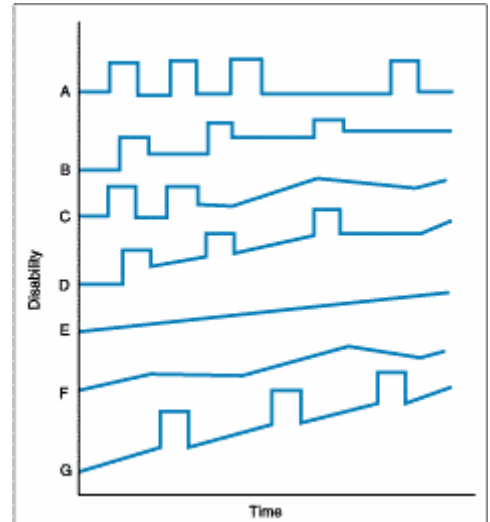


# Multiple Sclerosis

=.

## History of Presenting Illness: Initial symptoms in order of frequency

- Weakness
- Sensory Loss
- Paresthesia
- Optic Neuritis
- Diplopia
- Ataxia
- Vertigo
- Bladder urge incontinence
- Paroxysmal Symptoms (brief attacks of paraesthesia + spasm and tonic contraction)
- Lhermitte's sign (electric shock on neck flexion)
- Pain
- Dementia
- Visual loss
- Facial palsy
- Impotence



Clinical patterns of MS. A, B, relapsing-remitting; C, D, secondary progressive; E, F, primary progressive; G, progressive relapsing.

## Differential Diagnoses

Amyotrophic Lateral Sclerosis  
Bell Palsy  
Brain Abscess  
Guillain-Barre Syndrome  
HIV Infection and AIDS  
Lumbar (Intervertebral) Disk Disorders  
Neck Trauma  
Sarcoidosis  
Spinal Cord Infections

Spinal Cord Injuries  
Stroke, Hemorrhagic  
Stroke, Ischemic  
Subdural Hematoma  
Syphilis  
Systemic Lupus Erythematosus  
Tick-Borne Diseases, Lyme  
Transient Ischemic Attack  
Trigeminal Neuralgia

## Pertinent Findings on History

AIM is to exclude the diagnosis of every other disease on the list above; not easy

The review of systems should concentrate on the evidence of bladder, kidney, lung, or skin infection and irritative or obstructive bladder symptoms.

### Classic MS symptoms

- **Sensory loss** (ie, paresthesias) usually is an early complaint.
- **Motor** (eg, **muscle cramping** secondary to spasticity) spinal cord symptoms
- **autonomic** (eg, **bladder, bowel, sexual dysfunction**) spinal cord symptoms
- **Cerebellar symptoms** (eg, **Charcot triad of dysarthria, ataxia, tremor**) may occur.
- **fatigue** (which occurs in 70% of cases)
- **Dizziness**
- **Subjective difficulties with attention span, concentration, memory, and judgment** may be noted any time during the disease course.
- About 50% of patients with MS have impairment, usually mild, in information processing on neuropsychological testing.
- **Depression is common**, but euphoria is less common.
- Over the course of the disease, 5-10% of patients develop an overt psychiatric disorder (eg, manic depression, paranoia, major depression) or dementia.
- **Eye symptoms**, including diplopia on lateral gaze, occur in 33% of patients.
- **Trigeminal neuralgia** may occur.

### Family History:

Consider asking about ethnic background. The Norse cultures suffer most (except Eskimos, who are paradoxically immune.) Also, the risk seems to be associated entirely with childhood years spent in a temperate climate

**Optic neuritis** = the initial presentation of 15% of patients with MS.

**!! Fifty percent of all patients who present with ON have MS !!**

Isolated episodes of ON, even if they are recurrent, do not represent MS.

= Acute onset (minutes or hours) of

- **single eye visual blurring**,
- **decreased acuity** (ie, usually scotoma),
- **decreased color perception**,
- **discomfort of the moving eye**

**3 phenomena of optic neuritis:**

1. **Phosphenes:** flashes of light when you move your eyes
2. **Uhthoff phenomenon:** eye symptoms made worse by HEAT
3. **Pulfrich effect:** rate of transmission between the optic nerves are unequal, thus a sense of disorientation in traffic

**!! BILATERAL OPTIC NEURITIS IS RARE !!**

## **Findings on Examination**

---

**:focus on long white matter tracts:**

**Eye:Optic neuritis**

- **funduscopy** results are usually normal: UNLESS your pt is a chronic sufferer, in which case expect OPTIC NERVE ATROPHY: a pale and useless-looking optic disk  
*"The patient sees nothing and the doctor sees nothing."*
- **Light Reaction: afferent pupillary defect** (i.e cant see thus cant react) may be seen in the affected eye.
- **Visual acuity** usually is impaired (ie, subtle to total blindness).
- **internuclear ophthalmoplegia (INO)** = classic finding; a lesion in the median longitudinal fasciculus (MLF) resulting in
  - a weakness in adduction of the ipsilateral eye
  - nystagmus on abduction of the contralateral eye,
  - an incomplete or slow abduction of the ipsilateral eye upon lateral gaze,
  - complete preservation of convergence.
- abnormal pupillary responses,
- **acquired pendular nystagmus** : *rapid, small amplitude pendular oscillations of the eyes in the primary position resembling quivering jelly. Patients frequently complain of oscillopsia (subjective jumping/jerking of objects in the field of vision), which impairs visual performance*
- **loss of smooth eye pursuit.**

**YOU HAVE TO FIND ONE OF THESE SIGNS TO EVEN CONSIDER A DIAGNOSIS OF MS**

## **Spinal Cord Symptoms**

= indicative of upper motor neuron dysfunction, as long white matter highways is what the SC is all about

- **Sphincter paralysis** = bladder, bowel, and sexual dysautonomias.
- **Paralysis**
- **Spasticity**
- **hyperreflexia**
- **Decreased joint position and vibration sense**
- **Decreased pain and temperature (less common)**

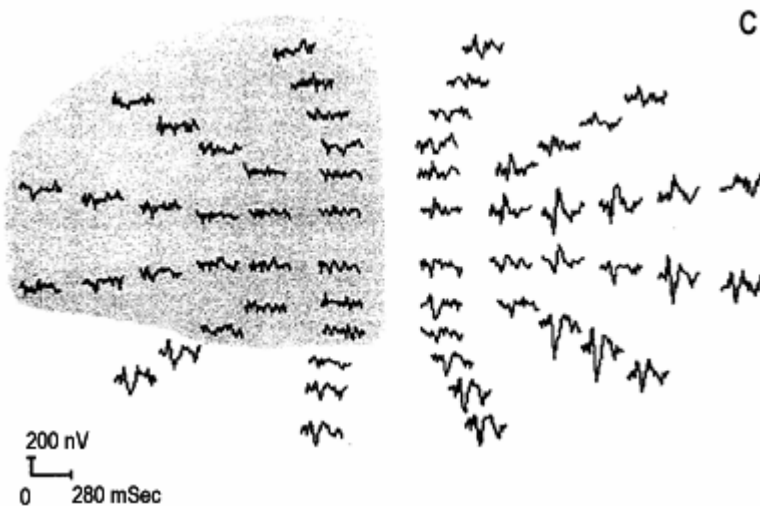
## **Cerebellar symptoms:**

- **Disequilibrium**,
- **truncal or limb ataxia**,
- **scanning (ie, monotonous) speech**,
- **intention tremor**,
- **saccadic dysmetria**

**Lhermitte sign:** Neck flexion results in an **electric shocklike feeling in the torso or extremities**

# Tests and Investigations

## Visually Evoked Potentials



The individual visual evoked potentials with the major scotoma superimposed (grey-shaded area).

Approximately 85% of clinically definite MS patients have abnormal VEPs.

SOMETHING VERY SIMILAR can be done for **somatic sensations** and **hearing**

## Full Blood Count

Should be **NORMAL**;

if white cells are increased, you may be looking at a case of meningitis or brain abscess

## VDRL: *Venereal Disease Research Laboratory test*

A blood test used to diagnose syphilis. Neurosyphilis has many manifestations, and can mimic MS in many ways; however it is not as common in civilised countries as it is in Calcutta or London

## ESR

Hopefully **NOT ELEVATED**

This is done to rule out infection and various nasty rare illnesses which cause raised ESR such as

- **Acute Disseminated Encephalomyelitis**

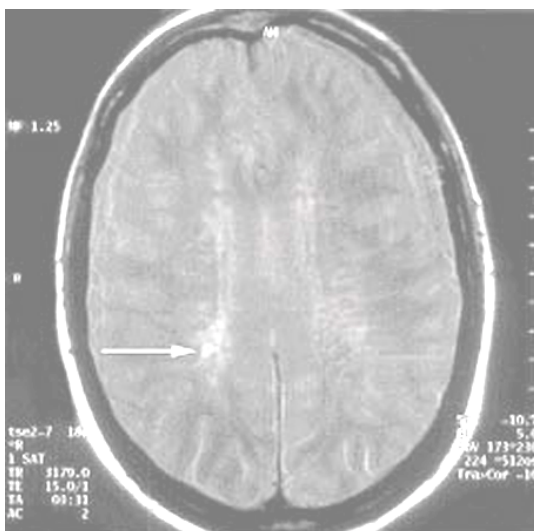
Immune-mediated encephalitis (IME), ADE, allergic treatment to prior infection, begins 1-2 weeks after event, occurs after viral infection or vaccination, affects corpus callosum and white matter (above and below tent), self-limited; steroids may help

- **Meningitis**

- **Wegener's granulomatosis**

(Sinuses, mucoperiosteal thickening, may destroy bone and cartilage, lungs, necrotizing granulomata, multiple round nodules (2 mm - 9 cm), may cavitate, kidneys, glomerulonephritis most likely to be necrosis of capillary tuft, generalised necrotizing vasculitis of arteries and veins, auto-immune: basement membrane, almost always involves lungs, M = F, 30-50 years of age, symptoms: cough, haemoptysis, fever, wt loss, multiple respecially infections, treatment: cytotoxins, immunosuppression)

## MRI with Gadolinium Contrast



- If there was a gold standard for MS diagnosis, MRI would be it.
- The MRI findings are *gadolinium-absorbing lesions over the white matter tracts* in the brain, where the BBB is broken and acute inflammation is taking place.
- This may not pick up small lesions during a period of remission, because some of them re-myelinate.

The signature lesions are the “**periventricular high signal areas**”, or “**Dawson’s Fingers**”

! Acute disseminated encephalitis may be radiographically indistinguishable from MS. **BEWARE!!**

## CSF:

### Immunochemistry

**selective increase in immunoglobulin G with oligoclonal bands;**

..and maybe elevated protein in acute phase

### Microscopy

Up to 50 mononuclear cells on cell count (lymphocytes dominate)

### Culture

Hopefully nothing; however this **excludes meningitis and encephalitis**

## How is this diagnosis made ?

**...BY EXCLUSION!!**

To call it MS, you must..

- Find **objective CNS abnormalities**, eg. **big scotoma**
- These **abnormalities are due to white matter tract destruction**, eg. *corticospinal tracts, dorsal column tracts, cerebellar pathways, medial longitudinal fasciculus or optic nerve problems*
- Must have at **least two sites** where this is occurring (four if you involve MRI)
- Symptoms must **last at least 1 day**, and **occur at least 1 month apart**
- **OR: 6 months of progressive decline with increased CSF IgG**
- That IgG has to be **OLIGOCLONAL with 2 or more bands**
- The patient must be between **15 and 60 years old**
- **After all that,**

**ITS MULTIPLE SCLEROSIS IF YOU CANT FIND A BETTER EXPLANATION**

## Disease Definition

*Multiple sclerosis (MS) is an idiopathic inflammatory demyelinating disease of the CNS.*

*MS is characterized by*

*(1) a relapsing-remitting or progressive course and*

*(2) a pathologic triad of **CNS** inflammation, demyelination, and gliosis (scarring).*

*Lesions of MS are classically said to be **disseminated** in time and space.*

## Management

### ACUTE:

Hit them with steroids right away if you suspect an acute lesion in progress:

**DRUG 'O' CHOICE: IV infusion Methylprednisolone 3-5days**

Mechanisms of action same as for Cortisol (but more potent (5x anti-inflammatory) and does not stimulate Na retention. *Decreases inflammation* by suppressing migration of polymorphonuclear leukocytes and reversing increased capillary permeability.

**NO LONG TERM BENEFIT** but **duration of attack is reduced**

### LONG TERM:

**Aim is to slow progression and delay onset of SUSTAINED PROGRESSION**

**DRUGS which do this include:**

- **INTERFERON BETA 1a**
- **INTERFERON BETA 1b**

IFNs have nasty side effects such as

- Injection site reactions;
- Flu-like symptoms;
- CNS disturbances incl. depression and suicidal ideation;
- Leucopenia;
- Menstrual disturbances
- Elevated hepatic enzymes;
- Hypersensitivity reactions;

- **COPAXONE (glatiramer acetate)**

**is practically the same except side-effects are nicer, eg. no menstrual disorders or depression.**

The mechanism is unknown, but it seems to decrease the frequency of relapses

- **MARIJUANA** : although patients report improvements in ataxia and spasticity, no objective improvement has been demonstrated by the narrow open trials, and the whole thing remains a medicolegal minefield.

## Prognosis

- 20-35% of Relapsing-Relapsing patients  
= complete or nearly complete recovery of acute exacerbation within **8 weeks**,
- **Optic Neuritis**: 90% = complete recovery of visual acuity within **8-12 weeks**.
- **BUT**: residual impairment of color vision and abnormal depth perception
- **Recurrence in either eye can be expected in 20-35% of ON patients**

In general, **patients who experience minimal neurologic impairment 5 years after the first symptoms are least likely to be severely disabled 10 to 15 years later**. By comparison, patients with persistent truncal ataxia, severe action tremor, or a disease course that is progressive from the onset are more likely to experience progression of disability.

**MS patients usually die from pyelonephritis and subsequent septicaemia (uncontrolled dysautonomia)**

Survival is typically 30 years; most patients will need help with walking after the first 15 years

## Epidemiology + Risk Factors

- **Twice as many females as males**
  - **Born further north = more risk**
    - *highest known prevalence (250 per 100,000) occurs in the Orkney islands, located north of the mainland of Scotland*
- incidence rises steadily from adolescence to age 35 and declines gradually thereafter (mean 20- 50)**

## Genetics

### Racial:

- prevalence of MS is higher in Caucasians

### Familial Aggregation

- **First-, second-, and third-degree relatives of patients with MS are at increased risk for the disease.**
- Siblings of affected individuals have a lifetime risk of ~5%,
- **familial aggregation is primarily determined by shared genetic, and not environmental, factors.**

### Twin Studies

Concordance **~30% in monozygotic twins**

**5% in dizygotic twins** (similar to the risk in nontwin siblings).

**Susceptibility is determined by multiple independent genetic loci (polygenic inheritance) each with a relatively small contribution to the overall risk.**

*The class II (HLA-D) region of the MHC is most strongly associated with MS, and susceptibility appears to result from the presence of the DR2 allele and its corresponding haplotype, defined by molecular criteria as DRB1\*1501, DQA1\*0102, DQB1\*0602. Other genetic regions implicated in MS susceptibility include loci on chromosomes 3, 5, 16, and 19.*

## Visual Field Testing possibly examinable, but hopefully forgettable

### Near and far point

Move an object along a ruler towards the eye until you can no longer see it in sharp focus. (this is the near point) Repeat, moving the object away. (far point)

Range of accommodation =  $1/d_n - 1/d_f$  [distance in metres; power in dioptres]

$d(n)$  is the near point distance;  $d(f)$  is the far point distance

**Myopia:** short sightedness (far point is too near)

**Emmetropia:** normal sightedness (far point vanishes in infinity, near point is quite near)

**Hyperopia:** long sightedness (near point too far)

**Presbyopia:** a result of reduced flexibility of the lens with increasing age

### Astigmatism

A simple test for astigmatism consists of **radiating black lines** that should appear equal in intensity and size to an emmetrope. If any of the lines are fuzzy or not sharp, astigmatism may be present

### Acuity

#### The Snellen chart:

Each symbol is of a size that can be read by a subject with normal acuity at some set distance from the eyes. Thus the "5 metre" line is read comfortably by a normal subject at 5 metres, and the "24 metre" line at 24 metres. These distances for each line are recorded on the chart.

$$\text{Visual acuity} = \frac{\text{testing distance (6m)}}{\text{distance at which smallest letter discriminated subtends } 5' \text{ (read from chart)}}$$

### Aperture effect

Small aperture is used to increase the quality of the image and to increase depth of focus.

BUT: brightness and contrast are lost.

THUS myopes may use a pinhole to see more clearly at a distance

### Colour vision tests: Ishihara and HRR

A **monochromat** (very rare indeed) will see no colour. Such a subject may be a:

*rod monochromat* - lacking all cones (see O. Sacks (1996) *The Island of the Colour-Blind*, Picador, Sydney). He or she is severely handicapped in bright lights (ie during the day time).

*red cone monochromat* - lacking all blue and green cones (cannot distinguish any differences in hue);

*green cone monochromat* - lacking red and blue cones (cannot distinguish any differences in hue);

*blue cone monochromat* - lacking red and green cones.

A **dichromat** has only two of the three cone types. Such subjects confuse colours that others distinguish with ease. The possibilities are that a subject may be a:

*protanope* - lacking red cones (1% of males, sexlinked);

*deutanope* - lacking green cones (2% of males; sexlinked);

*tritanope* - lacking blue cones (rare; not sexlinked; 1/10 000 of population).

A **trichromat** - the normal situation has 3 cone types.

In an **anomalous trichromat**, however, one of the cone types contains an abnormal pigment:

*protanomalous* - abnormal red pigment shifted towards green (2% of males; sexlinked);

*deuteranomalous* - abnormal green pigment shifted towards red (4% of males; sexlinked);

(tritanomalous has not been described).

### The HRR colour vision test: numerous plates of varying grades

Dotty symbols on dotty grey background; symbol only differs from background in colour.

(The dots help to break up the outline of the symbols, reducing non-colour cues to the subject.)

this test is very accurate and can describe the exact defect:

In succeeding plates, the saturation is reduced. As the differences between symbol and background are reduced it becomes progressively more difficult to recognise the symbols and anomalous trichromats fail to distinguish the symbols. Thus the HRR test not only differentiates between protanopes, deutanopes and tritanopes but can be used to measure the degree of anomalous trichromacy present.

### Ishihara test:

On a typical plate there is a number, formed of small dots, on a background of dots of a contrasting colour. The colours are chosen to be those commonly confused by dichromats. There is often a second number made out of dots of lesser contrast ignored by trichromats. A dichromat, lacking the greater colour contrast, selects the second number. (Many trichromats, especially if given time, can easily detect the background figure.) On other plates the subject is asked to trace a pathway.



## Estimating the size of the fovea

Shut one eye and fixate with the open eye on the central character (A). Note the furthest letters that can be seen distinctly. Don't move your eye!

e  
d  
c  
b  
e d c b A b c d e  
b  
c  
d  
e

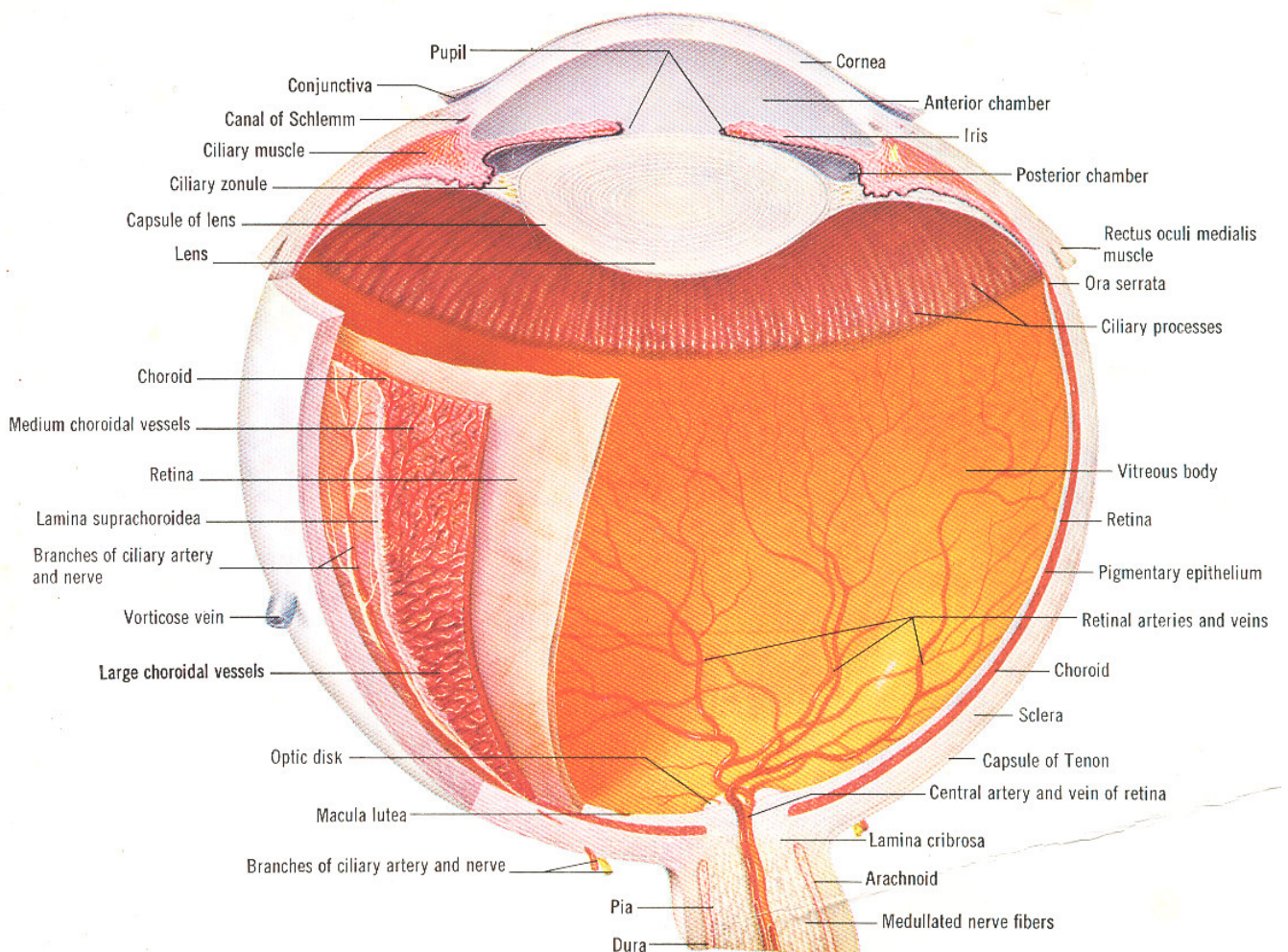
## Mapping the blind spot and the visual field

Everyone has one scotoma in each visual field. Its in the temporal region and can be found with a red hat pin.

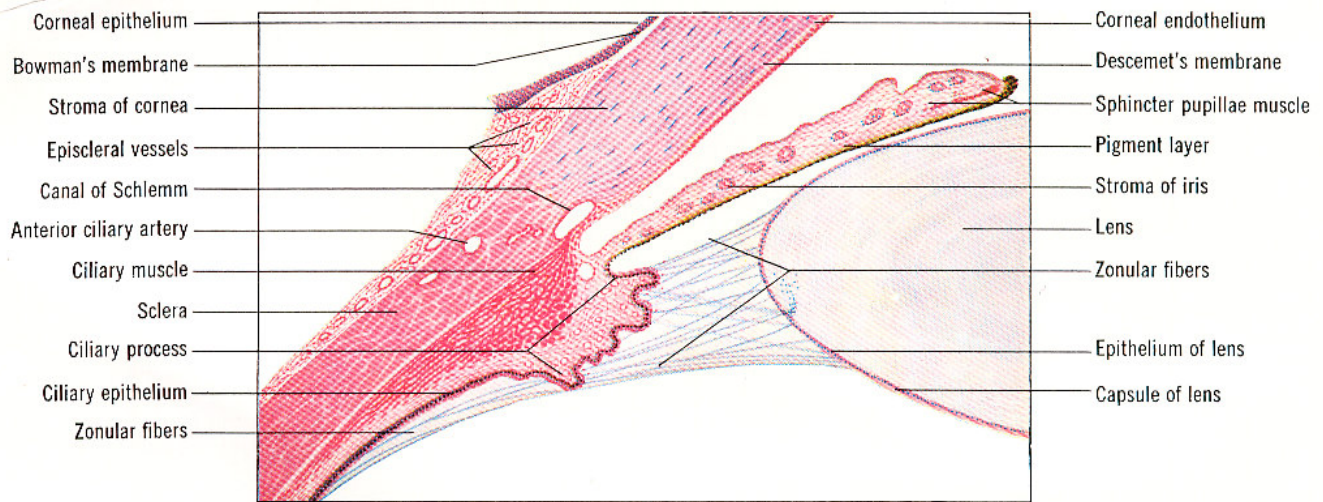
**The Bjerrum Screen** method is the most accurate, particularly for outlining scotomata. In the original version, the subject sits a fixed distance from a black screen, the observer positions a small white spot (usually on a long black staff) within the visual field. The subject indicates when they can see the spot. This method is used in class to demonstrate and measure the size of the blind spot. Nowadays, this method is often adapted by using a screen that contains an array of small bright lights that can be switched on and off within the field.

# Anatomy of the Eye

Pla1



HORIZONTAL SECTION OF EYEBALL—LOWER HALF



## CORNEA:

**Transparent, avascular, richly innervated by trigeminal nerve (ophthalmic branch)**

**5 layers:**

**-epithelium** (ant): allows **nutrient exchange between the tear film and cornea. (the only nutrient supply)**

**-stroma:** collagen fibrils have a uniform diameter and arranged very regularly in sheets inside a proteoglycan ground substance, allowing light to pass through.

**ONLY IF DEHYDRATED is the transparency maintained.**

**endothelium** (post): ionic pumps maintain corneal stromal dehydration

. Endothelial dysfunction therefore causes corneal oedema and opacity.

## Conjunctiva

**Thin mucus membrane overlying the sclera**

**reflected onto inner surface of eyelids** (tarsal conjunctiva).

**produces the mucin layer of the tear film**, which allows tears to spread over the eye surface.

## Sclera

**the white of the eye**

opens posteriorly for the optic nerve to exit (**lamina cribrosa**)= **sieve-like membrane to let axons through** the bricks and mortar of the eye; scleral strength makes it relatively un-gougeable

## Limbus

**Junction between the cornea and the sclera**

about 1.5mm wide.

Contains stem cells for corneal epithelium,

Contains the channels for aqueous humour circulation

## Angle of anterior chamber

**Junction of iris and cornea.** Viewed with a gonioscope.

**the internal scleral sulcus**, contains the **trabecular meshwork and Schlemms canal**.

**Function:** trabecular meshwork controls the outflow of aqueous, thus regulating the intraocular pressure.

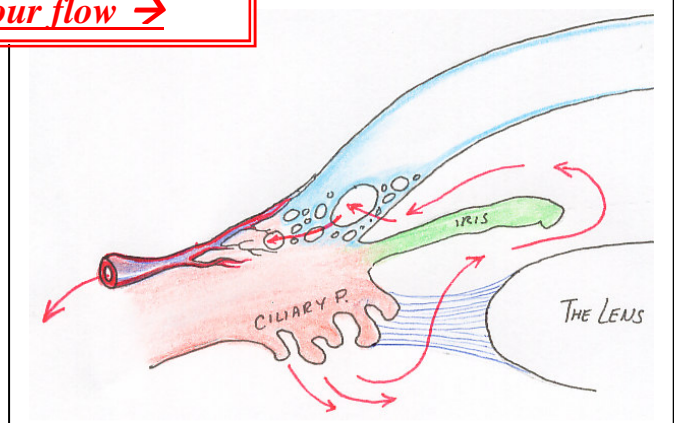
Raised intraocular pressure may be due to increased resistance to outflow.

### **← Path of aqueous humour flow →**

Produced by the ciliary processes of the ciliary body, **aqueous flows into the posterior chamber**

- passes in front of the lens
- through into the anterior chamber via the pupil
- exits at the angle of anterior chamber via the trabecular meshwork
- Schlemms canal
- collector channels
- aqueous veins
- cavernous sinus.

**•Function: Supplies cornea and lens with nutrients and metabolites.**





## Iris

- **Thin contractile structure with a central aperture-pupil.**
- **Divides space between cornea and lens into anterior and posterior chambers.**
- **Anterior surface-colour varies according to amount of pigment produced by melanocytes.**
- Divided by a circular ridge (collarette) into a central pupillary zone and a peripheral ciliary zone.
- Posterior surface-black in colour and contains radial contraction folds.
- Structure: i) stroma (ant) ii) anterior epithelial layer iii) posterior epithelial layer (pigmented).
- **Pupillary zone contains iris sphincter muscle - smooth muscle surrounding pupil**
- **Pupil constriction caused by sphincter contraction.**
- **Innervated by parasympathetic postganglionic fibres from CNIII which reach iris via the short ciliary nerves.**
- **Pupil dilation occurs when dilator pupillae muscle contracts- radiate from iris periphery to sphincter muscle.**
- **Innervated by sympathetic postganglionic fibres in long ciliary nerves.**
- **Function: controls amount of light entering eye**, thereby protecting the retina. Pupil also constricts in accommodation to reduce optical aberrations.

## Ciliary Body

Lies between the iris and choroid-approximately 6mm wide and triangular in cross section.  
Ciliary processes (about 70 in number) arise from the posterior surface and **produce aqueous humour**. Tight junctions between the epithelial cells of the processes form the **blood-aqueous-barrier**.  
Anterior surface has origin of fibres of suspensory ligament (zonules) which attaches the lens to the ciliary body.  
Important role in accommodation (near vision). Disruption of the zonules causes lens dislocation.  
Microanatomy: i) ciliary epithelium ii) stroma iii) smooth muscle, arranged in bundles.  
**Function: Production of aqueous and accommodation.** During accommodation the ciliary muscle contracts, the zonules relax and the **lens becomes more spherical**

## Choroid

**Thin brown layer beneath the sclera**, extending from optic nerve posteriorly to the ciliary body.  
Very vascular. Supplied by both the anterior and posterior ciliary arteries. Drained by vorticos veins.  
Inner surface attached to the retinal pigment epithelium.  
Microanatomy: 3 layers-vessel layer (outer), capillary layer, Bruchs membrane (inner).  
**Function: Supplies nutrients to the outer layers of the retina.**

## Lens

**Transparent, avascular structure suspended by elastic zonular plexus of fibres.**  
Grows throughout life.  
Becomes opaque with age (cataract).  
Microanatomy: i) anterior and posterior capsule enclosing ii) anterior epithelial cells and iii) lens fibres. Fibres formed after birth form the nucleus, which is surrounded by the cortex which consists of newer fibres.  
**Function: Refraction and accommodation.**  
Accommodation: When looking at a near object, the ciliary muscle contracts → zonule relaxes → lens becomes more convex. With age, lens becomes more dense and less pliable-ability to accommodate decreases with age (presbyopia).

## Vitreous

**Transparent hydrogel between lens and retina. Undergoes liquefaction with age.**  
Attached to ciliary body and peripheral lens anteriorly and posteriorly is attached to the retina at the ora serrata and optic disc.  
The hyaloid canal runs within vitreous between lens and retina-site of embryonic hyaloid artery.  
Microanatomy: **gel consisting mainly of water, fine collagen fibrils and occasional cells (hyalocytes).**  
**Function: Transmits light, and maintains shape of eye and helps keep lens and retina in position.**

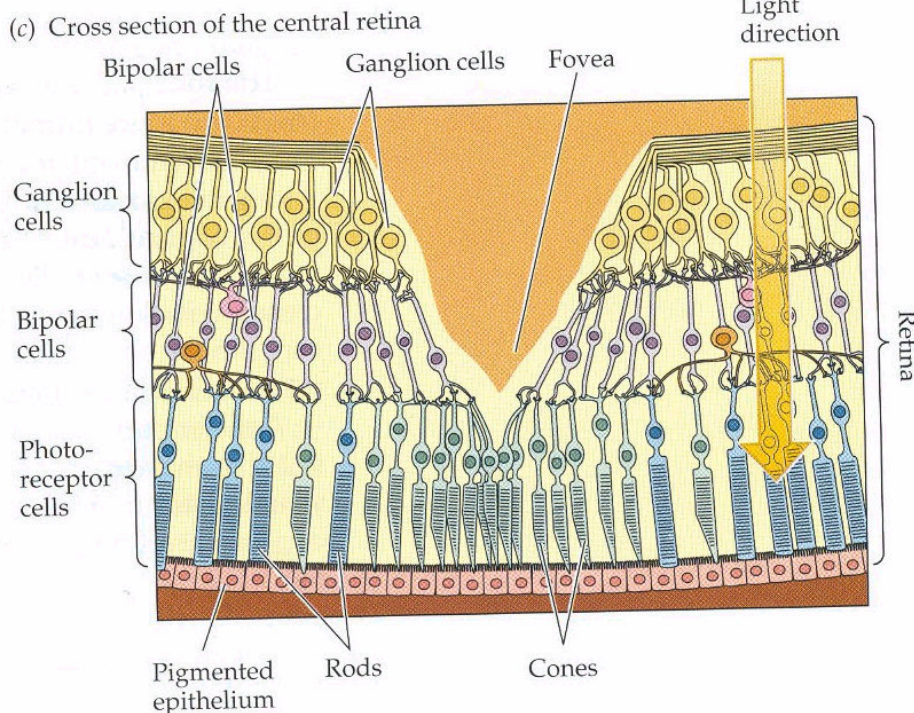
# Retina

Forms the 'film' in the camera. About 200 to 300 microns thick.

## PROVIDES FIRST LEVEL OF PROCESSING: Comparison of intensity levels.

Transparent so that light can reach the photoreceptors located on the outer surface of the retina.

Outer surface is in contact with the choroid, and the inner surface is in contact with the vitreous. Firmly attached at margins of optic disc and anteriorly at the ora serrata.



**Macula-oval area at the centre** of the posterior retina, site of most distinct vision. The fovea is the central depression in the middle of the macula.

- **The optic disc** is located 3mm medial to the macula, and is the exit site for the optic nerve and retinal vessels. On a visual field chart the optic disc is represented as the blind spot, as it contains no photoreceptors.

### Microanatomy:

- **outer layer of vascular pigment epithelium**

- **inner layers of neurons.** The RPE cells are joined by tight junctions, forming part of the retinal-blood-barrier.

- Light is received by the photoreceptors (outer layer),

- passed on to bipolar cells (first order neurons),

- then to ganglion cells (second order neurons, inner layer), the axons of which form the optic nerve,

and carry information to the lateral geniculate body. Horizontal, amacrine, and Muller cells are also present in the retina.

**The optic nerve** is formed by the convergence of retinal ganglion cells at the optic disc. Approximately 90% of its 1.2 to 1.3 million axons are derived from the fovea and macula (maculopapillary bundle).

Myelination of the optic nerve commences at the level of termination of the subarachnoid space (around the optic nerve) at the posterior limit of the lamina cribrosa.

## Physiology of Vision

**ROD signals are "low bandwidth" and get piggybacked onto the cone circuit**

### Cones: Short, Medium and Long wavelength;

- **Are depolarised at rest:** the "DARK CURRENT"
- This means  $\text{Na}^+$ ,  $\text{Ca}^{++}$  is moving in, and  $\text{K}^+$  is moving out (remaining in equilibrium of extra-vs-intercellular charge)
- A photon strikes the cone;
- **$\text{Na}^+$ ,  $\text{Ca}^{++}$  channels close: BUT  $\text{K}^+$  STILL LEAKS OUT**
- **Thus: cone cell is HYPERPOLARISED:**  
**This triggers Glutamate release at the Bipolar cell terminal**
  - There are about 10 bipolar cells servicing each cone ...and only 1 per every rod.
- There are **ON** and **OFF** sublaminae of bipolar cells;

### ON cells:

#### **INVERT the signal**

i.e if the cone is hyperpolarised (i.e very negative) the bipolar "ON" cell will **DEPOLARISE** and propagate its signal down the optic nerve

### OFF cells:

#### **CONSERVE the signal**

i.e if the cone is hyperpolarised (i.e very negative) the bipolar "OFF" cell will **REMAIN POLARISED** and consequently do nothing.

### FROM THE "ON" CELLS, the signal is passed to the GANGLION CELLS

There is a ganglion cell at every retinal area for every retinal processing function, eg. contrast, edge detection, motion and direction. CONTRAST is produced by the inhibition of neighbouring cells; thus an excited cell is surrounded by a ring of inhibited "edge" cells.



# Anatomy & Physiology of the Visual Pathways

## Physiological functions:

**Retina:** first place to process visual data  
**EDGE CONTRAST:** a ganglion cell will suppress its neighbours when it is excited on its own; thus there is CONTRAST

**Optic Nerve** does no processing of its own. Axons are myelinated after the optic nerve exits the eyeball at the back though the **Lamina Cribrosa**

**Optic Chiasm:** The **NASAL** retinal field **DECUSSATES** and the **TEMPORAL** does NOT. The Optic nerve sends fibres to the **HYPOTHALAMUS**

**Hypothalamus: Suprachiasmatic Nucleus**  
 Devoted to maintaining the **CIRCADIAN RHYTHMS**

**Optic Tract:** delivers all the information from the contralateral visual field to the LG.

**Superior Colliculus** of midbrain = receives fibres before the lateral; geniculate nucleus; involved in **MOTOR AVOIDANCE** i.e incoming missiles, plus **SACCHADES** (for smooth pursuit) and glancing at an unexpected touch, i.e attention focus

**Pulvinar Nucleus** of Thalamus is involved in **focussing attention and prioritising eye movements**; it projects to the visual assoc. areas

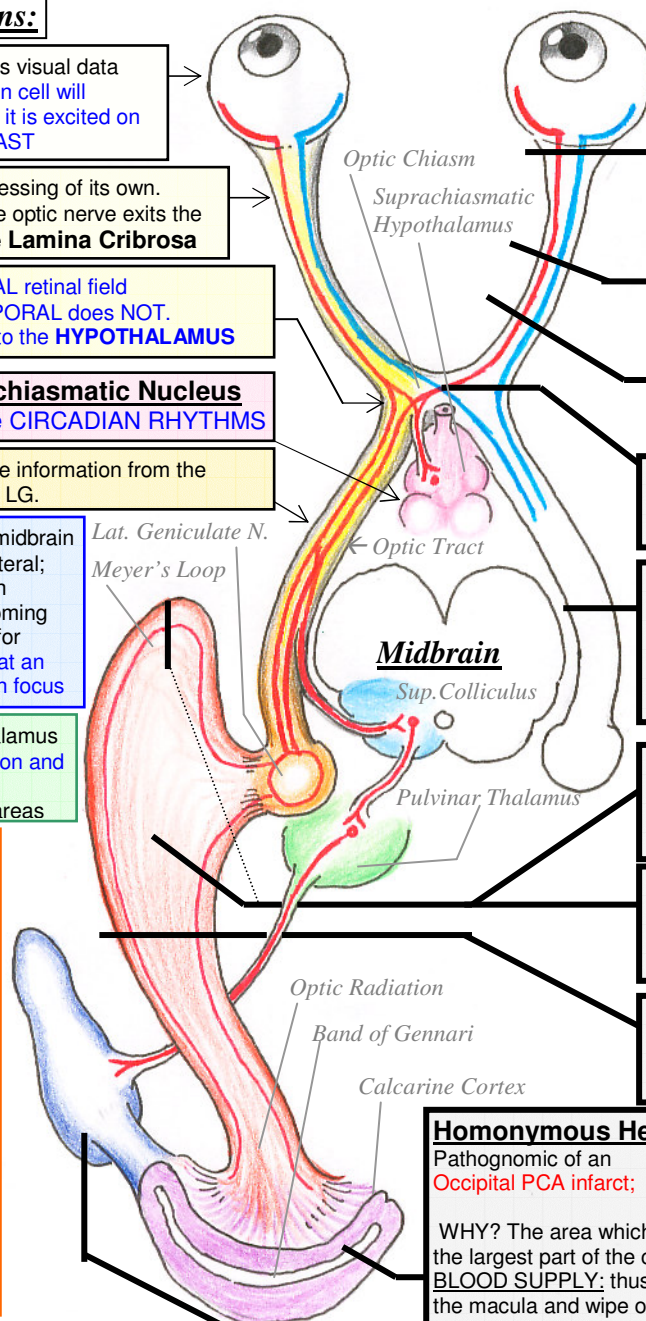
**Lateral Geniculate Nucleus** is the **FIRST PLACE** where the is accurate topographical representation of what the retina sees. PLUS L.G. also sorts function streams, i.e sorts the colour data from edge detection data, etc; PLUS L.G sorts data from each eye into its separate stream.

**!! VERY IMPORTANT!!**  
 Both eyes' images must be superimposed for **"REGISTRATION"** to happen, i.e depth perception- the inference of where the object is in space.

**Meyer's Loop**=fibres to the calcarine cortex curve around the lateral wall of the lateral ventricle, forming a broad sheet which sweeps across, covering much of the post. and inf. horns  
 INF VIS. FIELD = the fibres furthest → parietal  
 SUP VIS FIELD = the fibres furthest temporally  
 MACULA = the broad central area

**CALCARINE CORTEX: primary visual cortex**  
 First real **ANALYSIS** of visual information; the cortex contains **neurons which respond to various features of the image**; the neurons respond most strongly to edges of a particular orientation. This yields a **decomposition of the image according to its edges**. NOT SOMETHING YER BORN WITH: these features develop in infancy; ref. them kittens who were kept in the dark from birth and went blind despite having healthy eyes.

**SECONDARY VISUAL ASSOCIATION CORTEX:**  
**SEPARATION INTO COMPUTATIONAL STREAMS:**  
**Where is it?"** stream proceeds from the superior occipital lobe through the middle temporal gyrus to the parietal lobe. This stream places objects in space and detects whether they are moving, relative to their background or to other objects, or whether the background itself is moving.  
 = **ORIENTATION**  
**"What is it?"** stream proceeds through the inferior occipital to the inferior temporal lobe. **RECOGNITION** of all the separate objects, faces, and people, which or whom we are able to recognize. **COLOUR** information is extracted nearby in the V4 area (temporo-occipital)



## their LESIONS

and the Commonest Causes thereof

**Big Blind Spot**  
 Optic nerve head enlargement, eg. via **papilloedema**

**Tunnel Vision →**  
 Concentric diminution  
**Glaucoma, papilloedema and syphilis**

**Central Scotoma**  
 Internal optic nerve destruction, eg. **optic neuritis**

**Unilateral Blindness**  
 Total loss of one field:  
**Tumour, retinal artery infarct, Trauma**

**Bitemporal Hemianopia**  
 Loss of fields which cross over in the chiasm: **Pituitary Tumour, trauma**

**Homonymous Hemianopia**  
 Loss of one side of perception  
 Lesion is post-chiasm and could be anywhere, until the lat. geniculate  
 eg. **MCA infarct, tumour, Aneurism post-chiasm**

**Superior Quadrantinopia**  
**TEMPORAL LOBE LESION**  
**MCA lacunar infarct in penetrating arteries, tumour...**

**Inferior Quadrantinopia**  
**PARIENTAL LOBE LESION**  
**MCA lacunar infarct in penetrating arteries, tumour...**

**Homonymous Hemianopia**  
 Loss of one side of perception  
**MCA infarct or tumour**

**Homonymous Hemianopia with Macular Sparing**  
 Pathognomic of an **Occipital PCA infarct**;

WHY? The area which process information from the **MACULA** is the largest part of the calcarine (primary visual) cortex has a **DUAL BLOOD SUPPLY**; thus any infarct here will more than likely spare the macula and wipe out everything else.

**SYMPTOMS ARE STRANGE: "Blind Sighted"**

These patients are unable to process visual information, but still have **normal circadian rhythms** (the supra-chiasmatic hypothalamic connection is spared) and, oddly they **will avoid incoming projectiles** because the superior colliculus is still processing and transmitting "threat-identification" movement and attention-focussing information.

## SECONDARY VISUAL ASSOCIATION AREA:

**V2 to V5**

**LESIONS HERE = NO LOSS OF VISUAL FIELD: Much Worse!**

**Loss of processing:**

**V2 OR V3 INFARCT:** (posteriormost, next to the calcarine sulcus (V1)= **LOSS OF ORIENTATION + Mental Rotation**

**V4 INFARCT:** = Loss of **COLOUR** in vision, → monochrome

**V5 INFARCT:** = Loss of **MOVEMENT** detection, "photographic" vision where only still frames are perceived

The optic nerve contains about 1.3 million axons of ganglion cells.

**Most of them (over 90%) project to the lateral geniculate nucleus (LGN) in the thalamus, a smaller portion projects to other subcortical visual centres.**

### Partial decussation :

- axons from the nasal half of each retina cross over at the optic chiasm to innervate the contralateral half of the brain,
- axons from the temporal half of each retina innervate the same (ipsilateral) side of the brain.
- **THUS: right visual hemifield is represented in the left optic tract, and the left visual field is represented in the right optic tract.**

### The lateral geniculate nucleus (LGN)

- is organised into a number of neural layers.
- Each layer receives input from one eye.
- Each layer is **retinotopically organised**, i.e. neighbouring retinal ganglion cells project to neighbouring cells in the LGN.
- **Each LGN thus contains a "map" of the contralateral visual hemifield.**
- There are two divisions of the LGN based on cell size:  
**parvocellular and magnocellular.**
- These LGN divisions receive input from different types of retinal ganglion cells, and form parts of two parallel pathways.

**Parvocellular layer = colour and spatial detail of objects in the visual field,  
magnocellular cells = movement and the borders between different objects.**

**The axons of cells in the LGN form the optic radiation, and project to layer IVc of primary visual cortex in the occipital lobe.**

The primary visual cortex (**also called striate cortex, area V1 or area 17**)

- located along the calcarine fissure in the occipital lobes
- receives its main input the dorsal lateral geniculate nucleus (LGNd).
- The axons of the LGNd cells form the optic radiation.
- The LGNd axons terminate mainly in layer 4.

**The projections from the parvocellular layers (colour + spatial) of the LGNd terminate mainly in sublayers 4a and 4cb**

- projections from the magnocellular (movement and borders) layers terminate mainly in layer 4ca.

### AT THE CORTEX:

cells here form a number of distinct layers parallel to the pial surface.

Plus there are bands (stria) of myelinated fibres oriented parallel to the pial surface. This band of fibres is called **stria of Gennari**.

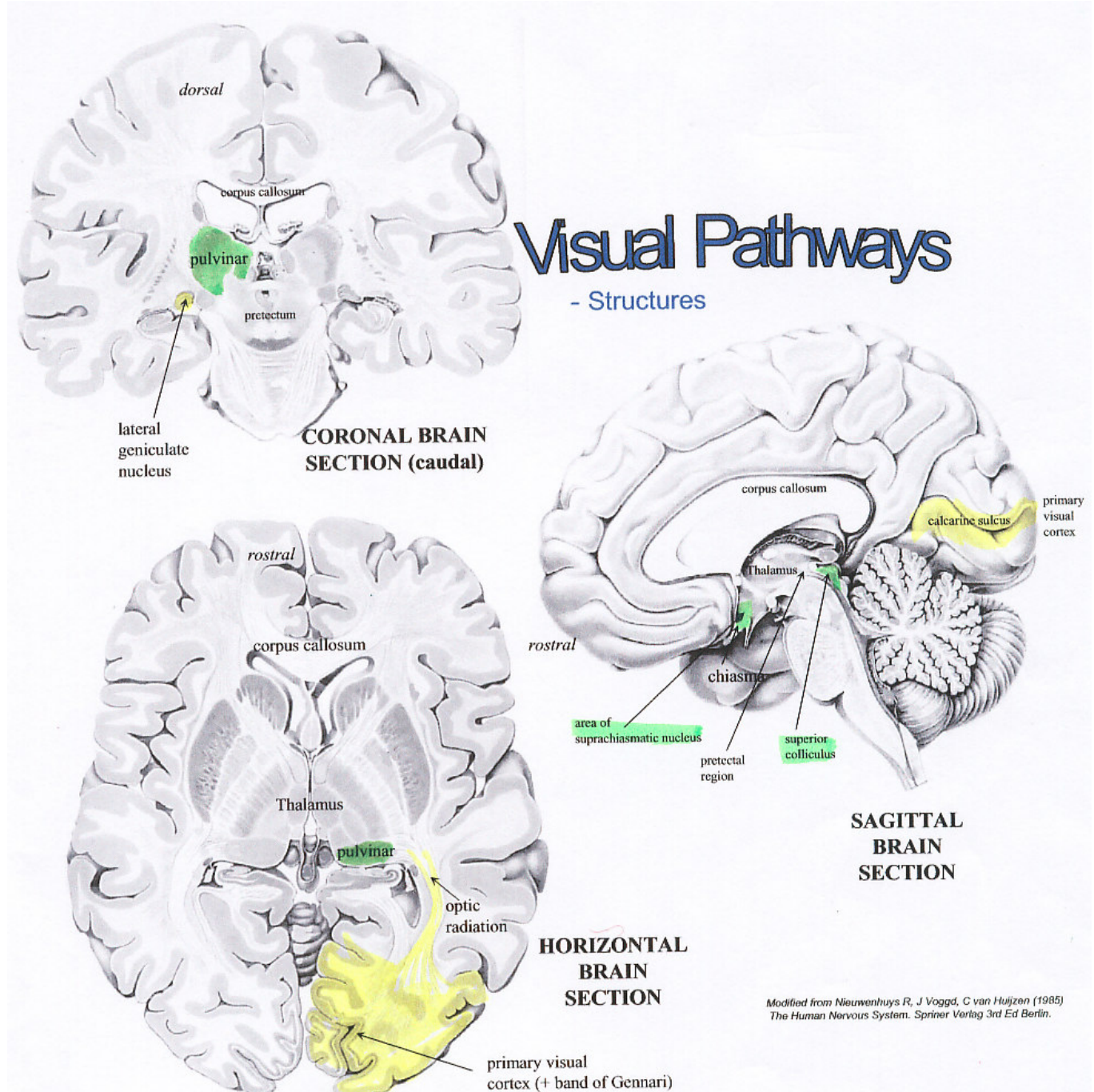
- The striate cortex, like the LGNd is topographically organized
- **The parts of the retinae with the highest density of cones (fovea centralis) is represented at the posterior tip of the occipital lobe.**
- the upper contralateral nasal and the upper ipsilateral temporal retinae (lower contralateral visual hemifield) are represented at the medial aspect of the occipital lobe at the upper lip of the calcarine sulcus,
- the lower retinae both the contralateral nasal and the ipsilateral temporal (upper contralateral visual hemifield) are represented on the medial aspect of the occipital lobe in the lower lip of the calcarine sulcus.

**Most of the cortical neurones (excluding those in layer 4) are binocular:** they receive input from both the ipsilateral and contralateral eye.

The receptive field properties of cortical cells also different to those of the dLGN cells. **Most cortical cells are selective for the orientation and direction of movement of objects in the visual field.** In a way, the image which is projected from the retina is 'analysed' by the cortex so that the borders between objects and their distance from the viewer represented by the pattern of responses in distinct sets of cortical cells.



## VISUAL CORTEX : GROSS ANATOMY



The primary visual cortices send "feedforward" projections to several extrastriate visual areas such as areas V2, V3 and V5 (called also a middle temporal area or area MT). The exact functions of these "association" areas is not completely understood, but they probably act as "processing" modules to enable objects to be recognised and acted upon. Imagine an apple falling from a tree. The retina and subcortical visual structures pick up the image of the apple and allow the eyes to follow its downward path. Cells in primary visual cortex analyse the borders of the object (round) and its colour (red, or green if it's a Granny Smith). The association visual areas calculate the speed of the apple, and are responsible for our ability to recognise it as an apple. Destruction of the striate cortex (or part of it) results in an apparent scotoma (blindness) in the part of the visual field represented in that part of the striate cortex which has been damaged. By contrast, destruction of association areas leads to higher order deficits, such as the inability to recognise faces. Furthermore, presumably due to the fact that some of the visual inputs to the extrastriate cortices bypasses the striate cortex, as long as the extrastriate cortices are not damaged a person with damaged striate cortices retains some visual functions, such as eye and hand movements towards high contrast visual stimuli. These residual visual capabilities are usually described by a paradoxical term "Blindsight".

## **Behavioural science: Chronic Illness and the Family**

*"I know you're sick. It makes me scream with pain Remembering the way you were and are". (From "Wife's needs" by George MacBeth, 1992. MacBeth was dying of motor neurone disease and was being cared for by his wife when he wrote this poem.)*

Chronic illness, especially if it causes significant disability, affects not just the patient, but the whole family. The experience of developing severe chronic illness has been likened to that of **finding an elephant in the living room.**

- There may be no obvious reason why the elephant had turned up in this house rather than in the house next door.
- The presence of the elephant is most inconvenient, explanations must be offered to friends and relatives, the whole household is affected by it.
- The elephant needs considerable care and attention,
- The elephant alters the way in which household members act and interact, but nobody has the power to make it go away.

**Anger, guilt, resentment, and other unpleasant emotions may all be experienced, occasionally may find an outlet in allegations against the doctor**  
eg. **"If only the doctor had made the diagnosis earlier, dad wouldn't be as ill as this now".**

Alternatively, such feelings may be displaced **onto other members of the family.**

This may be one reason why chronic, debilitating illness can lead to significant disharmony of marital and other relationships

**A substantial proportion of people with chronic illness and disability become clinically depressed**  
and other members of the family may also develop depressive illness.

While attention is being focussed on one member of the family, **other members may not seek advice about significant symptoms of their own.** The doctor caring for a family with a chronically sick member should always bear in mind the possibility of significant physical and/or psychological illness in other family members.

## **BIOPSYCHOSOCIAL treatment of Chronic Neurological Disability**

### **Patient interview**

- **Dealing with uncertainty and the trap of "premature closure"**  
uncertain neurological diagnoses make it difficult to plan for the future.  
The difficulty of dealing with uncertainty prompts doctors toward "premature closure"  
- ie. trying to develop more certainty than there really is.
- **Emotional responses to young adult patients**  
Doctors sometimes adopt evasive and placatory ways of communicating.  
They may offer false or inappropriate reassurances which create mistrust or compromise compliance with treatment.  
This may be more likely to happen when a patient is around the same age as the doctor.

## **The Public Health Impact of Blindness: according to the WHO**

Today, there is an estimated **180 million people worldwide who are visually disabled**

Of these, between 40 and 45 million persons are blind and, by definition, cannot walk about unaided

**9 out of 10 of the world's blind live in DEVELOPING COUNTRIES**

around 60% of them reside in sub-Saharan Africa, China and India.

Approximately 50% of the world's blind suffer from cataract. The majority of the remaining persons are blind from conditions that include, among others, glaucoma, trachoma, onchocerciasis (also known as river blindness) and different conditions of childhood blindness

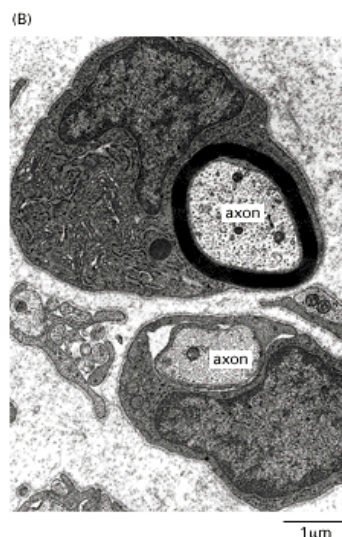
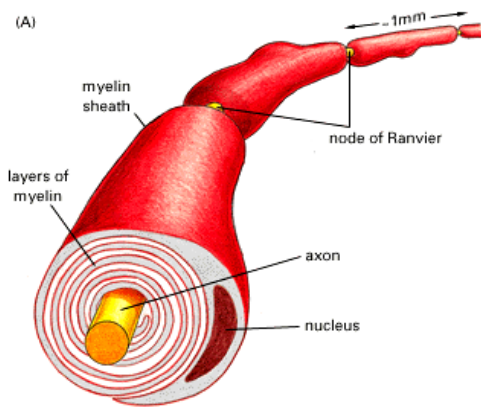
**According to WHO estimates, about 80% of global blindness is *avoidable***

VISION 2020 will allow the international community to fight avoidable blindness through:

- disease prevention and control;
- training of personnel;
- strengthening the existing eye care infrastructure;
- use of appropriate and affordable technology;
- and mobilization of resources.

**VISION 2020** is based on the concept of a broad coalition of all international, nongovernmental and private organizations, which collaborate with WHO in the prevention of blindness and eye care delivery. They share the objective of eliminating avoidable blindness as a public health problem by the year 2020, provided adequate resources are available. These organizations will also jointly work to mitigate the implications of blindness in developmental, social, economic and quality-of-life terms.

# Cell biology: the Magical Properties of Myelin



- The axons of many vertebrate neurons are insulated by a myelin sheath, which greatly increases the rate at which an axon can conduct an action potential.
- The importance of myelination is dramatically demonstrated by the *multiple sclerosis*, in which myelin sheaths in some regions of the central nervous system are destroyed by an unknown mechanism;
- Where this happens, the propagation of nerve impulses is greatly slowed, often with devastating neurological consequences.

Because action potential conduction requires passive and active flow of current, the rate of action potential propagation is determined by both of these phenomena.

One way of improving passive current flow is to increase the diameter of an axon, which effectively decreases the internal resistance to passive current flow. The consequent increase in action potential conduction velocity presumably explains why giant axons evolved in invertebrates such as squid, and why rapidly conducting axons in all animals tend to be larger than slowly conducting ones.

***If nerves were not myelinated and equivalent conduction velocities were maintained, the human spinal cord would need to be as large as a good-sized tree trunk***

**glial cells – nerves**

**central nervous system.**

**early spaced *nodes of Ranvier*,  
in the axon are concentrated.**

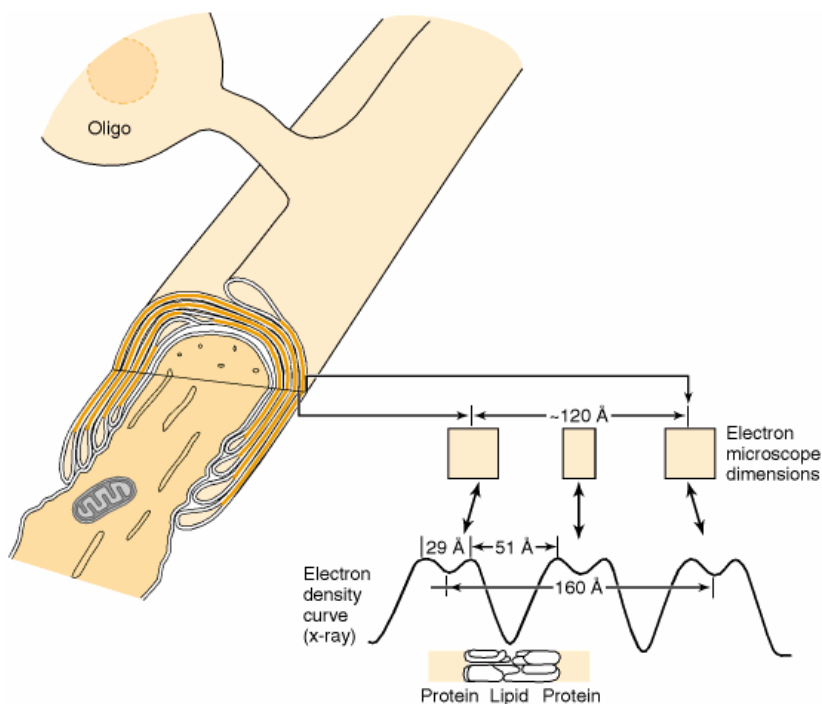
es along a  
om node to node,  
y conduction.

main advantages:

ster

onserved

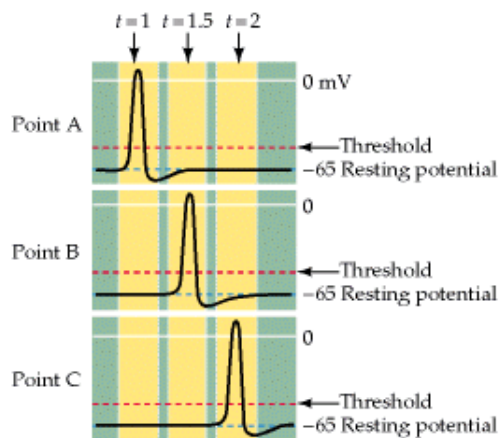
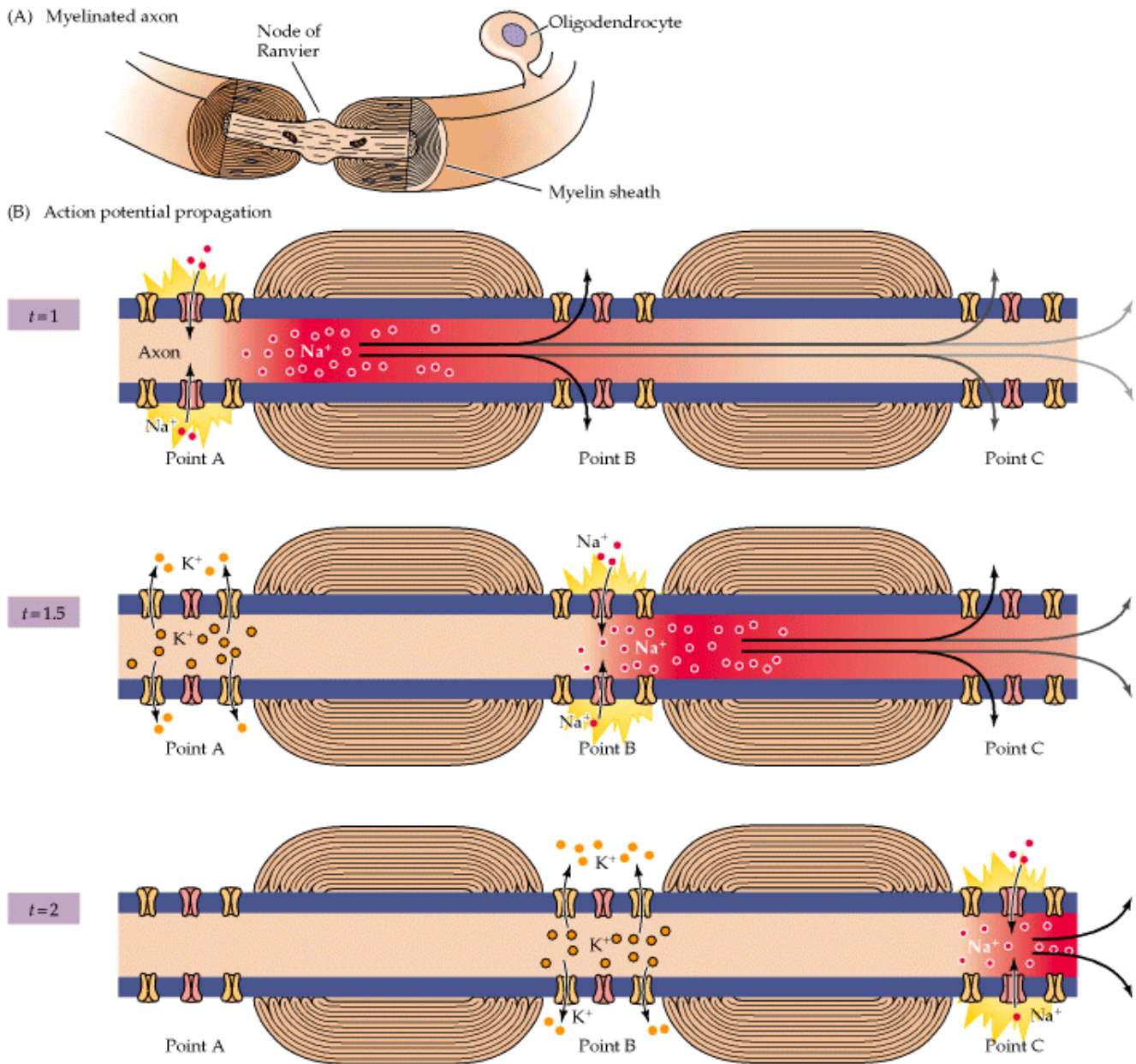
(because the active excitation is confined to the small regions of axonal plasma membrane at nodes of Ranvier.)



CNS myelin is a spiral structure similar to PNS myelin; it has an inner mesaxon and an outer mesaxon that ends in a loop, or tongue, of glial cytoplasm. Unlike the peripheral nerve, where the sheath is surrounded by Schwann cell cytoplasm, the cytoplasmic tongue in the CNS is restricted to a small portion of the sheath. This glial tongue is continuous with the plasma membrane of the oligodendroglial cell through slender processes. One glial cell can myelinate 40 or more separate axons



## PROPAGATION OF AN ACTION POTENTIAL:



### **Saltatory action potential conduction along a myelinated axon.**

an action potential generated at one node of Ranvier elicits current that flows passively within the myelinated segment until the next node is reached. This local current flow then generates an action potential in the neighboring segment, and the cycle is repeated along the length of the axon.

(A) Diagram of a myelinated axon. (B) Local current in response to action potential initiation at a particular site flows locally. However, the presence of myelin prevents the local current from leaking across the internodal membrane; it therefore flows farther along the axon than it would in the absence of myelin. Moreover, voltage-gated Na<sup>+</sup> channels are present only at the nodes of Ranvier. This arrangement means that the generation of active, voltage-gated currents need only occur at these unmyelinated regions. The result is a greatly enhanced velocity of action potential conduction. Panel to the left shows the changing membrane potential as a function of time at the points indicated.



# Pathology of Demyelination

---

## Central demyelination

Oligodendroglia are the myelin-forming cells in the CNS

The large processes of oligodendroglia wrap themselves around segments of axons, and the compressed layers of these processes are what constitute the myelin. One oligodendrocyte can myelinate a large number of segments from different axons.

**Primary central demyelination** refers to myelin loss from **damage to the oligodendrocyte cell body or its myelin**, in which the **axon is initially intact**.  
**This is the type of demyelination found in multiple sclerosis.**

**AN M.S. PLAQUE = area where myelin is stripped from the axons.**

Both macrophages and T cells have been implicated in inducing the primary oligodendrocyte injury, and humoral immunity is also implicated.

The axons within these plaques initially remain intact, though loss of axons occurs eventually since **previously-myelinated axons seem to rely on myelin for longterm survival**. Inflammatory cells, especially lymphocytes and plasma cells, are seen in these plaques early on, and macrophages can be seen removing the myelin debris. Later on, **astrocytes lay down processes in the plaque, causing the plaque to become firm (hence the "sclerosis" of multiple sclerosis)**.

Other types of primary central demyelination are due to toxins, viruses that attack oligodendrocytes, and osmotic imbalances caused by changes in serum sodium.

After central demyelination, **oligodendrocytes can remyelinate central axons**, though in multiple sclerosis this remyelination is usually partial only.

Identifying the appropriate cellular environment for remyelination, as well as inhibiting factors that seem to frustrate adequate remyelination, are major research areas in multiple sclerosis.

## Peripheral demyelination

Schwann cells are the myelin-forming cells in the peripheral nervous system. One schwann cell myelinates only one internode on a peripheral axon. **The myelin around central and peripheral axons looks morphologically similar, but different myelin proteins are found in each**. This is thought to underlie the selective loss of myelin in the central and peripheral nervous systems. For example, **in multiple sclerosis peripheral myelin is unaffected**. The commonest cause of primary demyelination in the peripheral nervous system is the Guillain-Barré syndrome, which presents usually as an ascending paralysis. Inflammatory cells strip the myelin off the peripheral axons, presumably on an auto-immune basis.

**Remyelination by schwann cells is very efficient in the peripheral nervous system.**

## Secondary demyelination

Secondary demyelination refers to the loss of myelin that occurs **after an axon has been damaged**. This is frequently seen in the central nervous system after injuries such as infarction, and in the peripheral nervous system after axons die back in some peripheral neuropathies. Macrophages and microglia are responsible for removing this myelin.

# Immunology of Autoimmune Demyelinating Disease

- These include Guillain-Barré Syndrome ([GBS](#)),
- chronic inflammatory demyelinating polyneuropathy ([CIDP](#)),
- multifocal motor neuropathy ([MMN](#))
- neuropathy associated with IgM gammopathy

The nervous system is an immunologically privileged organ, (evidence: tissue grafts implanted in the brain were not rejected efficiently).

**immune privilege of the CNS may be maintained by a variety of mechanisms including:**

- the **lack of an efficient surveillance function by T cells**;
- the **absence of a traditional lymphoid system**;
- **limited expression of major histocompatibility complex (MHC) molecules** required for T cell recognition of antigen;
- and also from **expression of fas ligand that can induce apoptosis of fas-expressing immune cells** that enter the brain.

*The blood-brain barrier (BBB) partially isolates the brain from the peripheral environment and contributes to immune privilege.*

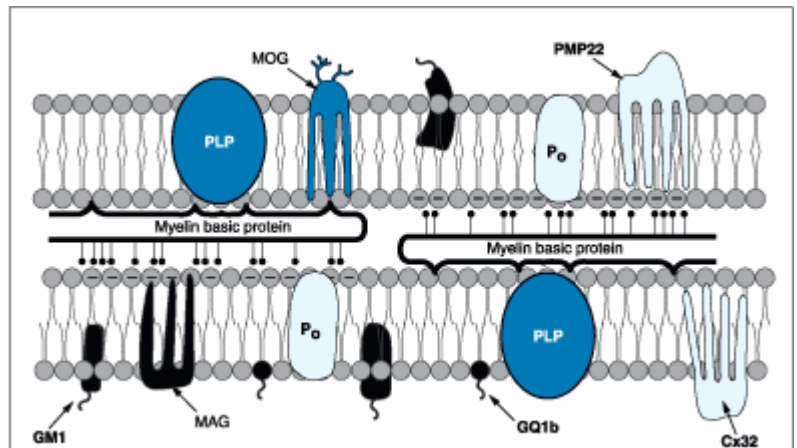
**Although primary (sensitizing) immune responses are not easily generated in the [CNS](#) for the reasons outlined above**, this is not the case for secondary immune responses. When sensitization to nervous system antigens occurs *outside* the nervous system (e.g., in a regional lymph node), activated autoreactive T lymphocytes are easily generated, and **these cells readily cross the [BBB](#) and induce immune mediated injury**. The paradigm for this mechanism of T cell-mediated CNS disease is experimental allergic encephalomyelitis (EAE), a laboratory model for the human autoimmune demyelinating disorders multiple sclerosis (MS) and acute disseminated encephalomyelitis.

**Under normal circumstances the [BBB](#) is impermeable to antibodies.** For autoantibodies to reach the [CNS](#), the BBB must first be disrupted. In inflammatory conditions it is thought that this disruption most often occurs via actions of proinflammatory cytokines elaborated within the brain consequent to interactions between pathogenic T cells and antigen-presenting cells (APCs).

**In contrast to the BBB, in the [PNS](#) the blood-nerve barrier is incomplete.** Endothelial tight junctions are lacking, and the capacity of charged molecules, including antibodies, to cross the barrier appears to be **greatest in two regions of the PNS: proximally in the spinal roots and distally at neuromuscular junctions**.

**This anatomic feature is likely to contribute to the propensity of antibody-mediated autoimmune disorders of the PNS to target proximal nerves ([Guillain-Barré syndrome](#))...**

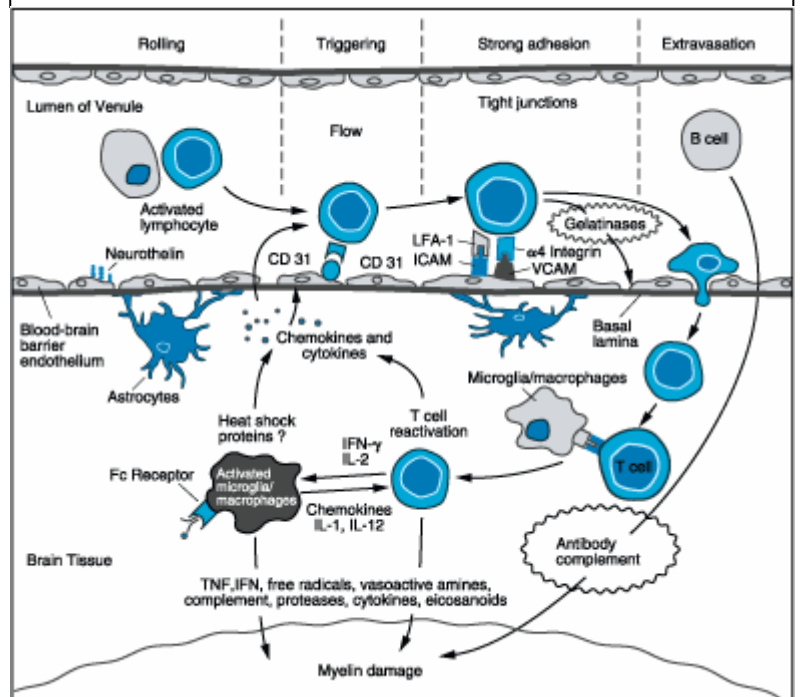
**...or the neuromuscular junction ([myasthenia gravis](#), [Eaton-Lambert syndrome](#)).**



In multiple sclerosis (MS), myelin basic protein (MBP) and the quantitatively minor CNS protein, myelin oligodendrocyte glycoprotein (MOG), are likely T cell and B cell antigens, respectively. The location of MOG at the outermost lamella of the CNS myelin membrane may facilitate its targeting by autoantibodies. In the PNS, autoantibodies against myelin gangliosides are implicated in a variety of disorders, including GQ1b in the Fisher variant of Guillain-Barré syndrome, GM1 in multifocal motor neuropathy, and sulfatide constituents of myelin-associated glycoprotein (MAG) in peripheral neuropathies associated with monoclonal gammopathies.

## BELOW:

**A model for experimental allergic encephalomyelitis (EAE).** Crucial steps for disease initiation and progression include peripheral activation of preexisting autoreactive T cells; homing to the CNS and extravasation across the blood-brain barrier; reactivation of T cells by exposed autoantigens; secretion of cytokines; activation of microglia and astrocytes and recruitment of a secondary inflammatory wave; and immune-mediated myelin destruction. ICAM, intercellular adhesion molecule; LFA-1, leukocyte function-associated antigen-1; VCAM, vascular cell adhesion molecule; IFN, interferon; IL, interleukin.



# Pathophysiology: a POSSIBLE MECHANISM for M.S.

