 gene
  - 17q11.2
  - Mechanism of action
- High penetrance but variable expresivity
  - Some express subtle features
  - Some show disease restricted to certain body parts “mosaicism”
  - Some with severe disease
    - Large chromosomal deletions



# Neurofibromatosis type 2

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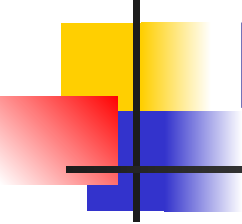
- Autosomal dominant
- NF2 gene on 22q12
  - Commonly mutated in sporadic meningiomas and schwannomas
  - “merlin”
  - Role
- 1/40000-50000



# Neurofibromatosis type 2

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- Tumors
  - Bilateral 8<sup>th</sup> nerve schwannomas
  - Multiple meningiomas and ependymomas of spinal cord
- Non neoplastic manifestations
  - Schwannosis
  - Meningioangiomatosis
  - Glial hamartia



# Neurofibromatosis type 2

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- Schwannomas in other syndromes
  - Schwannomatosis
  - Carney complex

