CEREBRAL CIRCULATION

Anatomy

▪ *Vessels*

• the principal arterial inflow is via 2 internal carotids & 2 vertebrals
• the later unite to form the ***basilar artery***
• the basilar artery and the internal carotids form the ***circle of Willis***
→ 6 arteries supplying the cerebral cortex
• majority of arterial flow is carried by the ***carotids***
• anastomotic flow is minimal due to small diameter and equal pressures on each side
• venous drainage via the deep veins and ***dural sinuses*** → internal jugular veins
• in the ***choroid plexuses*** there are gaps between the endothelial cells of the capillary wall, however the choroid epithelial cells are densely intermeshed and interlocking
• cerebral capillaries resemble ***nonfenestrated*** capillaries in muscle etc.
• however, there are ***tight junctions*** between the cells which prevent the passage of substances
• the cerebral capillaries are surrounded by the end-feet of ***astrocytes***, closely applied to the basement lamina of the capillary → gaps ~ 20 nm wide

▪ *Innervation*

• three systems of nerves supply the cerebral vessels,

1. postganglionic sympathetic from the ***superior cervical ganglion***

   → NA and neuropeptide-Y

2. cholinergic neurones from the ***sphenopalatine ganglion***

   → ACh, VIP, and PHM?

3. sensory nerves with cell bodies in the ***trigeminal ganglion***

   → substance P

NB: the actions of these neurotransmitters are,

i. vasodilators - substance P, VIP, PHM, CGRP
ii. vasoconstrictors - NA, neuropeptide Y

Cerebral Blood Flow

Normal Values			
CBF	• Global[1] • Cortical • Subcortical • 1400g brain	~ 45-55 ~ 75-80 ~ 20 ~ 700 ~ 12-15% CO	ml/100g/min ml/100g/min ml/100g/min ml/min
C-VO_2		~ 3-3.5 ~ 50 ~ 20%	ml/100g/min ml/min basal VO_2
Cerebral P_{vO2}		~ 35-40	mmHg
ICP (supine)		~ 8-12 ~ 10-16	mmHg cmH_2O

[1] autoregulated between cerebral perfusion pressures 60-130 mmHg

NB: a large proportion of the brains energy consumption (~ 60%) is used to support electrophysiological function & the maintenance of ***ion gradients***

local CBF & C-VO_2 are heterogeneous throughout the brain, both are ~ 4x greater in ***grey matter***

▪ ***Regulation of CBF***

• the determinants of total cerebral blood flow are,

1. the arterial pressure at brain level
2. the venous pressure at brain level
3. the intracranial pressure
4. the viscosity of blood
5. the tone of the cerebral arterioles

• normal ***cerebral perfusion pressure*** is determined by MAP - cerebral venous pressure
• the later is usually maintained ~ 2-4 mmHg above ICP

• factors which influence these, and therefore determine CBF include,

a. metabolic / chemical / humoral factors
   i. $C\text{-}VO_2$ - arousal, seizures
      - temperature
      - anaesthetic agents
   ii. $PaCO_2$
   iii. PaO_2
   iv. drugs - vasodilators/vasopressors
      - anaesthetic agents
b. myogenic mechanisms - ***autoregulation*** & MAP
c. rheologic factors - blood viscosity
   - temperature, proteinaemias
d. neurogenic mechanisms - extracranial sympathetic pathways
   - intracranial pathways

• although other intrinsic factors play a role, the most ***important factors*** are,

1. $C\text{-}VO_2$/CBF coupling $\rightarrow$ autoregulation
2. $PaCO_2$
3. neurogenic regulation

■ ***Coupling of $C\text{-}VO_2$ & CBF***

• in the normal state there is tight coupling between *l*-$C\text{-}VO_2$ and *l*-CBF
• the cerebral **RQ ~ 1.0**, $\therefore O_2$ consumption ~ CO_2 production **~ 3.5 ml/100g/min**
• factors proported, but not proven, to contribute to this include,

a. H^+
b. extracellular K^+ and/or Ca^{++}
c. thromboxane & prostaglandins
d. adenosine

• ***temperature*** reduction decreases $C\text{-}VO_2$~ 6-7% per °C
• the EEG becomes ***isoelectric* ~ 20°C**, however, in contrast to anaesthetic agents, further reduction in temperature ***does*** result in further reduction in $C\text{-}VO_2$
• at 18°C the $C\text{-}VO_2$ ~ 10% of the basal rate and accounts for the profound protective effect during deep hypothermic arrest

• hyperthermia has the opposite effect, with marked increases in $C\text{-}VO_2$ up to 42°C
• beyond which there is a reduction in $C\text{-}VO_2$, possibly due to inhibition of enzymatic function

■ ***Carbon Dioxide***

• CBF is ***linearly*** related to $PaCO_2$ over the range **~ 18-80 mmHg**

→ $\delta PaCO_2$ ~ 1 mmHg
→ δCBF ~ 1-2 ml/100g/min (~ 3-4%/mmHg)

• $PaCO_2$ ~ 60 mmHg → ↑ CBF ~ 50% & ↑ blood volume ~ 14 ml (20%)
~ 80 mmHg → ↑ CBF ~ 100%

• under normal circumstances, CO_2 ***sensitivity*** appears positively correlated with basal C-VO_2
• accordingly, agents which alter basal C-VO_2, also alter ***slope*** of the $\delta CBF/\delta PaCO_2$ curve
• H^+ acts directly on blood vessels, however, due to the impermeability of the BBB, metabolic acidosis has little immediate effect upon CBF

• hyperventilation is useful for both ***brain decompression*** and ***brain relaxation***
• loss of **$PaCO_2$ *reactivity*** is a good predictor of ***outcome*** after severe head injury
• the effects of $PaCO_2$ occur rapidly but are not sustained, CBF returning to normal over **~ 6-8 hrs**
• vasoconstriction by hyperventilation may ↓ CBF to marginally perfused areas and ↑ ischaemia
• studies of global O_2 extraction show hyperventilation → ↑ A-VO_2 difference

∴ argue $S_{jb}O_2$ is a better guide to the ideal V_M than measurement of ICP

• CSF bicarbonate adaptation occurs with a $t_{½\beta}$ ~ 6 hours and CSF pH gradually returns to normal despite the sustained alteration of arterial pH
• thereafter, acute normalisation of arterial pH will result in significant CSF ***acidosis*** and induced "hypocapnia" may carry a theoretical risk of ischaemia

■ ***Oxygen***

• changes in PaO_2 also affect cerebral vessels
• hyperoxia causes minimal vasoconstriction → from the range 60-300 mmHg CBF remains approximately constant and at 1 atm, CBF is decreased ~ 15%
• at a PaO_2 < 60 mmHg CBF begins to increase rapidly, such that at P_{aO2} ~ 35 mmHg

→ ↑ CBF ~ 30-35%

• the mechanisms mediating this vasodilatation are not fully understood
• EEG slowing is evident at P_{aO2} < 30 mmHg → CBF ~ 30 ml/100g/min
• EEG becomes flat at P_{aO2} < 20 mmHg → CBF ~ 15-20 ml/100g/min

▪ ***Autoregulation***

- maintenance of a near constant CBF over a range of **MAP ~ 50-150 mmHg**
- beyond these limits, perfusion is pressure passive
- there are a number of points relevant to anaesthesia / ICU,

1. hypertensive patients may have a ***right shift***
2. autoregulation is not instantaneous → ***dynamic*** changes in CBF ~ 3-4 minutes
3. induced hypotension should be achieved over a period of several minutes
4. volatile anaesthetics obtund autoregulation in a dose dependent manner

NB: therefore, the use of high dose volatile should be avoided if autoregulation is being relied upon to maintain CBF during induced hypotension

▪ ***Viscosity***

- ***haematocrit*** is the single most important determinant of blood viscosity
- variations within the range 33-45%, result in ***clinically insignificant*** alterations of CBF

1. polycythaemia vera → ↑ viscosity → ↓ CBF to ½ normal values
2. anaemia → ↓ CVR / ↑ CBF
   - though this may represent a response to the decreased CaO_2 and O_2 delivery

- the effects of viscosity are more obvious during focal ischaemia, when vasodilatation is already maximal, where a reduction in Hct. results in an increase in flow to the ischaemic territory
- pooled data for DO_2 in the setting of ***focal ischaemia*** suggests the ***optimal Hct*** **~ 30-34%**

Cerebrospinal Fluid

▪ *Formation & Absorption*

• there is ~ 150 ml of CSF in the adult, ½ within the cranium
• about 60-70% of the CSF is formed by the ***choroid plexuses***
• the remaining 30-40% by the cerebral vessels lining the ***ventricular walls***
• in humans the CSF turns-over ~ 4 times/day
• composition is essentially brain ECF, and there appears to be free communication between the brain extracellular space, the ventricles and the subarachnoid space
• brain ECF normally occupies ~ 15% of brain volume
• CSF flows out through the foramina of ***Magendie*** and ***Luschka*** and is absorbed through the ***arachnoid villi*** into the cerebral venous sinuses

• bulk flow via the villi is **~ 500 ml/d** (~ 3.5 ml/min)

a. ***formation*** is ***independent*** of ventricular pressure

b. absorption, being largely by bulk flow, is proportional to ventricular pressure
   - at ***normal pressure*** **~ 7.0-18.0 cmH_2O** (mean ~ 11), filtration = absorption
   - when pressure falls below ~ 7 cmH_2O absorption ceases

• factors resulting in a ***reduction*** in CSF formation,

1. metabolic & respiratory alkalosis
2. hypothermia
3. ***hyperosmolality*** ~ 95% ↓ formation with osmolality > 310 mosmol/kg
4. NaK-ATPase inhibition
   - digoxin, acetazolamide, frusemide, amiloride
   - may result in ~ 80% ↓ formation

▪ *CSF Functions*

1. support - brain dry weight ~ 1400g
   - boyant in CSF ~ 50g
2. constant metabolic environment
   - BBB buffers CSF against rapid plasma changes in K^+, Ca^{++}, Mg^{++}
3. transport of chemical messengers
4. sink for waste disposal

Intracranial Pressure

• the normal contents of the cranium are,

1. brain - neural tissue & interstitial fluid ~ 1400g
2. blood ~ 75 ml
3. CSF ~ 75 ml (+75 ml spinal cord)
4. ICP ~ 7-18 cmH_2O

NB: because each of these three components is relatively ***incompressible***, the combined volume at any one time must be constant → the ***Monro-Kellie doctrine***

▪ *ICP Measurement*

• continuous measurement was introduced into clinical practice ~ 1960 by ***Lundberg***
• ***indications*** for perioperative ICP monitoring include,

1. neurotrauma / head injury
2. hydrocephalus
3. large brain tumours
4. ruptured aneurysms
5. postoperative cerebral oedema / swelling
6. metabolic encephalopathy
   i. cerebral oedema 2° fulminant hepatic failure
   ii. Reye's syndrome
7. large CVA - ICH > infarction
8. proposed therapy to maximise CPP

▪ *Methods of Measurement*

a. ***intraventricular catheter*** - ventriculostomy
   - represents the "gold standard" for pressure measurement
   - normally placed frontal horn of lateral ventricle
   - difficult with large tumours & compressed ventricles
   - allows therapeutic ***CSF drainage***
   - requires ***destruction*** of brain tissue
   - creates a pathway for ***infection***
   - potential for ***accidental venting*** of CSF
     → possible subdural haemorrhage or upward brain herniation
   - catheter obstruction & ventricular haemorrhage may occur
   - Camino Laboratories OLM uses a fibreoptic device within the ventricular catheter

b. ***subdural bolt*** - "Richmond Screw" or "Leeds device"
- inserted through a burr hole & an opening in the dura
- arachnoid remains intact, ∴less risk of infection, theoretically ??
- connects via a fluid couple to a transducer
- less invasive than (a) and does not require penetration of brain tissue
- doesn't allow CSF drainage or study of cerebral compliance
- may underestimate high ICP and damping is a problem

c. ***subdural catheter***
- usually subdural space over frontal lobe of non-dominant hemisphere
- prone to signal damping and calibration drift
- Gaelic Model ICT, Camino Laboratories OLM
- potential risk of infection
- does not allow CSF drainage
- doesn't require penetration of brain tissue

d. ***intracerebral transducer*** - Camino Laboratories
- may also be implanted extradurally
- requires catheter placement into brain tissue
- inability to check zero calibration, drain CSF
- risk of infection

- the incidence of ***infection* ~ 2-7%** with monitoring ≥ 5 days, and the risks are slightly greater with dural penetration
- LIGW states rates reported up to 20%, but should be ~ 1% with care
- ***intracranial haemorrhage*** may be associated with coagulopathy or difficulty during insertion
- with all methods, the zero reference point of the transducer is usually taken as the external auditory meatus
- hydrostatic potential differences between the heart and the brain need to be evaluated when calculating CPP
- LIGW states,

1. line from tragus to angle of eye
2. perpendicular line at middle and posterior thirds of line above
3. zero reference = 2.5 cm cephelad on perpendicular

NB: patient 15° head-up in neutral position
same zero reference for MAP transducer

- if patient nursed flat, then reference is the external auditory meatus
- ICP values are often ~ 5 mmHg higher with later method

▪ ***Intracranial Hypertension***

Def'n: ***sustained*** pressure with the subarachnoid space ³ **20 mmHg***

variable definitions & lack of agreement*
Cucchiara (ASA) states a figure of ≥ 40 mmHg
other authors use upper limits of 15-25 mmHg

• compensatory mechanisms

a. ***CSF displacement*** to the spinal SA space

b. ***CSF reabsorption***

i. by the arachnoid villi - pressure dependent up to ~ 30 mmHg ICP

ii. intraventricular transependymal CSF reabsorption

c. reduction in blood volume via compression of the ***venous sinuses***

• results in collapse of the bridging veins entering the saggital sinus
→ back-pressure to the capillary bed with further elevation of ICP

d. obliteration of cisternal and convexity CSF spaces →

i. distortion of CSF reabsorptive pathways & vicious cycle

ii. ***craniospinal disparity*** → ICP ≠ LP pressure

NB: cerebral compensation is described in terms of ***compliance***,
however the true relationship is dP/dV → ***elastance***

• sustained pressure > 15 mmHg is abnormal & associated with,

a. ↑ amplitude of arterial oscillations

b. ↓ respiratory waveform

• these effects become more evident > 20 mmHg & > 30 mmHg CBF is reduced
• tissue expansion leads to pressure gradients → localised pressure on areas of brain tissue
• thus, ***focal ischaemia*** is usually evident prior to ***global ischaemia***
• ***cerebrovasomotor paralysis*** occurs as the areas of ischaemic tissue increase and global autoregulation fails
• this is often heralded by the development of ***Cushing's triad***,

1. intracranial hypertension
2. arterial hypertension
3. reflex bradycardia

• under these circumstances the normal compensatory mechanisms become counterproductive and central to the generation of ***global ischaemia***

ICP Wave Types[1]	
A waves:	• Lunberg's plateau • large waves, 5-20 min duration £ **50-100 mmHg** • associated with a ***baseline ICP*** > **20 mmHg** • rapid rise & descent, several times / hr • exhaustion of intracranial spatial compensation • associated with increased CBV & decreased CBF • ? due to a variable CPP with intact autoregulation **** pathological ****
B waves:	• rhythmic (1/min) oscillations £ **50 mmHg** • partly related to depression of consciousness • often associated with periodic breathing • usually disappear with mechanical ventilation
C waves:	• rhythmic (4-8/min) oscillations £ **20 mmHg** • associated with Traube-Herring-Mayer BP waves

[1] rather than the waveform type,
the important factors appear to be the ***degree*** and ***duration*** of ICP elevation

NB: various authors state, "ICP monitoring has been shown to decrease ***mortality*** and improve outcome by guiding optimal therapy to prevent reduction in CPP < 40 mmHg" ?? reference

- ***Aetiology of Intracranial Hypertension T.Oh***

a. ***intracranial***
   i. head injury
   ii. tumours
   iii. subarachnoid haemorrhage
   iv. intracranial haemorrhage
   v. hydrocephalus
   vi. pseudotumour cerebri
   vii. post ischaemia ?? oedema omitted
   viii. infective

b. ***extracranial***
   i. hypertension - strokes
      - encephalopathy
   ii. impaired venous drainage
   iii. infection - SIRS
   iv. metabolic encepalopathy
   v. Reye's syndrome
   vi. osmolar imbalance
   vii. dialysis related
   viii. hypoxia & hypercarbia

• these produce raised ICP by 1 of, or any combination of 4 mechanisms,

1. intracranial ***mass effect***
2. cerebral ***oedema***
3. ***CSF*** retention
4. increased cerebral ***blood volume***

NB: management is then directed at these 4 mechanisms

Oxygen Consumption

• the cerebral rate of O_2 usage ($C\text{-}VO_2$) **~ 49 ml/min** for a 1400g brain
• this equates to ~ 20% of the total body O_2 consumption
• the brain is extremely sensitive to hypoxia, occlusion of the blood supply resulting in unconsciousness in **< 10 secs**
• the vegetative structures in the brainstem are more resistant to hypoxia than the cortex
• the ***basal ganglia*** also use O_2 at a rapid rate and hypoxic injury, therefore, frequently results in intellectual dysfunction and Parkinsonian symptoms

▪ *Energy Sources*

• glucose is the major ultimate energy source under normal conditions
• the normal ***respiratory quotient*** for cerebral tissue is ~ 0.95 to 0.99
• during prolonged starvation appreciable utilisation of other substances occurs
• even under normal conditions, as much as 30% of glucose taken up by the brain is converted to amino acids and lipids
• ***insulin*** is not required for the cerebral uptake of glucose
• uptake is increased in active neurones, as is that of 2-deoxyglucose, however the later is not metabolised and uptake of radioactive labelled tracer is used to map cerebral activity
• there is an average decrease of 30% uptake in all areas during slow wave sleep

▪ *Hypoglycaemia*

• the symptoms of hypoglycaemia include,

1. mental changes, confusion
2. ataxia, convulsions
3. sweating
4. coma

• the available glucose and glycogen is exhausted within ***2 minutes*** of cessation of arterial flow
• thus, the brain can withstand hypoglycaemia for longer periods than hypoxia
• as for oxygen, the cortical areas are more sensitive to sublethal exposures to hypoglycaemia
• diabetic patients exposed to chronic hyperglycaemia exhibit a reduced transport of glucose across the BBB and, therefore, may exhibit symptoms of hypoglycaemia at a "normal" BSL

▪ *Glutamate & Ammonia Removal*

• the brain uptake of ***glutamate*** is ~ equal to its output of ***glutamine***, thereby clearing the CNS of ammonia
• this is effectively the reverse process to the clearance of ammonia by the kidney
• ammonia is very toxic to nerve cells and this process is necessary for normal CNS function, eg. the CNS effects of hepatic coma

Lumbar Puncture

- ***Indications***

1. diagnosis
   i. meningitis / encephalitis
   ii. CNS malignancy - haematological
   iii. Guillain-Barre syndrome
   iv. spinal obstruction
   v. subarachnoid haemorrhage - rarely these days
2. treatment
   i. antibiotic / cytotoxic therapy
   ii. anaesthesia / analgesia / chronic pain
   iii. antispasmodic therapy

- ***Normal Findings***

1. culture - negative
   * bacterial, fungal, viral, mycobacterial
2. cell count < 5 mononuclear cells /mm^3
   - ***no*** neutrophils or rbc's
3. biochemistry
   i. protein < 0.45 g/l
   ii. glucose > 2.2 mmol/l *60-70% plasma levels
4. pressure ~ 6.0-15.0 cmH_2O
   > 19.0 cmH_2O abnormal (~ 15 mmHg)

- ***Common Patterns***

1. bacterial meningitis
   - culture +'ve in most cases if not given ABx previously
   - ↑ PMN count
   - ↑ protein
   - ↓ glucose → CSF:serum ratio < 0.31 in 70%
2. fungal meningitis
   - commonly ***cryptococcus*** - especially in AIDS
   - culture +'ve in ~ 60-70% of cases
   - ↑ mononuclear cell count
   - ↑ protein
   - low-normal glucose
   - Indian ink stain → cell halos in ~ 20-50%

3. viral meningitis
   - culture rarely of value, -'ve for other pathogens
   - high mononuclear cell count * up to 1000/mm^3
   - normal-elevated protein
   - normal glucose
4. other causes of elevated ***mononuclear cell*** count
   - encephalitis, multiple sclerosis, TB * rarely > 300/mm^3
   - mild rise in cerebral tumours, abscesses, venous thrombosis, poliomyelitis
5. SAH
   - only performed following CT scan if diagnosis in doubt
   - last specimen should be centrifuged ASAP & supernant for ***xanthochromia***
   - becomes +'ve after 1-2 hrs, maximal at 7 days & lasts for 3-4 weeks
6. malignancy
   - detects meningeal spread in lymphoma / leukaemia
   - associated elevation of protein with normal glucose
7. GBS
   - elevated protein ***without*** increase in cell count or decreased glucose
     → cytoalbuminologic dissociation
   - levels are characteristically ***very high*** (up to 10x)
   - other causes of elevated protein are rarely as high & have other changes
     → meningitis/encephalitis, haemorrhage/infarction, MS, poliomyelitis, tumours

- ***Complications***

1. bleeding
   - traumatic tap ~ 10-20%
   - clinically significant spinal / epidural haematoma is exceedingly rare
2. pain & paraesthesiae
   - up to 10%, requiring no specific therapy
3. post-spinal headache
   - standard recommendation is ***not*** to perform a blood-patch, cf. spinal anaesthesia
   - most indications for LP mean the patient will be lying flat > 24 hrs anyway
4. infection
5. coning
   - may occur in up to 12% of patients with raised ICP
   - associated mortality ~ 40%

DISORDERS OF CONSCIOUSNESS

Def'n: ***confusion***: state of cognitive impairment where the patient is unable to think with customary speed and clarity

disorientation: state of cognitive impairment where the patient has impaired attention, concentration & ***immediate memory***

delerium: state of ***increased*** arousal and cognitive impairment, characterized by hallucinations, delusions, agitation, seizures and autonomic hyperactivity

stupor: a sleep-like state from which the patient can be aroused only by vigorous, repeated stimulation

coma: a sleep-like state from which the patient ***cannot*** be aroused

Acute Confusional State

NB: common → pain, metabolic, sepsis, electrolytes, drugs

1. medical
2. psychological
3. environmental
4. staff

- ***Medical***

NB: ie. all the causes of ***acute delerium***, especially,

1. pain, bladder distension
2. anxiety, disorientation
3. sleep deprivation, insomnia
4. metabolic changes
   - hypoxia, hypoglycaemia, hypercarbia
   - fever, hyperthermic syndromes, hypothermia
   - uraemia, hepatic encephalopathy
5. electrolyte disturbance - Na^{+}, Ca^{++}, Mg^{++}, acidosis
6. haemodynamic
   - hypertensive encephalopathy
   - hypotension/hypoperfusion

7. drugs
   i. direct toxicity
      - alcohol, addictive drugs, amphetamines
      - sedatives, anaesthetics, narcotics
      - anti-depressants, antihistamines, steroids
   ii. overdose | withdrawal
   iii. idiosyncratic
8. endocrine
   - thyrotoxicosis, hypothyroidism
   - Cushing's, Addison's
   - hyperparathyroidism
   - porphyria
9. vasogenic cerebral oedema
   - metabolic
   - osmolar change
   - fluid shifts
10. pre-existing cerebral disease
    - dementia, senility
    - CVA
11. fat embolism syndrome
12. pancreatitis
13. severe burns

- ***Psychological***

1. personality, anxiety
2. age, dementia
3. previous psychiatric history
4. perception of self / illness / prognosis
5. 'defence' mechanisms, coping abilities
6. lack of support
7. sleep deprivation, altered sleep-wake cycle

- ***Environmental***

1. privacy
2. light, noise, visual input
3. monotony
4. equipment / monitors

- ***Staff***

1. communication
2. unguarded comments
3. pre-occupation
4. stress

- ***Management***

1. resuscitation & supportive therapy
2. elimination of contributory factors
3. physical restraint
4. pharmacological restraint
   i. benzodiazepines
   ii. phenothiazines
      - D_1 & D_2 receptor blocking agents ± $M_{1/2}$, H_1, α_1-adrenergic
      - ***antipsychotic*** activity is largely 2° D_2 receptor activity in the ***limbic system***
      - elimination half-life of chlorpromazine ~ 24-48 hrs, however, CNS half-life is clinically shorter
      - side-effects include
        - dry mouth, constipation, urinary retention
        - blurred vision, hypotension, hypothermia
        - Parkinsonism, opisthotonus, tardive dyskinesia
        - long QT_C / torsade de pointes
        - malignant neuroleptic syndrome
        - cholestatic jaundice, photosensitivity
        - leukopaenia, eosinophilia
   iii. ethyl alcohol
      - used in DT's and prevention at very low plasma levels with some success
   iv. propranolol / atenolol
      - for autonomic hyperactivity, especially in drug withdrawal
   v. clonidine
      - also used by some in withdrawal states to combate ANS hyperactivity
      - inherent sedative effects & potentiation of other sedatives

COMA

Def'n: *"a sleep-like state from which the patient cannot be roused"* (LIGW)

*many researchers add a factor of ***time*** ³ **6 hrs**

no ***verbal*** response	≤ 2
no ***eye opening***, spontaneous or to stimuli	= 1
motor, not obeying commands	≤ 5
→ Glasgow Coma Score, ***GCS***	≤ **8**

- ***Aetiology***

1. ***intracranial***
   - i. vascular - infarction, haemorrhage
   - ii. infection - meningitis, encephalitis, abscess
   - iii. tumour - mass effect | cerebral oedema
     - haemorrhage
   - iv. trauma - primary parenchymal damage
     - vascular disruption
     - oedema, late infection
   - v. hydrocephalus - communicating | non-comunicating
   - vi. post-ictal
   - vii. psychiatric - conversion reaction, depression, catatonia
2. ***extracranial***
   - i. metabolic - hypoxia, hypercarbia, acidosis, hypoglycaemia
     - severe ↑↓ osmolality
     - severe ↑↓ Na^{+}, Ca^{++}, Mg^{++}, K^{+}, $HPO_4^{=}$
     - hepatic | uraemic encephalopathy
     - Reye's syndrome, porphyria
   - ii. "infection" - severe SIRS | sepsis
   - iii. CVS
     - embolism - thrombotic | mycotic | air | fat | amniotic
     - hypotension - cardiogenic | hypovolaemic shock
     - hypertensive encephalopathy
   - iv. endocrine - pituitary | thyroid | adrenal dysfunction
   - v. drugs - sedatives, analgesics, ethanol, other alcohols
     - lead, other toxins
   - vi. physical - hyper | hypothermia
     - electrocution
   - vii. nutritional - Wernicke's encephalopathy
     - thiamine, B_{12}, pyridoxine

- ***Aetiology: Diabetic***

a.	hyperglycaemic ***ketoacidosis***	~ **75%**
b.	euglycaemic ketoacidosis	~ 18%
c.	hyperosmolar, hyperglycaemic, non-ketotic	~ 5-15%
d.	hypoglycaemia	
e.	alcoholic hypoglycaemic ketoacidosis	
f.	lactic acidosis	
g.	cerebro-vascular disease	
h.	common causes	- trauma, drug ingestion, etc.
i.	uraemia	
j.	bacterial infections	- meningitis, septicaemia

- ***Complications of Coma***

a.	respiratory	- airway obstruction - acute respiratory failure - neurogenic pulmonary oedema - abnormal respiratory patterns (Cheyne-Stokes, hyperventilation) - aspiration (macro, micro) - sputum retention, collapse - pneumonia
b.	CVS	- euvolaemic hypotension - hypovolaemia - arrhythmias - venous thrombosis - pulmonary emboli
c.	eyes	- keratitis, ulcers
d.	skin	- pressure areas - decubitus ulcers (heals, buttocks, sacrum, shoulders)
e.	GUS	- retention / overflow - UTI
f.	GIT	- gastric erosions - functional ileus / constipation - malnutrition
g.	metabolic	- hypothermia - hypoglycaemia - electrolyte abnormalities
h.	muscle contractures	

Glasgow Coma Score			
Motor response	**Verbal response**[1]	**Eye opening**	**Total**
1. nil 2. extensor response 3. abnormal flexor response 4. withdraws to pain 5. localises to pain 6. obeys command	1. nil 2. incomprehensible sounds 3. inappropriate words 4. confused conversation 5. orientated speech	1. nil 2. to pain 3. to speech 4. spontaneous	
6	**5**	**4**	**3-15**

[1] GCS - intubated = 'X' out of 10

- ***GCS: Problems***

  a. doesn't record
     i. abnormal ***pupil signs***
     ii. neurological ***asymmetries***
     iii. the strength of stimulus required to elicit a response
     iv. other brainstem reflexes, eg. oculocephalic reflex

  b. limited usefulness in
     i. intubated / ventilated patient
     ii. language disturbances
     iii. presence of aphasia, hemiplegia, or quadriplegia
     iv. "middle" ranges of impaired consciousness

- ***Investigation - Stage 1***

a. history and examination - family, observers

b. immediate
   i. BSL
   ii. urinalysis - glucose, ketones

c. S_pO_2 / AGA's

d. biochemistry
   i. glucose
   ii. U+E's - Na^+, K^+, Mg^{++}, Ca^{++}, $HPO_4^=$
   * ***osmolar gap***
   iii. LFT's
   iv. blood alcohol
   v. paracetamol & salicylates
   vi. urine drug screen

e. FBE / ESR

f. ECG - AMI, AF

g. CXR - malignancy, infection
   - collapse, aspiration
   - LVF

h. CT head

i. lumbar puncture

j. skull and C_X spine X-ray

- ***Investigation - Stage 2***

a. angiography

b. EEG

c. evoked potentials

d. MRI scanning

e. nuclear medicine

- ***Specific Investigations***

a. EEG
- useful for epilepsy
- depth & type of coma
- technically difficulty

b. Cortical EP's
- less affected by sedatives
- useful in paralysed patient
- tests ***brainstem*** functions
- dynamic investigation
- some correlation with outcome in trauma
- technically difficult
- easier than continuous EEG

c. Ultrasound A scans
- show midline shifts
- rapid portable
- non specific

d. CT scan
- macro-anatomic picture
- readily available
- technical difficulties, eg. transfer, airway, monitoring
- no indication of function or microanatomy
- static investigation
- expensive
- radiation hazards

i. non-contrast
- haemorrhage
- hydrocephalus
- oedema
- infarction
- tumours
- bony abnormalities

ii. contrast
- abscess
- tumours eg. glioblastoma
- vascular anomalies
- subacute subdural

e. ICP monitoring qv.

Prognosis in Non-Traumatic Coma

- ***All Non-Traumatic Coma Patients***

• only **~ 16%** made a satisfactory neurological recovery

1. ~ 61% died
2. ~ 12% did not improve from a vegetative state
3. ~ 11% had moderate disability

NB: SAH and CVA had a *worse* prognosis than metabolic and non-structural damage

• most of the improvement occurred within the first months
• those suffering hypoxic damage had an intermediate survival

- ***Poor Prognostic Signs***

a. **on admission**
   - ***no*** signs useful for discriminating outcome from coma at this stage

b. **day 2**
   i. absent light reflexes
   ii. absent corneal reflexes
   iii. abnormal caloric and/or oculocephalic reflex
   iv. absent motor response to pain

   *normal responses in the above tests had a *better* prognosis

c. **day 4**
   i. absent light reflexes
   ii. absent corneal reflexes
   iii. absent motor response to pain

d. **1 week**
   i. absence of eye opening
   ii. absence of spontaneous eye movements
   iii. absent light reflexes or absent corneal reflexes
   iv. abnormal oculocephalic and oculovestibular reflexes

▪ ***Hypoxic-Ischaemic, Non-Traumatic Coma Patients***

• most patients who recover,

a. do so within a short ***time*** ~ 90% by day 3

b. had normal ***pupillary reflexes***

c. continued to improve over the first 1-3 days

▪ ***Poor Prognostic Factors***

a.	on admission	- no pupillary light reflex ? ***no factors*** actually predictive at this stage
b.	day 1	- GCS:M ≤ 3 - abnormal flexor response to pain - disconjugate, or no spontaneous eye movements
c.	day 3	- GCS:M ≤ 3 - abnormal flexor response to pain - disconjugate, or no spontaneous eye movements
d.	1 week	- GCS:M ≤ 5 - no motor response to command - disconjugate or no spontaneous eye movements
e.	2 weeks	- GCS:M ≤ 5 - no motor response to command - no improvement in eye movements from day 3 - no oculocephalic reflex
f.	myoclonic seizures, any stage	

Myxoedema Coma

- usual scenarios,
  a. hypothyroidism unmasked by ***concurrent illness***
  b. known hypothyroid → ***emergency surgery***

- precipitating factors for coma,
  a. surgery, trauma, anaesthesia
  b. sepsis, severe illness
  c. hypothermia
  d. sedatives, narcotics

  NB: mortality ~ 50%

- ***Clinical Features***

a. ↓ BMR ~ 40-50%

b. CVS
- ↓ LV function ~ 50-60%
- ↓ CO ~ 40%
- cardiomegaly, pericardial effusion ~ 60%
- ↑ CAD

c. ↑ SNS activity → ± hypertension (? 2° hypercarbia)

d. ↓ blood volume ~ 10-25%

e. baroreceptor dysfunction & blunted response to
- IPPV
- hypovolaemia
- valsalva

f. ECG
- low amplitudes
- flattened or inverted T waves
- ↓ phase 4 depolarization, bradyarrhythmias
- ↑ APD

g. respiratory
- ↓ MBC
- ↓ D_{CO}
  - impaired respiratory drives
    - O_2 ~ 10-15%
    - CO_2 ~ 30-40% of normal

h. electrolytes
- ↓ BV
- ↑ ECF volume
- inappropriate ADH
- low Na^+
- impaired renal function

i.	drugs	- increased $t_{½\beta}$'s - impaired liver and renal excretion - ↓ **MAC** for volatile agents - ↑ sensitivity to sedatives and narcotics
j.	CNS	- ↑ sensitivity to sedatives and narcotics - tendency to hypothermia * $C\text{-}VO_2$ ***not*** decreased, except with hypothermia

- ***Assessment***

a.	severity	- ***bradycardia*** - ***hyporeflexia*** with slow recovery - ***temperature*** - skin, hair, facies, voice
b.	CVS	- bradycardia - hypertension - ischaemia - CCF
c.	respiratory	- hypoventilation, P_{aCO2} - pulmonary oedema - infection
d.	CNS	- conscious state - airway protection reflexes
e.	essential Ix	- U&E's, glucose, TFT's if not already done - Hb, WCC - CXR, ECG

- ***Treatment***

a. assisted ventilation with *slow* correction of ***hypercarbia***

b. IVT with glucose for ***hypoglycaemia*** - may need CVC & $D_{50}W$*

c. water restriction &/or hypertonic saline for ***hyponatraemia****

d. passive rewarming for ***hypothermia*** (raise by < 0.5°C/hr)

e. **T_3** ~ 5-20 µg IV in 100 ml N.saline slowly over 30-60 min, or
T_4 ~ 200-500 µg IV (→ more constant T_3 levels)

** ***no*** studies as to best dose or form of replacement

f. ***hydrocortisone*** 300 mg on first day, reducing over a few days

g. treat underlying illness

h. avoid sedatives, narcotics, etc.

- ***Preparation for Emergency Surgery***

a. avoid sedatives, narcotics

b. ? antacids, Ranitidine, intubate if airway reflexes absent

c. ***hydrocortisone*** 100 mg IV 6 hrly for first 24 hrs

d. commence T_3 replacement if,
   i. no active IHD
   ii. no depression of conscious state (pre-coma or coma)
   iii. surgery can be delayed a few hours to assess the effect of T_3
   iv. continuous ECG monitoring available, viz.
      - **T_3 ~ 5-20 µg** in 100 ml N. saline IV slowly over 30-60 min

NB: otherwise withhold until ***after*** surgery and give low dose slowly

COMA: Common, Non-traumatic Causes

1. hypoglycaemic
2. hyperglycaemic ketoacidosis
3. hyperosmolar, hyperglycaemic, non-ketotic
4. alcoholic hypoglycaemic ketoacidosis

Hypoglycaemic Coma

a.	drugs	- excess insulin - oral hypoglycaemics - β-blockers ?? induce or perpetuate - alcohol
b.	severe liver disease	- fulminant hepatic failure, any cause
c.	endocrine	- hypopituitary - hypothyroidism - hypoadrenalism
d.	malignancy	- insulinoma - sarcoma - metastatic carcinoma
e.	post-gastrectomy	
f.	factitious	?? how
g.	post-ictal hypoglycaemia	

Hyperosmolar, Hyperglycaemic, Non-ketotic Coma

Def'n: hyperglycaemia, ***without*** ketosis
dehydration
hyperosmolarity ≥ 320 mosm/l → ***mortality* ~ 50%** (40-70%)

NB: Osmolarity ~ (2 x Na^+) + glucose + urea
True Na^+ ~ measured Na^+ + [(glucose - 6)/3]

- ***Pathogenesis***

a. insulin lack & hyperglycaemia * but enough insulin to prevent ketosis
b. impaired renal function exaggerating high glucose and hyperosmolality
c. fluid restriction (eg. impaired thirst mechanism from CNS disease or sedatives)
d. osmolality ≥ 350 mosm/kg → ***coma***

- ***Presentation***

a. precipitating event
- infection
- AMI
- stroke
- haemorrhage
- trauma

b. drugs
- phenytoin
- propanolol
- immunosuppressants
- thiazides
- cimetidine

→ all impair insulin ***secretion*** or insulin ***action***

c. fever - with or without infection

d. neurological
- disorientation
- tremors
- seizures ~ 30%
- coma ~ 50%

e. dehydration ~ 99%
+ tachycardia, hypotension
+ hyperventilation

Investigations[1]			
glucose	~ **50-60**	mmol/l	
acetone (ketones)	~ 4-6	mmol/l	• normal or slightly elevated
osmolality	~ **380**	mosm/l	• often > 50%
pH	~ 7.3-7.4		• normal or mild acidosis
HCO_3^-	~ 17-22	mmol/l	
Na^+	~ 144	mmol/l	~ 160 mmol/l "corrected"
K^+	~ 5	mmol/l	
urea	~ 10-15	mmol/l	→ ***low*** U:C ratio
creatinine	~ 0.4	mmol/l	
average fluid deficit	~ 10	litres	
DIC			• occasionally

[1] average values, Arieff 1972, HPIM 12th Edition

- ***Treatment***

  a. ABC

  b. expand ECF initially with N. saline, then 0.45% saline, according to CVP and U/O

  c. replace K^+

  d. infuse insulin at ***slow rate*** ~ 3 U/hr
     - elderly are sensitive to insulin
     - a rapid fall in plasma glucose may result in ***cerebral oedema***
     - therefore, aim to reduce glucose by ≤ 3 mmol/l/hr

  e. low dose ***heparin*** ??? anticoagulate

  f. treat underlying cause

- ***Causes of Death***

  a. cerebral oedema - post-resuscitation

  b. cerebral infarction - thrombosis
     - haemorrhage

  c. primary disease

Hyperglycaemic Ketoacidosis

Def'n: coma resulting from an imbalance in the ***insulin:glucagon ratio***, resulting in,

1. extracellular hyperglycaemia
2. intracellular glucose deficit
3. ketoacidosis
4. marked fluid & electrolyte shifts

• the ↓ insulin:glucagon ratio → directly results in,

1. hyperglycaemia
2. ↑ lipolysis
3. hepatic ketogenesis
4. ↑ catecholamines, cortisol, GH, and glucagon

NB: small amounts of insulin will prevent ***ketosis*** (cf. basal pancreatic secretion)

- ***Causes of Death***

a. mortality ≤ **5%**

b. adults
- precipitating cause * AMI, CVA, sepsis
- hypokalaemia
- aspiration pneumonitis, ARDS
- respiratory failure

c. children
- cerebral oedema * too rapid treatment
- hypokalaemia

- ***Precipitants***

a. unknown ~ 30%

b. acute infection ~ 30%

c. undiagnosed diabetic ~ 15%

d. no insulin in known diabetic, especially with poor diet control

e. trauma/surgery

Typical Early Biochemical Abnormalities		
Acidaemia • pH • P_{aCO2} • HCO_3^- • ketoacidosis • lactic acidosis	 ~ 6.9 - 7.15 ~ 8-15 mmHg ~ 5 mmol/l ~ 5 mmol/l ~ 10-15 mmol/l ~ 4-6 mmol/l	 • acetoacetate (N < 0.3) • β-OH-butyrate (N < 1.2)
hyperglycaemia	~ 20-40 mmol/l	
hyperkalaemia	~ 5-8 mmol/l	• total ***deficit*** ~ 200-700 mmol
hyperosmolar hyponatraemia	~ 130 mmol/l	• 2° to high glucose & lipids
hyperosmolality	~ 310-350 mosm/l	
hyperuricaemia		• protein breakdown
↑ FFA	~ 2-4 mmol/l • if higher may → lower Na^+ ~ 110 mmol/l	
uraemia	~ 25 mmol/l	
high creatinine	~ 0.3-0.5 mmol/l	

- ***Late Biochemical Abnormalities***

• following treatment these may progress to,

1. hypernatraemia
   - especially if correction solely with normal saline
2. ***severe hypokalaemia***
3. hypophosphataemia
4. hypomagnesaemia
5. hypochloraemia

- ***Other Features***

a.	fluid loss	~ 5-10 litres
b.	full blood count	- high Hct - leukocytosis ~ 15-90,000/µl with left shift → B_{12} or folate deficiency
c.	fever usually absent	- if febrile suspect infection & do ***septic screen***
d.	NaCl usually normal	- vomiting → low Cl^- & lower Na^+
e.	normal or low K^+ →	* severe deficiency ≥ 400 mmol
f.	uraemia	- raised creatinine - low ***urea:creatinine ratio*** (∝ ketones)
g.	anion gap > 17	- predominantly ketones + some lactate ± $SO_4^=$ & $PO_4^=$
h.	increases in	- amylase (salivary glands) - triglycerides, VLDL and CM - uric acid - LFT's (ketones interfere with assays, acute fatty liver)
i.	phosphate	- initially high but with R_X may fall precipitately like K^+ - replacement no proven benefit on mortality - may reduce the time to recovery and insulin needs

j. ketones drag H^+ with them in urine, up to 10 mmol H^+/hr

k. ***lactic acidosis*** may mask a small ketoacidosis ∝ ***low redox state***
- ↑ β-OHB - which is ***not*** measured by ketone tests
- ↓ AcAc - which is measured by ketone tests

- ***Treatment***

a. resuscitate - ABC

b. fluid/volume resuscitation

i. colloid ~ 10-20 ml/kg prn

ii. crystalloid*

- **0.9% saline**
- **0.45% saline** - if corrected Na^+ > 150 mmol/l

iii. dextrose - when BSL < 20 mmol/l
- total body ***deficit*** in energy substrate

Fluid Requirements	
Hour	Crystalloid*
1st	• 15-20 ml/kg
2nd	• 10-15 ml/kg
3rd	• 5-10 ml/kg
4th	• 5-10 ml/kg
5th & over	• 2-5 ml/kg

c. ***insulin***

i. loading dose ~ $10\text{-}20^U$ IV
~ 0.25U/kg

ii. infusion (U/hr) ~ BSL / 8 (mmol/l)

d. ***potassium*** ~ 20 mmol/hr
~ 0.3 mmol/kg/hr
* 30-50 mmol/hr if HCO_3^- used
± $H_2PO_4^-$ and Mg^{++}

e. HCO_3^- - consider if persistent pH < 7.0
- give 1 mmol/kg in 500 ml (~1.4%) over 1 hr
* ***no*** evidence for benefit

f. Na/K-H_2PO_4 - consider if [plasma] < 0.7 mmol/l
- give as K^+ salt 7-10 mmol/hr

g. $MgSO_4$ - no need unless tachyarrhythmia

h. ***treat underlying cause***

- ***Other Management***

  a. repeated monitoring
     - vital signs
     - UO, CVP
     - pH, P_{aO2}, K^+, Na^+, glucose

  b. low dose ***heparin***

  c. appropriate ***antibiotics***
     - no benefit unless good evidence for infection, ie. febrile & symptoms

  d. other Ix:
     - ECG
     - blood cultures and sepsis workup
     - coagulation

- ***Causes of Hypokalaemia***

  a. extracellular shift with acidosis
     + osmotic diuresis → major cause

  b. vomiting

  c. neutralisation of ketones

  d. renal Na^+/K^+ exchange ∝ 2° hyperaldosteronism

  e. total body K^+ deficit **~ 200-700 mmol**
     ~ 15-55 grams !

- ***Complications of Rapid Correction***

  1. ***hypokalaemia***
  2. hypophosphataemia
  3. hypernatraemia
  4. ***hypomagnesaemia*** & dysrhythmias
  5. ***cerebral oedema*** * especially children

Cheyne-Stokes Breathing

Def'n: abnormal crescendo-decrescendo pattern of periodic breathing

- ***Physiological***

  a. infants during sleep

  b. occasionally in otherwise healthy persons

- ***Pathological***

  a. cerebral injury
     - vascular
     - trauma
     - oedema
     - infection

  b. overdose of respiratory depressants, esp. narcotics

  c. slow circulation time
     - cardiac failure
     - elderly

BRAIN DEATH

Def'n: ***1. irreversible*** cessation of ***all functions*** of the brain,

1. loss of consciousness
2. loss of brainstem reflexes
3. loss of respiratory centre function, ***OR***

Def'n: ***2. irreversible*** cessation of intracerebral ***blood flow***

the terms "whole brain death" and "brainstem death" ***should not*** be used

- ***Preconditions***

1. presence of an identifiable cause for ***non-remediable*** structural brain damage
2. absence of,
   - i. CNS depressant drugs > 72 hrs with normal renal function
   - ii. hypothermia T > 35°C
   - iii. metabolic or endocrine disturbances

- ***Testing***

1. absence of ***brain stem reflexes***
   - i. fixed, dilated, unresponsive pupils
   - ii. corneal reflex
   - iii. vestibulo-ocular reflexes - clear intact tympanic membranes
     - 20 ml iced saline
     - oculo-cephalic reflex *optional, not formally required
   - iv. cranial nerve motor response to pain
   - v. gag reflex
2. no spontaneous ***respiration*** with 1. P_{aCO2} > 60 mmHg
   2. pH < 7.3
3. confirmation of the above on ***two occasions***, independently by ***two examiners***

NB: ***spinal reflexes*** may be present

- ***Guidelines: ANZICS***

• "rule of 2's"

1. 2 separate examinations
2. 2 different examiners
3. 2 separate occasions
4. ***at least* 2 *hrs apart***

• the first examination should not take place until the patient has been comatose for ***at least* 4 *hrs***
• following ***hypoxic*** brain injury, the first examination should occur after ***at least* 12 *hrs***
• during this time there must be a continuous period of ***observation*** by nursing staff
• the 2 practitioners may choose to be present at each examination, however, each must perform and be responsible for one of the 2 examinations
• there is no legal requirement for certification of persons not considered for removal of organs for transplantation, though, this is ***encouraged***

• if the ***preconditions*** for clinical diagnosis of brain death cannot be established, then,

1. 4 vessel contrast, or digital subtraction ***angiography***, or
2. radionuclide cerebral perfusion scanning

may be used to demonstrate ***absent intracranial blood flow***

NB: the final certificate of death, however, should be signed by 2 practitioners qualified as such, but not including the practitioner who performed the scan

• the ***time of death*** should be recorded as the time of completion of the second examination

CEREBRAL OEDEMA

Def'n: an increase in the total water content of brain tissue, classically divided into 3 types

1. ***vasogenic***
2. ***cytotoxic***
3. ***interstitial***

Vasogenic Cerebral Oedema

Def'n: oedema resulting from increased ***capillary permeability***

- forms in the grey matter but distributed mainly in the more compliant ***white matter***
  a. ECF ~ plasma filtrate, including the plasma ***proteins***
  b. ECF volume is increased

- the EEG shows ***focal slowing***
- associated with,
  a. tumour[§]
  b. cerebral abscess[§]
  c. encephalitis, meningitis
  d. traumatic head injury * mixed vasogenic/cytotoxic
  e. haemorrhage
  f. cerebral vasospasm, hypertensive encephalopathy
  g. TTP/HUS, pre-eclampsia
  h. cerebral vasculitis, SLE
  i. metabolic encephalopathy
     - sepsis
     - hepatic, uraemic
     - electrolytes, hypoglycaemia

- ***Treatment***
  a. ***steroids*** are only useful in abscess or tumour[§]
  b. osmotherapy
     - only useful acutely
     - only if ***autoregulation*** is normal
     - reduces the volume of remaining ***normal*** brain tissue
  c. management of primary condition

Cytotoxic Cerebral Oedema

Def'n: oedema resulting from cellular ***membrane failure*** & swelling

- neuronal, endothelial and glial cells involved
- both grey and white matter are involved
- there is increased ***intracellular*** water and Na^+
- ECF volume is decreased & there is ***no*** increased permeability of capillaries *???
- the EEG shows generalised slowing
- occurs in association with,
    a. hypoxia / ischaemia, cerebral anoxic damage
    b. hypo-osmolar syndromes, water intoxication
    c. dialysis disequilibrium
    d. Reye's syndrome, acute hepatic failure
    e. meningitis / encephalitis

- ***Treatment***
    a. steroids of ***no benefit***
    b. osmotherapy - only in hypo-osmolar setting

Interstitial Cerebral Oedema

Def'n: oedema resulting from ***hydrocephalus*** or raised CSF pressure

- results from CSF circulation blockade
- oedema occurs mainly in ***periventricular white matter*** & ECF is increased
- the EEG is often normal
- occurs in association with,
    a. obstructive hydrocephalus
    b. pseudotumour cerebri
    c. meningitis

- ***Treatment***
    a. steroids, osmotherapy and acetazolamide are of uncertain or little use
    b. ***shunting*** is beneficial for,
        i. high pressure hydrocephalus
        ii. normal pressure hydrocephalus + neurological signs

CEREBRAL ISCHAEMIA

NB: has come to encompass: *"any diminution of flow sufficient to cause symptoms"*
this may result from reduction in O_2 and substrate delivery,
and/or insufficient removal of toxic metabolites,

a. ***global ischaemia*** - cardiac arrest

b. ***global hypoxaemia*** - drowning, suffocation
- other causes of respiratory failure
- initially associated with *hyperaemia*

- LIGW divides these into ***incomplete*** and ***complete global ischaemia***
- clinical & experimental studies suggest normothermic brain is unable to withstand complete ischaemia for > 8-10 min
- ICP is rarely elevated significantly & severe cerebral oedema rarely follows
- in all cases, except ***intentional cardiac arrest***, brain protection is limited to reducing the period of the insult and resuscitation measures

c. ***focal ischaemia***

i. stroke - thrombotic, embolic, haemorrhagic
- atherosclerosis, remote/local
- valvular heart disease

ii. aneurysms, AVM's

iii. tumours

iv. surgical - SAH, CEA

- ***focal ischaemia***, is far more likely to occur during anaesthesia
- the frequency of ***perioperative stroke*** varies,

a. carotid endarterectomy ~ 1-20%

b. CABG surgery - at least 1%
- most authors ≤ 5%

NB: given the finding that CEA is superior to medical treatment
with ***symptomatic stenosis*** **> 70%**, the frequency is not likely to decrease

- accordingly, as with intentional circulatory arrest, cerebral protective measures should include,

1. prophylactic pharmacology
2. procedural intervention during detected ischaemia
3. initiation of resuscitative measures prior to irreversible neuronal death

▪ ***Normal Cellular Events***

• the brain uses **~ 20%** of total body VO_2 ~ 50 ml/min
~ 3.5 ml/min/100g

a. preservation of ***cellular integrity*** **~ 40%**

b. transmission of ***neuronal impulses*** **~ 60%**

• when O_2 is abundant, glucose is metabolised to pyruvate, generating ATP from ADP & Pi and NADH from NAD^+
• complete metabolism of pyruvate in the CAC results in regeneration of NAD^+
• in the mitochondria, conversion of $NADH + H^+ \rightarrow NAD^+$ is coupled (albeit indirectly) to the production of ATP from ADP & Pi

a. the energy from 1 NADH yielding 3 ATP molecules

b. on balance this results in the generation of **38 ATP** per glucose molecule

• the brain contains low concentrations of ATP & stores minimal glucose as glycogen
• therefore it requires a near constant energy supply
• glucose is transported into the CNS by facilitated diffusion, ***independent*** of the action of ***insulin***

• failure of the Na^+/K^+-ATP'ase $\rightarrow$ $\uparrow$ intracellular Na^+, which in turn,

1. depolarises the membrane, activating ***voltage dependent*** Ca^{++} channels
2. reduces the clearance of intracellular Ca^{++}

NB: reduction of intracellular Ca^{++} is an energy dependent process, however, accumulation is passive

• ***calcium*** plays an integral role in intracellular function,

a. inhibition of certain enzyme systems - hexokinase

b. stimulation of enzyme systems - Ca^{++}-ATP'ase
- adenylate cyclase
- ***phospholipases A & C***

c. regulation of actin-myosin interaction - MLCK (smooth muscle)

d. Ca^{++}-dependent neurotransmitter release

■ ***The Ischaemic Penumbra***

• in the face of declining O_2 supply neuronal function deteriorates progressively rather than in an "all or none" fashion
• the ***ischaemic thresholds*** for CBF have been well established,

a.	normal CBF	~ 45-55	ml/100g/min	
b.	EEG evidence of ***ischaemia***	~ 22	ml/100g/min	~ 40-50%
c.	EEG becomes ***isoelectric***	~ 15-18	ml/100g/min	~ 30%
d.	irreversible ***neuronal death***	~ 6-10	ml/100g/min	~ 15%
NB:	CBF / SaO_2 combinations	< 2 ml O_2	/min/100g	

• as CBF falls below ~ 15 ml/100g/min the decrease in energy supply is ***progressive*** and neuronal damage occurs, but over a time course of hours rather than minutes
• this region will display EEG evidence of ischaemia but may the recovery some time later if flow is restored

■ ***Pathophysiology During Ischaemia***

a. ***ATP depletion***
- in the absence of O_2, the mitochondria neither generate ATP nor regenerate NAD^+ from NADH
- in order to allow glycolysis to proceed, pyruvate is metabolised to ***lactate***, regenerating the NAD^+ required for the conversion of phosphoglyceraldehyde to 3-phosphoglycerate
- Pinsky *et al.* would argue that the reduction in ICF pH is due to,

i. the unreplenished hydrolysis of ATP $\rightarrow$ ADP + H^+

ii. ***not*** pyruvate $\rightarrow$ lactate, as this generates no net H^+
  - H^+ reduction of pyruvate released when PGA $\rightarrow$ 3-PG

- on balance this results in the generation of **2 ATP** per glucose molecule
- after ~ 20 sec of complete ischaemia synaptic transmission is no longer possible and the EEG becomes ***isoelectric***
- creatine phosphokinase approaches zero at 1 min and ATP at 5-7 minutes

b. ***Ionic failure***
- the later process is insufficient to sustain homeostatic cellular function
- initially there is a failure of the Na^+/K^+-ATP'ase
  $\rightarrow$ an efflux of K^+ and an influx of Na^+ and Cl^-
- when ECF K^+ reaches ~ 15 mmol/l membrane depolarisation and opening of ***voltage dependent*** Ca^{++} channels results in massive Ca^{++} influx
- membrane bound Ca^{++} pumps fail, in part due to the reduction in ATP, but also due to the increased load of Ca^{++} & the raised intracellular Na^+
- these ion exchange failures become unabated within 2-4 minutes

c. ***Excitatory neurotransmitter release***

- depolarisation leads to the release of excessive ***glutamate & aspartate***
  → excitatory neurotransmitter at NMDA, AMPA & kainate receptors
- these receptors are,

i. concentrated in areas most vulnerable to ischaemia

ii. coupled to an ionophore → extremely high Ca^{++} conductance
→ ***ionotropic***

iii. coupled to metabolic processes → ***metabotropic***

- activity is raised during periods of neuronal hyperactivity, eg. following ischaemia
- activation induces "burst-firing" which may be responsible for ***ischaemic seizures***
- unlike other excitatory receptors, there is ***no down-regulation*** during ischaemia

Receptor	**Functions**	**Modulatory Sites**
NMDA	• opens Ca^{++}/Na^{+} channels • modulates 2nd messengers	• glycine binding site • channel site Mg^{++} MK-801 pH-sensitive polyamine site NO binding site
AMPA	• opens Ca^{++}/Na^{+} channels	• benzodiazepine modulatory site
Kainate	• opens mainly Na^{+} channels	
	<u>Up-Regulation</u> • O_2 free radicals • Ca^{++} • glycine • substantia nigra input • nitric oxide	**<u>Down-Regulation</u>** • hypothermia • Mg^{++} • adenosine • catecholamines (AD, NA) • zinc • GABA'ergic neural input

d. ***Calcium accumulation***

- raised ICF Ca^{++} leads to activation of ***phospholipases A & C***, with subsequent hydrolysis of membrane lipids and accumulation of ***arachidonic acid***
- FFA's have been shown to increase throughout the ischaemic period
  → membrane damaging effects & organelle dysfunction
- during incomplete ischaemia, as in ***reperfusion***, arachidonic acid is further metabolised to ***prostaglandins, thromboxanes & leukotrienes***
- oxidation also produces ***free radicals*** which lead to lipid and protein damage

e. ***Nitric Oxide***

- one of the principal neurotransmitters of the CNS
- synthesized from ***l-arginine*** by ***NO-synthase***
- three major forms of NOS → brain, endothelial and macrophage
- 2 functional subtypes,

i. constitutive NOS (cNOS) - brain & endothelium
- activated by Ca^{++} / calmodulin

ii. inducible NOS (iNOS) - macrophages

- when l-arginine concentrations are low, cNOS can form toxic free radical species
→ superoxide & hydrogen peroxide
- iNOS is ***calcium independent*** and can form large quantities of NO in response to cytokine & lipopolysaccharide stimulation
- CNS NO levels show a ***triphasic*** response with,

i. ischaemia - [NO] increases then decreases with prolonged ischaemia

ii. reperfusion - [NO] increases again

- studies have given variable results, probably as reduced species also exist,

i. NO - activates the NMDA receptor

ii. $NO\cdot$ - reacts with superoxide to form ***peroxynitrite*** ($ONOO^-$)

iii. NO^+ - reacts with thiol groups on NMDA & blocks the receptor

f. ***Lactic acidosis***

- animal studies using MCA occlusion show almost a 4-fold rise in lactate within 30 minutes, with levels rising to ~ 17 mmol/kg by 3 hours
- levels in the region 16-20 mmol/kg are considered the threshold above which tissue damage occurs

i. necrosis of endothelial cells & rupture of astrocytes
→ reduced collateral flow

ii. denaturation & inactivation of cellular proteins

iii. suppression of the generation of NAD^+ from NADH

iv. production of O_2 free radicals

- other authors claim lactate itself is fairly ***innocuous*** and that it is the associated pH change which results in cellular damage

g. ***Glucose potentiation of ischaemic damage***

- supported by primate models of focal and global ischaemia, and by ***retrospective*** outcome studies of global ischaemia in humans
- during complete ischaemia, high brain levels of glucose allow continued anaerobic glycolysis, with the production of H^+ and lactate
- IV administration of glucose during or prior to an ischaemic event may worsen neurological outcome and should ***perhaps*** be avoided in high risk situations, ie. cardiac surgery and carotid endarterectomy

h. ***Free radical generation***

- a free radical is a chemical species with an ***unpaired electron***
- ***superoxide*** (O_2^-) appears to be one of the important species
- ischaemia increases levels of reducing species (NADH, lactate, H^+, xanthine)
- xanthine dehydrogenase is converted to ***xanthine oxidase***, ? 2° to Ca^{++}
- this enzyme is the major source of O_2^- during ***reperfusion*** of ischaemic tissue
- other species produced include lipid peroxide (ROO^-), lipid hydroperoxide ($RHOO^-$) and hydrogen peroxide (HO^-)
- mechanisms of damage include,

i. ↑ ***phospholipase*** activity & arachidonic acid formation
ii. ↑ membrane permeability & Ca^{++} influx
iii. protein cross-linking and strand scission
iv. release of enzymes from liposomes
v. mitochondrial disruption and decreased ATP formation

- ***superoxide dismutase*** catalyses the conversion of O_2^- to H_2O_2, which is then converted to water and oxygen
- there is no physiological defence system against HO^- radicals (? catalase)

■ ***Reperfusion Injury***

• during ischaemia ***autoregulation*** is non-functional and perfusion is dependent upon CPP and vessel calibre
• reperfusion results in a 15-30 minute period of 100-200% ***hyperaemia***
• this is the result of formation of ***NO*** and ***adenosine*** from the breakdown of AMP
• ***adenosine*** has protective effects during ischaemia, but its breakdown products may lead to a surge of free radical formation
• followed by a prolonged (6-48h) period of ***hypoperfusion***, which is usually heterogeneous
• CBF decreases to ~ 5-40% of 'normal' due to arteriolar vasoconstriction, the ***no reflow phenomenon***, which is proportional to the decrease in C-VO_2
• ***endothelial*** cell damage results in an imbalance of the production of PGI_2 & TXA_2
• free radicals react with membrane phospholipids to produce ***lipid peroxides***, which selectively inhibit the formation of prostacycline
• upon reoxygenation the large pool of arachidonic acid is then converted predominantly to

thromboxane → vasoconstriction
platelet aggregation
microvascular occlusion

• other factors contributing to the decrease in CBF include,

a. ↑ Ca^{++} in vascular smooth muscle → ***vasoconstriction***
b. ↓ RBC deformability during ischaemia → ↑ blood ***viscosity***
c. ischaemic ***cytotoxic oedema*** → ↑ extravascular resistance
d. ***vasogenic oedema*** (hours-days) → ↑ extravascular resistance

Mechanisms of Repair

• excititoxic neurotransmitters, eg. ***glutamine***, and subsequent Ca^{++} entry

→ transcription / translation of ***immediate early genes*** **IEG's**

• IEG's, like ***cfos*** and ***cjun***, signal the coding for ***repair proteins***
• requires coordinated production of "stress proteins",

1. HSP family
2. nerve growth factor NGF
3. glucose transporters GT_{1-3}
4. brain-derived neurotrophic factor BDNF
5. neurotroponin-3 NT_3

• highest levels occur in damaged cells capable of survival, and as a part of ***diachisis***
• induction of these substances prior to ischaemia, or enhanced production following ischaemia is protective in animal models
• conversely, with inhibition damage is enhanced

NB: thus, agents which block ***excitotoxicity*** can themselves be harmful, depending upon the time-frame of administration

• IEG's also stimulate the expression of genes for ***programmed cell death*** **PCD**
• neurones dying from necrosis ultimately succumb from disrupted membrane integrity
• those dying from PCD shrivel up with their membrane intact, while DNA is autodigested
• this is the same process as ***apoptosis*** which occurs during development, weeding-out approximately half of the neurones produced during neurogenesis, selecting those with appropriate functional interconnections

NB: much of the delayed neuronal death subsequent to reperfusion appears to be due to PCD, ∴the assumption that all neuronal death is bad may be quite incorrect;

this is supported by the known ***poor correlation*** between functional outcome and histological damage

• damaged circuits may effectively add ***noise*** and render the system non-functional unless removed

Cerebral Protection

Def'n: physical or pharmacological actions aimed at mimising ***neuronal death*** secondary to an ischaemic event, including ***neuronal salvage*** following such an event

- ***Strategies for Protection***

1. increasing regional ***blood flow*** and $\mathbf{DO_2}$
2. decreasing ***metabolism***
3. preventing/reducing loss of normal cellular ***ion gradients***
4. blocking production of ***toxic metabolites***
5. ***scavenging*** those metabolites which are produced

- ***Methods of Protection***

1. ***physiological / homeostatic***
   - i. maintenance of — MAP, CPP, DO_2
   - ii. prevention of — hypoxia, hypercarbia, acidosis; * ***hyperglycaemia***; hyponatraemia, hypoosmolality
2. ***physical***
   - i. hypothermia — deep hypothermic arrest / mild hypothermia; * following arrest, no benefit & may be harmful
   - ii. haemodilution
   - iii. hypertension
   - iv. surgery — CSF drainage, decompression
3. ***pharmacological***
   - i. depression of C-VO_2 — barbiturates, propofol, etomidate, benzodiazepines; volatile GA's
   - ii. Na^+-channel blockade — lignocaine, QX-314, QX-222
   - iii. Ca^{++}-channel blockade — nimodipine, nicardipine, flunarizine, Mg^{++}
   - iv. glutamate receptor blockade
     - NMDA — ***dizocipline*** (MK-801), dexmedetomidine, dextromethorphan
     - AMPA — NBQX
   - v. membrane stabilisation
     - steroids — methylprednisolone
   - vi. free radical scavenging
     - vitamin E, steroids, dihydrolipoate, PEG-SOD

NB: some agents, eg. STP, may act via ***multiple effects***

Hypothermia

• remains the most effective means of reducing C-VO_2,

a. Temp ~ 27°C → C-VO_2 ~ 50%

b. Temp ~ 17°C → C-VO_2 ~ 8%

NB: the need for formal testing is obviated by the observation that human brains often recovery after an hour of intentional circulatory arrest at 12-15°C

• although hypothermia to 28°C is routinely used during non-circulatory arrest bypass surgery, its efficacy has not been ***prospectively*** established
• Wong *et al.* (Lancet 1992) compared warm CPB (34.7°C) with hypothermic CPB (27.8°C)

a. all seven neuropsychological tests were "better" in the "warm" group, however, only one test difference achieved statistical significance

b. this would support that ***mild hypothermia*** is equally "protective", though, this is a preliminary study and numbers are too small to draw statistical significance

• recent laboratory work suggests that the principal protective effects of hypothermia are due to reduced ***glutamate & dopamine*** release
• unfortunately, the deleterious membrane effects of hypothermia are quantitatively similar to those of ischaemia, but simply take longer to develop
• hypothermia, however is not nearly as deleterious as ***normothermic hypoxia***
• accordingly, patients subjected to deep hypothermia & circulatory arrest can usually re-establish ion gradients if ***perfusion*** is restored
• this is a reasonable prospect following bypass, but is unlikely if the heart is relied upon for circulation, as the adverse membrane effects impair cardiac function

Mild Hypothermia

• in distinction to deep hypothermia, the beneficial effects of ***mild hypothermia*** are likely to outweigh the manageable adverse effects (NB: Sano *et al.* Anesth., 1992)
• effects of intraoperative mild hypothermia are attributed to,

1. reduction of ***glutamate, glycine*** and ***dopamine*** release
2. recovery of ***ubiquitin*** synthesis
3. inhibition of protein kinase C
4. reduction of free-radical induced ***lipid peroxidation***

NB: however, probably relates to diminution of ***all*** of the adverse effects of ischaemia

• Berntman *et al.* (Anesth.1981) found that **1°C** of hypothermia maintained ATP levels during a hypoxic insult which resulted in 50% depletion at 37°C
• hypothermia to 34°C more than doubles preservation of PCr
• the initial decline in C-VO_2 during hypothermia appears ***exponential***, not linear
• 4 recent (animal) studies have shown improved CNS ***outcome*** even when hypothermia (31-34°C) was induced ***subsequent*** to the injury
• LIGW states ***no benefit*** post-global ischaemia, but references are old

Induced Hypertension

- in focal ischaemia, improved outcome is the result of better ***colateral flow***
- following global ischaemia, this may reduce the degree of post-ischaemic hypoperfusion
- gaining some evidence for reduction of deficits
- however, associated risks of,

1. elevating ICP
2. rebleeding / ICH
3. aggravating oedema

Anaesthetic & Adjuvant Drugs

- reducing C-VO_2 is the main theory for pharmacological management of ischaemia
- ***barbiturate*** administration is the only such intervention which has proven useful in humans
- only during ***focal ischaemia***, where BBTs have been shown in numerous studies to reduce infarct volume
- in addition to lowering C-VO_2, pentobarbital often reduces ICP refractory to mannitol & hyperventilation
- some experimental work in animals suggests that a part of the protective effect of the barbiturates is due to vasoconstriction in healthy brain with shunting of CBF to the injured area
- however, other workers have argued against this effect, "***reverse steal***" (GOK)
- other effects include,

1. reducing the influx of Ca^{++}
2. inhibiting free radical formation
3. potentiation of GABA'ergic activity
4. reduction of cerebral oedema
5. ability to block Na^{+} channels *may be 1° mechanism of ↓ C-VO_2

- the ability of the barbiturates to be protective after ***global ischaemia*** remains controversial

NB: the one large randomised study (NEJM Study Group 1986) found only a statistically ***insignificant*** trend in favour of barbiturate therapy following cardiac arrest

" therefore, use of barbiturates should be restricted to management of status epilepticus, and to facilitate mechanical ventilation" (LIGW)

- ***propofol*** reduces CBF, C-VO_2 and ICP similar to STP, but with a faster recovery
- may cause dramatic falls in CPP 2° to reductions in MAP >> ICP
- has been shown to be protective of hippocampal neurones following ~ 7 minutes of anoxia
- protective effects have been disputed by more recent studies

- ***midazolam*** reduces C-VO_2 in humans and animals and has shown some protective effects for hippocampal neurones following anoxic damage, by maintaining ATP and reducing Ca^{++} efflux

Calcium Channel Blockade

• early studies with ***nimodipine*** showed benefit, however even the benefit following acute ***subarachnoid haemorrhage*** has now been seriously challenged (Mercier *et al.*, Neurosurg '94)
• the National Stroke Association (USA) still recommends nimodipine 60 mg qid for grade 1,2 & 3 SAH patients, preferrably starting within 6 hours of haemorrhage
• initial enthusiasm for use following ***ischaemic stroke*** and head injury has diminished
• a meta-analysis of pooled data from 5 studies showed a small benefit if administered early (12-18 hours) after the onset of symptoms (Gelmers *et al.*, Stroke 1990)
• some of the lack of efficacy may relate to the presence of multiple Ca^{++} channels, as the ***dihydropyridine*** class only block voltage gated L-channels
• PRCT of 51 cardiac arrest patients showed a reduction in the "no reflow" phenomenon, but there was no alteration of ***outcome*** (Forsman, *et al*, Anesth-Anal '89)
• PRCT of 520 cardiac arrest patients & IV ***lidoflazine*** showed no improvement in neurological outcome (Brain Resuscitation Clinical Trial II Study Group, NEJM 1991)

• ***nicardipine*** is another agent with cerebrovascular relaxant properties, similar to nimodipine, but is easier to administer IV
• recent multicentre trial in SAH patients showed similar results to nimodipine,

a. angiographic and CBF measurements showed a reduction in ***vasospasm***
b. "no improvement in ***outcome*** at 3 months when compared to standard management"

• however, this study essentially compared the nicardipine group to a ***hypertensive/hypervolaemic*** group in ICU, monitored with PA and radial artery catheters, with the nicardipine group requiring significantly fewer days ICU

• other **Ca^{++}** ***channel blockers***, particularly ***flunarizine*** have shown potential for direct neuronal protection in laboratory work
• more recent work suggests the effects of flunarizine are probably due to Na^{+}-channel blockade
• **Mg^{++}** is a potent inhibitor of Ca^{++} entry and has shown protective action *in vitro* and has recently been shown to be beneficial *in vivo*

• **Na^{+}** ***channel blockers*** should contribute to the stabilisation of neuronal membranes
• both lignocaine and phenytoin have shown some promise in laboratory work
• quaternary LA derivatives **QX-314** and **QX-222** have been shown to be more protective than either lignocaine or procaine, with less conduction blockade
• ***riluzole*** has shown some protective action in animal models, and has been shown to be useful in the treatment of amyotrophic lateral sclerosis in humans

■ ***Excitatory Neurotransmitters***

• there has been a lot of recent research into the ***excitotoxic hypothesis*** of cerebral damage
• ischaemia results in the excessive release of the excitatory neurotransmitter ***glutamine***

> ***NB:*** "reducing glutamate release, either by direct inhibitors **BW1003C87** or **BW619C89**, or indirectly through modulation of ***adenosine***, is likely to prove more effective than blockade of glutamate receptors"

• the adenosine modulating agent ***acadesine*** has reduced perioperative stroke rate in 634 CABG patients from 4.5 to 0.5% (Mangano, A&A Refresher Lectures 1994)

• both NMDA and non-NMDA glutamate receptor blockers have proven beneficial in some studies but not in others,

1. **MK-801** → ***dizocipline***, a non-competitive NMDA receptor antagonist
   - protective in a variety of laboratory models
   - effective both with and without hypothermia
   - in conjunction with nimodipine, nicardipine and the σ-agonist SKF-10,047
   - results from less sensitive models disappointing
2. **NBQX** → an ***AMPA*** glutamate receptor antagonist (non-NMDA)
   - results may prove better than dizocipline
   - beneficial in a laboratory model of global ischaemia
3. ketamine & ***dexmedetomidine*** → NMDA receptor antagonism
   - both may show some protective effects due to catecholamine reduction
4. ***dextromethorphan*** → non-competitive NMDA antagonist
   - protective effects in focal ischaemic models
   - undergoing phase I trials in humans
5. CGS-19755
   - competitive NMDA blocker
   - beneficial in a laboratory model of global ischaemia
6. 2 endogenous inhibitors of excitatory AA receptors, ***kynurenic acid*** and ***IL-1 receptor antagonist*** have been shown to reduce excitotoxic damage
7. ***muscimol*** → increases levels of the inhibitory neurotransmitter GABA
   - derived from *Amanita muscaria*
   - has been effective in animal models in combination with dizocipline

• ***free radical scavengers*** should theoretically be beneficial
• NO and CO are examples of free radicals which are normal neurotransmitters but are toxic in higher concentrations
• these and other radicals are removed by ***superoxide dismutases***

> ***NB:*** there are no randomized clinical trials showing benefit, post cardiac arrest, for any of these agents

• large studies of ***glucocorticoids*** following cardiac arrest have shown ***no benefit*** in outcome
• conversely, a large randomised controlled trial has shown that the administration of ***methylprednisolone*** administered within 8 hours of injury reduces spinal cord deficit
• this has not been supported by a subsequent study and routine administration post spinal injury is now uncertain
• ***vitamin E*** has proven protective *in vitro* with some supportive evidence *in vivo*

• the 21 amino-steroid ***tirilazad*** (U74006F) has recently entered phase 3 trials
• initial reports showed substantial benefit in SAH

• ***superoxide dismutase*** has recently been shown to be of benefit during reperfusion
• a preliminary study showed some benefit in CHI
• subsequent RCT (PEG-SOD) showed ***no benefit*** in acute head injured patients
• the hydroxyl scavenger dimethylthiourea has been shown to reduce the infarct size and brain oedema following MCA occlusion in rats, without affecting CBF

NB: the principal problem with scavenging is the production of free radicals occurs after ischaemia has run its course & other methods of protection are likely to be required in conjunction, ie.

i. reduction in C-VO_2
ii. tolerance of ischaemia without loss of membrane ionic gradients

- ***Agents & Techniques to Avoid***

• ***hyperglycaemia*** has long been known to worsen the outcome following cerebral ischaemia
• laboratory evidence indicates that even a ***mildly*** elevated plasma glucose may be deleterious
• the assumption is that an increased supply of glucose leads to increased anaerobic metabolism and lactate production
• however, recent *in vitro* work suggests that an elevation of lactate per se ***does not*** lead to neuronal damage and may actually ameliorate some of the effects of ischaemia
• ***insulin*** has been shown to have a protective effect partially independent of a reduction in plasma glucose, however, ***hypoglycaemia*** is equally as detrimental

> ***NB:*** until the controversy regarding this is settled, glucose containing fluids are best avoided and ***normoglycaemia*** should be maintained

• all 3 of the commonly used volatiles increase CBF and ICP
• although ***isoflurane*** is considered safe for neuroanaesthesia, early enthusiasm for its protective effects ***have not*** been substantiated
• the association between C-VO_2 reduction and protection has been challenged upon these grounds, see argument by Todd & Hanson to follow
• others argue that all methods of CMR reduction have deleterious effects, and the net result is a combination of these superimposed upon the protective effect of CMR reduction (Cottrell, ASA)
• ie., the benefit of C-VO_2 reduction remains constant, but the cost of achieving this varies with the method used, ranging from mild hypothermia to irreversible neurotoxins

• ***nitrous oxide*** has been shown to,

1. ***elevate ICP*** in humans
2. aggravate the potential for ***gas embolism***
3. negate the protective effects of the barbiturates in laboratory studies
4. attenuate the beneficial effects of isoflurane relative to N_2O alone
5. reduce recovery subsequent to anoxia in the hippocampal slice model

• recent work has shown that the effects of N_2O on ICP and metabolic stimulation are markedly attenuated by the prior administration of thiopentone, or in the isoelectric brain

C-VO_2 & Cerebral Protection

• Todd and Hansen comment that we have long taken an approach to cerebral protection similar to that used for cardiac physiology, ie. control of ***supply and demand***
• the value of increasing supply is unarguable, however, that agents reducing C-VO_2 are also "protective" is open to debate

• Sano *et al.* compared three groups of rats anaesthetised with either 1.3MAC halothane or isoflurane, or halothane plus ***mild hypothermia*** (35°C)
• both normothermic groups showed histological evidence of severe damage, cf. the hypothermic/halothane group where damage was dramatically reduced
• at the levels used in this study, isoflurane

a. reduces the CMR for glucose by 30-50% more than halothane

b. produces burst suppression on the EEG

c. produces a far greater reduction in C-VO_2 compared with hypothermia to 35°C

NB: therefore, the degree of neuropathological injury in the 3 groups ***did not*** correlate with the magnitude of ***metabolic depression***

■ ***Michenfelder 1978***

• argued that the barbiturates acted by reducing C-VO_2 linked to synaptic activity
• he concluded that barbiturates would offer little protection if the brain were already ***isoelectric***
• he also carefully avoided the conclusion that protection is directly related to C-VO_2 *per se*
• most subsequent studies have interpreted his work as saying "*metabolic depression protects*"
• this idea requires modification for two major reasons,

1. the protective efficacy of the various anaesthetic agents ***does not*** parallel their ability to depress the EEG or C-VO_2
2. the protective efficacy of ***hypothermia*** is not proportional to depression of C-VO_2, nor is it clearly related to the accumulation of metabolic by-products

Alternative Approaches

- ischaemic injury can be temporally divided into three phases,

1. ***diminished energy reserve***
   - if ischaemia is mild, then anaesthetic agents and hypothermia can reduce C-VO_2 and "buy time"
   - with severe ischaemia this target period is short, less than 1-2 min, and probably of little clinical significance
   - once membrane depolarisation has occurred other means of protection are required

2. ***complete energy failure***
   - signalled by membrane depolarisation, marked Ca^{++} influx, triggering of metabolic pathways, excessive release of certain neurotransmitters
   - there are two basic mechanisms of protection during this phase,

   i. prevention of synthesis or release of these compounds

   ii. blockade at their site of action

   - it is well known that ***mild hypothermia*** can block the release of ***glutamate***, however, the effects of the anaesthetic agents is largely unknown
   - drugs such as ***dizocipline*** and NBQX block the action of glutamate at two of its receptors, NMDA and AMPA (quisqualate)
   - other agents, such as dexmedetomidine may act by augmenting inhibitory transmission

3. ***reperfusion injury***
   - the liberation of ***free radicals*** upon the reintroduction of oxygen
   - most anaesthetic agents are relatively poor free radical scavengers
   - in the absence of seizures, post-ischaemic hypermetabolism ***does not*** occur
   - therefore, agents directed at C-VO_2 are unlikely to have a profound influence

'Nontraumatic' Cerebral Ischaemia

Def'n: ***brain protection*****:** treatment implemented ***before*** a cerebral insult to prevent or minimise brain damage

brain resuscitation**:** treatment that is implemented ***after*** an insult to restore brain function

▪ *Cardiac Arrest / Global Cerebral Ischaemia*

• factors associated with improved cerebral ***outcome***,

1. short ischaemic time
2. rapid defibrillation - majority VF, pulseless VT
3. correct CPR with ~ 50% compression (depth)
4. use of adrenaline - animal models only, not in human PRCTs
5. no hyperglycaemia at time of arrest

• factors most important in improving cerebral outcome ***after*** successful CPR,

1. maintenance of oxygen delivery
2. prevention of secondary injury
   - hypotension, hypoxia, hypercarbia
   - convulsions
   - hyperpyrexia
   - see "reperfusion injury syndrome"

• modalities ***not*** associated with improved cerebral outcome,

1. IPPV - unless respiratory failure exists
2. ICP monitoring - ICH rare in this group
3. hypothermia
   - OK if pre-event but detrimental if prolonged
   - technically difficult, therefore no justification
4. haemodilution
   - may be of some use in ***regional ischaemia***
   - no proven benefit in global ischaemia
5. osmotherapy - mannitol, diuretics
6. steroids
7. barbiturates
   - conflicting animal studies
   - multi-centre UK clinical trial showed ***no benefit***
   * useful for 2° seizures or excessive posturing
8. Ca^{++} entry blockers
   - improvement in reperfusion flows
   - conflicting results about neurological outcome
   * but cause vasodilatation and negative inotropy
9. free radical scavengers, iron chelators, anti-inflammatories

• ***outcome*** may be classified as,

1. good recovery - recovery without demonstrable neurological deficit
2. moderate disability - sufficient cerebral function for daily living
   - clearly demonstrable neurological deficit
3. severe disability - neurologcial deficit requiring institutional care

• alternatively, may use Glasgow outcome score,

1. dead
2. vegetative
3. severely disabled - conscious but dependent
4. moderately disabled - independent but disabled
5. good - neuropsychological impairment or better

■ ***Immediate Outcome 48-72 Hrs***

• bad prognostic signs, in the absence of persistent drug or metabolic effects,

1. decerebrate, or no response to pain $M \leq 2$
2. no verbal response $V = 1$
3. no eye response $E = 1$
4. development of ***myoclonic seizures***

■ ***Delayed Outcome***

• ***delayed postanoxic encephalopathy*** may follow a lucid interval
• results from diffuse demyelination of the cerebral hemispheres
• occurs at 1-4 weeks post-event with,

1. cognitive or psychiatric impairment
2. cerebellar or pyramidal signs
3. may progress to coma

HEAD INJURY

- leading cause of ***death*** between the ages of ***15-24 years***
- incidence ~ 25-28:100,000 in Australia (1977) ***~ 1:4,000***
- hospital admission rates for head injury are ~ 200-300:100,000
- motor vehicle accidents accounting for ~ 60% of deaths 2° to head injuries
- ***severe*** or "malignant", **GCS < 7**, head injuries,
    a. form **~ 9-11%** of the total group
    b. incidence depends upon definition of "severe", (GCS < 9, 7, or 5!)
        - LIGW defines as head injury resulting in ***coma*** **> 6 hrs**

NB: aggressive management / ICU therapy has been shown to ***improve outcome***, ***without*** increasing the number of vegetative or severely disabled survivors (T.Oh)

▪ ***Pathology***

1. ***primary*** brain injury →
    i. diffuse axonal damage
    ii. expanding mass lesions - intracerebral, subarachnoid, subdural
        - extradural haematoma
    iii. dural tearing
2. ***secondary*** brain injury →
    i. cerebral ischaemia - hypotension, hypoxaemia, anaemia
        - hyperpyrexia, seizures
    ii. intracranial hypertension - hypertension, vasodilatation, ↑ CBF/CBV
        - venous obstruction
        - mass lesions

▪ ***Extradural Haematoma***

- classical presentation of LOC then ***lucid interval*** with subsequent rapid LOC
- has a high ***mortality*** £ ***30%*** in some series
- this relates to already comatose patients undergoing surgical evacuation
- LIGW states ~ **10-20%** & significantly lower than subdural due to relative absence of underlying cerebral injury
- mortality is significantly higher in those,
    1. requiring operative evacuation within 12 hours of admission
    2. with an ICP ≥ 35 mmHg
    3. age > 70

- administration of ***barbiturates*** is usually effective in reducing refractory intracranial hypertension

Subdural Haematoma

- results from shearing acceleration/deceleration forces & rupture of bridging veins
- ∴ relatively high ***mortality* ~ 42-63%** ∝ underlying injury
- collections presenting ***within* 72 *hrs*** of head injury are termed ***acute***
- following haematoma evacuation, acute ***cerebral oedema*** may complicate surgical closure
- these patients frequently require intensive pharmacological control of ICP

NB: Seelig *et al.* NEJM 1981 → significant reduction in mortality in the subgroup of ASDH with midline shift > 5 mm if operated on ***within 4 hrs***

- chronic subdural haematomas develop slowly and liquefaction has frequently already commenced
- therefore, they can frequently be managed by ***burr hole*** drainage
- outcome in this group largely relates to the ***preoperative state***

Dural Tear

- CSF rhinorrhoea following fracture to the frontal bone is often transient & requires only prophylactic flucloxacillin/gentamicin for 1 week after the leak stops
- identifiable by ***glucose*** > 2.2 mmol/l
- CSF otorrhoea indicates fractured base of skull & significant cerebral injury

NB: Infection in Neurosurgery Working Party, Lancet 1994
"review of the published work ***has not*** shown that prophylaxis is beneficial in patients with skull fractures complicated by CSF leaks; indeed, there is evidence that this strategy may be harmful.....antibiotics should be withheld and the patients should be monitored closely for signs and symptoms of early meningitis"

Intracranial Hypertension

- autoregulation is lost and perfusion becomes pressure dependent
- virtually all patients with severe head injury have ***reduced*** cerebral metabolism
- however, only ~ 45% have a reduction in CBF → ***luxury perfusion***
- this results in diffuse cerebral hyperaemia & ↑ ICP, usually lasting ~ 3-4 days

NB: there is ***no correlation*** in head injury between cerebral blood flow and GCS, or outcome at 6 months

ICP[1]		%Head Injury	Mortality
< 20	mmHg	30%	19%
20-40	mmHg	50%	28%
> 40	mmHg	20%	79%

[1] Miller *et al.* BJA 1985

Management

- about 75% of all HI patients admitted to hospital have a GCS ≥ 9 and recover irrespective of the standard of care
- of those with GCS < 9, many have a lethal primary injury and the level of care is virtually insignificant to outcome
- ∴ ~ **10%** have a borderline injury, with ***mortality* ~ 35-50%**, depending upon,
    1. extent of 1° brain injury
    2. age
    3. duration of coma
    4. degree of raised ICP
    5. associated injuries

- therapy in this group is directed at preventing ***secondary injury***, which may result from,
    1. hypoxia, hypercarbia, acidosis
    2. hypotension, vasospasm & hypoperfusion
    3. expanding intracranial lesions - focal masses
       - generalised oedema

- all patients GCS < 9 (?7) require immediate ***intubation***, mild hyperventilation and increased F_IO_2
    a. in-line axial head stabilisation if ***cervical pathology*** (~ 10%) has not been excluded
    b. nasal intubation should be avoided

    NB: hyperventilation to P_{aCO2} ~ 30 mmHg pre-CT in case there is an expanding mass lesion; once this is excluded, aim for 'normocapnoea' → P_{aCO2} ~ 35 mmHg

- correction of ***hypovolaemia*** 2° to blood loss takes precedence over either,
    a. CT scanning
    b. definitive neurosurgical intervention

- maintain normal ***C-VO$_2$***
    a. seizure prophylaxis
    b. normothermia - or mild hypothermia > 35°C
    c. control sympathetic hyperactivity

- maintain ***cerebral perfusion pressure*** → **60-90 mmHg**

- ***Neurological Sequelae***

a. malignant intracranial hypertension

b. acute mass effect
   - rebleeding
   - acute cerebral oedema

c. brain herniation syndromes
   i. nerve palsies
      - 3rd nerve palsy
      - 6th nerve palsy
   ii. cingulate gyrus
   iii. uncal gyrus
   iv. brainstem

d. epileptic seizure activity
   - **1-2%** of head injury patients have grand mal seizures within 48 hrs of injury
   - 5% of CHI and 40% of penetrating HI have seizures following major injury requiring prolonged antiepileptic therapy

e. posterior pituitary
   i. SIADH
   ii. central salt wasting syndrome
   iii. central DI

f. focal neurological deficits

g. vegetative survival

h. brain death

- ***Systemic Sequelae***

a. ***cardiopulmonary***

i. resuscitation
- airway obstruction
- hypoxia, hypercapnia, acidosis
- hypovolaemic shock

ii. ARDS
- aspiration pneumonitis
- pulmonary trauma, contusion

iii. neurogenic pulmonary oedema (NPE)

iv. ECG changes

b. ***haematological***
- DIC
- anaemia in children

c. ***endocrinological***

i. ant. pituitary * rarely

ii. central salt wasting syndrome

iii. nonketotic hyperglycaemic coma
- unrecognised diabetics
- prolonged steroid therapy
- mannitol, water restriction
- NG enteral feeding
- phenytoin

d. ***gastrointestinal***
- stress ulceration ± haemorrhage
- steroid therapy

• a number of these complications can occur in ***nontraumatic*** neurological disease
• persistent hypoxaemia requiring raised F_IO_2 or PEEP occurs in ~ 25%
• abrupt onset acute neurogenic pulmonary oedema can accompany severe head injury in young patients ***without*** a history of CVS disease
• this frequently proves refractory to conventional therapy and only resolves with reduction of ICP
• NPE is associated with intense ***sympathetic discharge***, with systemic ± pulmonary vasoconstriction
• thus, management aimed at blocking sympathetic outflow / activity may be useful

• ***tachyarrhythmias*** and ST segment changes may accompany SAH and severe head injury
• the sympathetic overactivity associated with these changes may actually result in punctate areas of myocardial necrosis
• bradycardias requiring treatment with atropine are also seen with raised ICP

• clotting abnormalities have been described following trauma and also manipulation of brain tissue during tumour resection
• this is thought to relate to the release of ***brain thromboplastin*** into the circulation
• ***mortality*** increases markedly when DIC complicates acute head injury
• the DIC is usually self-limiting and resolves with management of the primary problem
• blood component therapy is rarely required

Severe Head Injury

NB: competent early resuscitation is the most important factor

30-90% are ***hypoxic*** and/or ***hypercapnoeic*** on arrival at hospital

Factors in Secondary Injury	
Early	Delayed
• hypoxia | hypercarbia • hypotension • convulsions • hyperpyrexia • obstructed venous return • pain	• haemorrhage • hydrocephalus (high or normal pressure) • infection • chronic subdural • cystic hygroma

- ***Indications for Intubation / IPPV***

a. airway obstruction / protection

b. hypoventilation - P_{aCO2} > 45 mmHg

c. hypoxia on 60% F_IO_2 - P_{aO2} < 80 mmHg

d. tachypnoea - RR > 25

e. GCS < 9

f. hyperthermia

g. seizures

h. severe chest or abdominal injury

i. CT scan & need for sedation

j. ICP > 30 mmHg and unresponsive to therapy

Investigation	
Indications for ***CT head***	Indications for ***Skull XR***
• focal CNS signs	• moderate risk group • CT scan not necessary
• GCS < 9	• GCS ≥ 9
• deteriorating GCS without 2° cause	
• penetrating or depressed skull #	

ICP Monitoring

NB: those that ***may benefit*** from ICP monitoring (~ 40%)
are ***severe head injuries*** with,

a. GCS ≤ 8 and coma ≥ 6 hours
b. abnormal CT scan, plus either,
   i. evidence of ↑ ICP
   ii. focal lesion *with or without mass effect
   iii. abnormal motor posturing
c. where specialised ICP control measures will be undertaken,
   i. hyperventilation, muscular paralysis
   ii. mannitol
   iii. hypothermia
   iv. barbiturates

- ***Contraindications***

a. GCS > 8
b. normal CT * no evidence of ↑ ICP, but normal scan ***doesn't*** exclude oedema
c. bone flap or cranial decompression undertaken *relative
d. lack of technical expertise

- ***Alternatives***

a. repeat CT scans → "radiological ICP monitoring"
b. treat all high risk patients,
   - hyperventilation for 2-3 days
   - dehydration ± 1 or 2 doses of mannitol (if CT evidence of ICH)
   - prevent hyperthermia, seizures, hypotension, hypoxia, etc.

ICP & Intracranial Hypertension

Def'n: normal ***ICP*** ~ 10-15 cmH_2O
~ 7-10 mmHg

normal ***compliance*** > 0.5 ml/mmHg
< 0.25 ml/mmHg → ***pathological***

• significance of ICP is that it influences ***cerebral perfusion pressure***, **CPP = MAP - ICP**

a. for adequate perfusion, CPP ≥ 60 mmHg
b. normal autoregulation is ***impaired*** at, CPP < 50 mmHg
c. cerebral perfusion becomes ***critical*** at, CPP < **30** mmHg

- ***Raised ICP Physiological***

1. lowering of head
2. obstruction of jugular veins with head positioning
3. sleep
4. coughing, straining, Valsalve manoeuvre

- ***Raised ICP Pathological***

1. cerebral tumour, abscess
2. intracranial haemorrhage
3. cerebral oedema
4. hydrocephalus
5. hypercarbia / hypoxia / acidosis
6. severe hypertension
7. venous obstruction
8. metabolic - uraemia, Reye's syndrome

- ***Causes of Lowered ICP***

1. CSF leakage (chronic > 500 ml/day)
2. wasting diseases
3. hypocapnia
4. barbiturate therapy
5. elderly

Monitoring of ICP in Head Injury

- ***Rationale***

  a. intracranial hypertension is associated with a ***high mortality***

  b. ***clinical signs*** of raised ICP present only at very late stage

  c. of severe head injury patients,

i.	ICP > 10 mmHg	mild	~ 80%
ii.	ICP > 20 mmHg	moderate	~ 40%
iii.	ICP > 40 mmHg	malignant	**~ 15%**

  - ***'malignant ICH'*** → ICP > 40 mmHg for 15 min
  - those with normal CT scan (10-20%) rarely have raised ICP
  - neurological deterioration at levels above 15-25 mmHg

  d. studies claim up to **40% *reduction*** in mortality with treatment,
  without an increase in the number of vegetative/poor outcome patients

- ***Evidence Against***

  a. not ***conclusively*** proven to be of benefit
  - many studies have been uncontrolled, not blinded and sequential

  b. of all head injuries only 25% are severe, of which ~ 50% die from the primary damage
  - ICP monitoring → only affects **~ 10-15%** of head injuries

  c. the correlation between ICP and functional status is not always consistent and must be tempered by clinical assessment

  d. risk of ***infection*** varies widely between studies from 1-20%!

  e. rises in ICP may take up to 2 weeks to dissipate even in good outcome patients

  f. subarachnoid bolt is unreliable at high ICPs

  g. pressure in one compartment is not necessarily indicative of global pressure

- ***Major Dangers***

  1. haemorrhage
  2. patient / cerebral injury
  3. infection ~ **2-7%**
  4. system inaccuracy or failure
  5. sole reliance of management on ICP

Treatment: Intracranial Hypertension

1. treat ***hypoxia***, acidosis, & hypotension - cerebral O_2 supply
2. hyperventilation and hypocapnia
   - useful as an interim measure to reduce ICP prior to definitive or other therapy
   - chronically of little use → 75% of $S_{jb}O_2$ desaturation (Lewis *et al.* AIC 1995)
   - current recommendation → **P_{aCO2} ~ 30-40 mmHg**
   - plus sedation/paralysis as required
   - article in J.Trauma → ↓ outcome with use of paralysis
3. ***posture*** → 0-10° head up
   - avoid extreme rotation
   - Rosner (1986) showed that for every 10° head up
     → ICP fell 1 mmHg but CPP fell 2-3 mmHg, ∴ may be ***no advantage***
4. ***osmotherapy / mannitol***
   - mannitol effective only if autoregulation intact
   - reduces viscosity, increases flow, ∴ reflex vasoconstriction
   - maximal ICP reduction at ~ 15-20 min, lasting ~ 3-4 hrs
   - mild hyperosmolarity ~ 320 mosm/l ≡ 2x increase in urea
   - a serum:CSF osmolar gradient ~ 30 mosm/kg required to reduce brain H_2O
   - fall in CBF → ? adenosine
   - ***hypertonic saline*** has also been used, advantages of no diuresis & ability to monitor plasma levels more accurately
5. ***diuretics***
   - frusemide inhibits Na/H_2O transport across the BBB → ↓ CSF formation
   - acetazolamide also reduces CSF formation but is less effective in ↓ ICP
   - frusemide / mannitol are synergistic when frusemide administered first (15 min)
6. ***hypothermia***
   - may be helpful if initiated very early
   - prolonged deep hypothermia is equally detrimental as ischaemia
   - technical difficulties, therefore not used
   - recent work (Sano *et al.*) mild hypothermia may offer significant benefits
   - ***hyperthermia*** is definitely detrimental & requires aggressive treatment
7. ***barbiturates***
   - STP ~ 10 mg/kg/30 min, then 5 mg/kg/hr x 3 hrs, then 1 mg/kg/hr
   - no improvement in outcome
   - may result in increased number of vegetative patients
8. propofol → too much hypotension & ↓ CPP
9. Ca^{++} entry blockers - Nimodipine
   - questionable role in prevention of vasospasm
   - still recommended for SAH, but studies divided

Post-Traumatic Hydrocephalus

a. incidence - depends on definition and measurement of ventricular size
~ 30-72%

b. mechanisms
- impairment of ***absorption*** of CSF
- impairment of ***flow*** of CSF
- blockage is usually around the convexities (extra-ventricular)
- subarachnoid blood
- skull fracture involving meninges
- cerebral contusion or oedema
- cerebral infarct

▪ ***Clinical Features***

• presentation can be quite variable and at times atypical,

a. deep coma

b. failure to improve neurologically

c. gradual deterioration in neurological signs

d. obtundation with
- decerebrate posturing
- pupil dilatation
- respiratory arrest

e. "NPH" syndrome
- dementia
- incontinence
- gait disturbance
- psychomotor slowing

* in the setting of post-traumatic head injury

• ***outcome*** is related to,

1. the extent underlying of brain injury
2. the severity of ventriculomegaly
3. response treatment

▪ ***Diagnosis - CT Scan Criteria***

a. distended anterior & temporal horns

b. enlargement of 3rd ventricle

c. normal or absent sulci - ie. no sign of ***cerebral atrophy***

d. ± enlargement of basal cisterns and 4th ventricle

e. periventricular decreased density → communicating hydrocephalus

- ***Response to Shunting***

NB: good if the CT scan is positive ***and***,

a. increased ICP/LP found > 18 cmH_2O
   - especially acute onset

b. features of "NPH" syndrome - especially chronic onset

c. progression of CT changes over 2-4 weeks

d. CSF ***dynamic studies*** show flow or absorption problems

Outcome

- ***Glascow Outcome Score***

1. dead
2. vegetative
3. severely disabled - conscious but dependent
4. moderately disabled - independent but disabled
5. good - neuropsychological impairment or better

NB: Jennett, Lancet 1975, performed at 6 months post-injury

- ***Factors Associated with Poor Outcome***

1. depth of coma
2. motor response
3. pupil reactions
4. eye movements
5. patient age
6. presence of an intracerebral haematoma
7. intractable intracranial hypertension
8. ? central hyperthermia / hyperventilation

SPINAL CORD INJURY

- ***Aetiology of Spinal Dysfunction***

1. traumatic
2. mechanical
   - i. vertebral body/disc lesion
   - ii. haemorrhage, abscess, neoplasia
     - → epidural, dural, subdural or intramedullary
3. ischaemic
   - i. post-surgical - aortic, spinal
   - ii. atherosclerosis
   - iii. aortic dissection
   - iv. hypotensive shock
4. transverse myelitis
   - i. idiopathic
   - ii. MS
   - iii. carcinoma
   - iv. syphilis
   - v. viral - influenza, HZV, EBV, Echoviruses, rabies, measles
   - vi. vasculitis - SLE, PAN
     - Bechet's syndrome

Anterior Spinal Artery Syndrome

- anterior spinal artery originates from branches of both vertebral arteries
- segmental feeding vessels, most notable artery of Adamkiewicz (left 10th intercostal)
- supplies the ***anterior two-thirds*** of the cord, loss resulting in bilateral,

1. paralysis
2. loss of pain & temperature
3. preservation of proprioception, light touch & vibration

Transverse Myelitis

- a ***monophasic illness*** usually commencing with paraesthesia of the lower limbs and altered sphincter function
- in contrast to GBS,

a. neuronal loss is ***both*** motor and sensory, and

b. localized to a spinal level

- in ~ 30% there is an antecedent history of viral or bacterial infection
- CSF shows mild pleocytosis and elevated protein levels
- functional recovery is good in ~ 33%, though, ~ 25% have severe disability

Cord Hemisection Brown Séquard

1. ipsilateral
   i. paralysis
   ii. loss of proprioception, light touch and vibration sense
   iii. normal pain & temperature sensation
2. contralateral
   i. normal power
   ii. loss of pain & temperature sensation

Management

1. decompressive & stabilising surgery
2. methylprednisolone ~ 30 mg/kg bolus, then 5.4 mg/kg/hr x 24
   - for acute traumatic spinal injury within 8 hrs
   - this is now questionable as a repeat study showed no benefit
3. GM-1 ganglioside
   - used to induce neuronal regeneration
   - may improve outcome
4. supportive care

CEREBROVASCULAR DISEASE

- ***Presentation***

1. TIA / RIND - deficit lasting < 24 hrs duration
   - ~ 70% will ultimately develop a stroke ~ 50% within 5 years
   - cerebral embolic episodes present with transient events in **~ 10%**

   i. carotid or MCA **~ 80%** of TIA's
   - hemiplegia, monoplegia, monocular blindness
   - sensory inattention, speech disturbance

   ii. vertebrobasilar - diplopia, dysarthria, dizziness

2. ***stroke***

   i. aetiology ~ 85% infarction (thrombotic or embolic)
   ~ 10-15% haemorrhage

   ii. mortality
   - infarction ~ 30% at 1 mth
     ~ 50% at 12 mths
   - haemorrhage ~ 50% at 1 mth *"~ infarct + 20%"*
     ~ 70% at 6 mths

3. multi-infarct dementia

- ***Predisposing Factors: Cerebral Infarction***

1. ***major***
   i. age
   ii. hypertension
2. ***minor***
   i. diabetes
   ii. hyperlipidaemia
   iii. heart disease
   iv. smoking
   v. obesity
   vi. OCP
   vii. hypotension

- ***Predisposing Factors: Cerebral Arterial Thrombosis***

1. hypertension
2. atherosclerosis
3. arteritis - SLE, temporal arteritis, PAN, Takayasu's arteritis
4. aortitis, syphilis
5. arterial dissection
6. vasospasm - migraine, pre-eclampsia, LSD, cocaine, amphetamines
7. angiography
8. infection
9. haematological - HITTS, TTP

- ***Predisposing Factors: Cerebral Venous Thrombosis***

1. raised ICP
2. malignancy
3. septicaemia
4. hyperviscosity syndromes
   i. hyperproteinaemic states - MM, Waldenstrom's, MGUS
   ii. severe dehydration - HHNKC
   iii. polycythaemia
5. hypercoagulable states
   i. ATIII, proteins C & S deficiency
   ii. polycythaemia, paroxysmal nocturnal haemoglobinuria
   iii. HITTS, TTP

- ***Predisposing Factors: Cerebral Embolism***

1. mitral stenosis, AF
2. AMI, mural thrombus, LV aneurysm
3. prosthetic valve replacement
4. endocarditis
5. atrial myxoma
6. cardiomyopathies
7. paradoxical thromboembolism, or air emboli via ASD

NB: in **50%** of embolic cases the origin is the heart

- ***Investigation***

a. history & clinical examination
b. FBE / Coags ± protein C, S, ATIII, anti-phospholipid Ab's
c. CT head
d. carotid ultrasound / doppler
e. angiography - DSA
f. echocardiography
g. MRI
h. LP - rarely

- ***Clinical Features***

1. carotid / middle cerebral artery
   - altered conscious state
   - spastic paralysis of arm, leg or face
   - receptive / expressive ***dysphasia***
   - perseveration - repetitive feeling of clothes
   - astereognosis - inability to name an object in hand
   - Gerstmann's syndrome * AALF, dominant parietal lobe

   i. **a**calculia - serial 7's
   ii. **a**graphia - inability to write
   iii. **L**↔R confusion
   iv. **f**inger agnosia - inability to name fingers

   - dressing apraxia, constructional apraxia
   - sensory inattention
   - cortical blindness
   - cranial nerve palsies

2. vertebrobasilar

   i. ***medial*** medullary syndrome
      - ipsilateral 12th nerve palsy - wasting & paralysis of tongue
      - contralateral arm/leg paralysis - sparing the face

   ii. ***lateral*** medullary syndrome
      - ipsilateral - pain/numbness & impaired sensation over face (V)
        - arm/trunk/leg numbness
        - bulbar palsy (IX and X), loss of taste
        - Horner's syndrome
        - nystagmus, diplopia, vertigo, N&V
        - limb ataxia & falling to side of lesion
      - contralateral - pain/temperature loss over body (rarely face)

- ***Management***

a. general
- supportive care
- supplemental oxygen per PaO_2
- treat associated cardiac disorders
- treat anaemia (Hct ~ 0.3-0.33)

b. ***hypertension***
- control severe hypertension (> 200/115 mmHg)
- in patients with TIA's, reduction in MAP ~ 5-10 mmHg reduces stroke ~ 40%
- prevent hypotension

c. aspirin for TIA's
- reduces incidence (~ 20-30%) & severity of subsequent CVA
- * no reduction in ***mortality***

d. anticoagulation
- embolic stroke ≤ 48 hrs + absence of hypertension
  + no haemorrhagic lesion on CT scan
- crescendo TIA's with carotid or vertebrobasilar stenosis

e. haemodilution
- may be of possible benefit
- ?? hypervolaemic or normovolaemic

f. carotid endarterectomy
- TIA's or minor strokes & > 70% stenosis
- complication rate < 3% for asymptomatic stenosis
  < 5% for TIA's
  ~ 10% for recurrent carotid disease

- ***Therapy of Unproven Benefit***

a. surgery in asymptomatic patients with < 70% stenosis

b. hyperbaric O_2

c. pentoxifylline
- methylxanthine derivative
- unknown mechanism of action
- reduces viscosity & RBC 'stiffness'

d. anticoagulants in acute stroke

e. other antiplatelet drugs in TIA's (dipyridamole, sulphinpyrazone)

f. thrombolytic agents * rTPA
- European Cooperative Acute Stroke Study, JAMA 1995
- may benefit subgroup, but unacceptable incidence of ***haemorrhage*** overall

g. steroids, barbiturates and hyperventilation

h. NMDA receptor antagonists

i. Ca^{++} entry blockers

Haemorrhagic Stroke

NB: incidence ~ 10-12% of CVA

a. ***major*** risk factors
   i. hypertension ~ 35% of all intracerebral haemorrhage
   ii. anticoagulation

b. other causes
   - tumours
   - raised ICP
   - cerebral arteritis
   - mycotic aneurysms
   - coarctation of the aorta
   - Marfan's syndrome
   - amyloidosis, sarcoidosis

c. site
   - ***putamen*** ~ 55%
   - cortical ~ 15%
   - thalamic ~ 10%
   - pontine ~ 10%
   - cerebellum ~ 10%

d. mortality **~ 68%** at 6 months

- severe headache occurs in ~ 50%
- if there is subarachnoid spread of blood then ***meningism*** occurs
- in the absence of coagulopathy, unlike berry aneurysms, rebleeding is ***rare***
- surgical evacuation of the clot is ***seldom*** beneficial, unless,

1. located superficially
2. patient is conscious
3. CT shows midline shift > 5 mm

NB: this contrasts acute ***cerebellar*** haematoma

→ evacuation is the Rx of choice

Subarachnoid Haemorrhage

a. ***aetiology***

i. saccular aneurysm* ~ **6-8%** - of all strokes
~ 90-95% - ***anterior*** circle of Willis
~ 5-10% - vertebrobasilar

ii. atherosclerotic

iii. mycotic

iv. traumatic

v. arteriovenous malformations

b. ***incidence*** (USA)* ~ 11:100,000

- increased incidence with - coarctation of the aorta
  - polycystic kidney disease
- 20% of patients have ***multiple aneurysms***

c. ***mortality**** **~ 35-40%**
~ 10% in the first week
~ ½ the remainder within 3 months
~ ½ the long-term survivors have ***major disability***

- outcome is related to,

1. the amount of subarachnoid blood, and
2. the neurological condition at presentation

- the major causes of death are,

1. neurological injury from the ***initial haemorrhage***
2. ***rebleeding***
3. ischaemia from ***vasospasm***

- ***saccular aneurysms*** were originally thought to be congenital
- recent evidence is that they are ***acquired***, due to degeneration of the internal elastic membrane at the apex of bifurcations, secondary to ***haemodynamic stress***

NB: ***hypertension*** and turbulent flow lead to further degeneration & saccular enlargement

→ increased risk of rupture **~ 5-15 mm**

- ***Clinical Presentation***

1. ***prodromal*** symptoms — - headache, dizziness, orbital pain
   - often vague & not diagnosed
   ≤ 50% of patients
2. sudden onset of ***severe headache***
3. ***meningism*** — - photophobia, neck stiffness, vomiting
   - Kernig's sign
4. transient ***neurological deficits*** — ∝ site & size of aneurysm
5. ***loss of consciousness***
6. subhyaloid haemorrhages on fundoscopy

Clinical Neurological Classification of SAH	
Grade I	• conscious patient ± meningism
Grade II	• drowsy patient ± neurological deficit
Grade III	• drowsy patient with a neurological deficit (localising) • probable intracerebral haematoma
Grade IV	• deteriorating patient + major neurological deficit • large intracerebral haematoma
Grade V	• moribund patient, extensor rigidity & failing vital centres

• the World Federation of Neurological Surgeons has suggested another classification scheme, incorporating the GCS and the presence of absence of motor deficit (grades I-V)

1. ***haemorrhagic compression***
   - severe SAH with loss of consciousness and persistently raised ICP
2. ***noncompressive SAH***
   - minimal mass effect, ICP usually normalises 10-15 minutes post-bleed

• of patients presenting with an acute bleed,

a. 12% lapse into coma & die
b. a further 40% die within 2 weeks without surgical treatment

- ***Complications: Cerebral***

1. ***rebleeding*** **~ 20%** (16-25%)
   - ~ 4% within the first 24 hours
   - peak incidence at ***days 4-9***
   - ↓ incidence 30-50% with antifibrinolytics, but mortality is unchanged
   - early 2nd haemorrhage → **~ 40% *mortality***
   - late rebleed ~ 3% / yr → ~ 67% mortality
2. ***vasospasm*** **~ 70%** of all SAH by ***angiography***
   ~ 40% demonstrate ***clinical vasospasm***
   - peak incidence at ***days 6-7***
   - * major cause of morbidity / mortality
   - requires exclusion of other causes of neurological deficit

     → - rebleeding / ICH
     - hydrocephalus, oedema
     - hypoxia, hypercarbia, acidosis, hyponatraemia
3. ***hydrocephalus*** **~ 30%** of SAH
   ~ 7% require surgical decompression
4. ***cerebral oedema***
5. ***seizures***

- ***Complications: General***

1. sympathetic hyperactivity
   i. ECG changes - ST segment depression, T-wave inversion
   - U-waves, prolonged Q-T
   - arrhythmias

   ii. acute neurogenic pulmonary oedema
2. hyponatraemia - SIADH
   - cerebral salt wasting syndrome
3. reduced total blood volume & RBC mass
4. complications related to depressed CNS state
   i. respiratory failure / insufficiency
   ii. aspiration
   iii. pressure sores
   iv. venous thrombosis / thromboembolism
   v. gastric stasis, constipation, gastric ulceration
   vi. nosocomial infection

- ***Preoperative Management***

a. general supportive care

b. control of ***hypertension*** - but avoid hypotension
   - sedation & analgesia
   - antihypertensives
   - β-blockers, α-methyldopa, CEB's
   - * avoid cerebral vasodilators

c. control of ***vasospasm***
   - * CEB's, ***nimodipine***
   - reduces the delayed ischaemic deficit & improves outcome in patients with aneurysmal SAH
   - less effect, and contradictory studies, once vasospasm established
   - most consistent results are obtained with ***hypertension & hypervolaemia***
   - may require the use of antidiuretics
   - generally requires ***early surgery***
   - LIGW states there are no PRCT's to support this view

d. control of ***seizures***

e. control of ***cerebral oedema*** & raised ICP

f. control of ***hydrocephalus***

g. ***antifibrinolytics***
   - epsilon aminocaproic acid (EACA) & tranexamic acid
   - inhibit clot lysis & reduce rebleeding
   - * problems of cerebral ischaemia, hydrocephalus and thrombosis
   - no change in ***mortality***, therefore ***not recommended***

h. prevention of ***gastric erosion / ulceration***

i. maintenance of ***fluid & electrolyte*** balance

j. intrathecal rTPA
   - small studies of patients undergoing early clipping (< 72h)
   - reduced incidence of vasospasm

- ***Anaesthetic Management***

1. preoperative assessment
   i. evidence of raised ICP
   ii. presence & extent of CNS deficit
   iii. volume status
   iv. biochemical derangement
   v. ECG changes ± CE's
   vi. other system diseases
2. ***management goals***
   i. prevention of aneurysmal ***rebleed***[§]
      - intraoperative rupture → > 60% mortality
   ii. avoidance of ischaemia 2° to ***vasospasm***
   iii. brain ***decompression*** - surgical access
      - retractor ischaemia
   iv. ***controlled hypotension*** when required

NB: [§]the risk of rebleeding is determined by the vessel wall gradient, MAP - ICP changes in MAP are of ***far greater*** significance cf. reductions in ICP

- ***Operative Management***

1. direct clipping
   - good risk patients, ***mortality*** **~ 5%**
2. encasement with various materials
3. occlusion of the feeding vessel
4. stereotaxic thrombosis

Postoperative Management

a. general supportive care

b. adequate analgesia & sedation

c. ICP measurement/monitoring

d. medical complications
- seizures
- SIADH, CSWS, hyponatraemia
- cardiac arrhythmias, AMI, CCF
- pneumonia, PTE
- UTI's

e. surgical complications
- vasospasm
- rebleeding
- cerebral oedema
- subdural/extradural haematoma
- hydrocephalus
- intracranial hypertension
- persistent neurological deficit

f. vasospasm
- ***hypervolaemia & haemodilution***
- CVP ~ 8-12 mmHg / PAOP ~ 10-12 mmHg
± PAOP ~ 16-20 mmHg if no improvement
- Hct ~ 30-35%
± antidiuretics
- digoxin/inotropes with CCF

NB: patients with oedema and vasospasm may require mannitol, cautious volume loading with colloid, and IPPV

• ***hypervolaemia*** is reported to produce transient improvement in 80-90%, and permanent improvement in ~ 60% of cases
• ***complications*** of this therapy include,

a. pulmonary oedema

b. cerebral oedema

c. haemorrhagic cerebral infarction

d. biochemical derangement

e. complications from insertion of invasive monitoring

Summary

• only ~ 30% of SAH patients ever have surgery
• of patients who reach hospital, a favourable outcome is reported in ~ 43% of surgical cases
• of Grade I & II SAH patients ~ 60% will have a favourable outcome
• in patients without a preoperative neurological deficit, an operative mortality ≤ 5% is possible

HYPERTENSIVE ENCEPHALOPATHY

Def'n: potentially life-threatening syndrome of acute severe hypertension with ***neurological*** and ***retinal*** signs

- ***Risk Groups***

a. < 1% of all hypertensives

b. increased in smokers

c. 2° hypertensives
- renovascular
- endocrine
- vasculitis

- ***Clinical Features***

1.	diastolic ***hypertension***	³ **140 mmHg**
2.	hypertensive ***retinopathy***	- haemorrhages & exudates * papilloedema
3.	***neurological***	- headache, confusion, apprehension - focal neurological signs - coma, seizures - SAH, CVA
4.	cardiac	- angina, AMI - palpitations, cardiomegaly, LVF - aortic dissection
5.	renal failure	- oliguria, uraemia
6.	GIT symptoms	- nausea, vomiting - mesenteric ischaemia, haemorrhage - pancreatitis
7.	microangiopathic haemolytic anaemia	

- ***Treatment***

→ reduce ***diastolic*** £ **100 mmHg**

a.	nitroprusside	~ 30 µg IV bolus plus 1-5 µg/min
b.	hydrallazine	~ 5-20 mg IV
c.	esmolol	~ 0.5 mg/kg bolus plus infusion 0.05 mg/kg/min
d.	nifedipine	~ 10-20 mg SL
e.	GTN infusion	~ 25-250 µg/min
f.	diazoxide	~ 50 mg/min, up to 300 mg

- ***Investigations***

a. E,C&U, CaP, LFT

b. FBE - film for haemolysis
- platelets

c. INR/APTT

d. CXR - heart size, LVF

e. ECG - AMI, ischaemia, LVH

f. CT Head - when clinically stabilised

g. urine - 5HIAA, VMA, metanephrine
* drug screen

h. plasma renin activity

- ***Differential Diagnosis of Hypertension + CNS Signs***

a. CVA

b. encephalitis

c. vasculitis

d. uraemia

e. drugs - ergot poisoning
- amphetamines
- phencyclidine
- cocaine

f. head injury

g. intracranial hypertension

CNS INFECTIONS

Cerebral Abscess

- majority are from ***haematogenous*** spread or by ***direct*** extension
- associated conditions,

1. sinusitis - frontal, sphenoidal, ethmoidal
2. chronic otitis media / mastoid infection
3. cyanotic congenital heart disease
4. pulmonary AV fistulae
5. suppurative lung disease - bronchiectasis, lung abscess, empyema
6. bacterial endocarditis
7. dental sepsis
8. penetrating cerebral trauma

- common organisms,

1. staphylococci
2. anaerobic streptococci
3. *Bacteroides*
4. *Enterobacter*

- in immunocompromised hosts, *Nocardia*, other fungal and protozoal pathogens occur
- cerebral abscesses ***almost never*** result from meningitis,
  ∴*Pneumococcus*, *Meningococcus* and *H.influenzae* are ***rarely*** causes

- ***Investigation***

1. CT with contrast ± MRI
   - LP is ***contraindicated***
2. blood cultures x 3
3. CXR, SXR, sinus XRays
4. echocardiogram
5. FBE / E,C&U

NB: often diagnosed at craniotomy, ie. suspected intracerebral malignancy; may be difficult to distinguish on CT, ∴must use ***contrast***; MRI will give better differentiation

- ***Management***

• majority of morbidity results from ***compression***, not direct brain destruction
• abscesses with brainstem compression → mortality ~ 40%

cf. treated prior to ↓ CNS state → mortality ~ 10%

a. high dose antibiotic therapy ~ 6-8 weeks
   i. empirically
      • penicillin G 4^{MU} q4h + metronidazole 20 mg/kg/day
      • chloramphenacol may be used if penicillin allergic
      • R&B suggest penicillin + metronidazole + 3rd generation cephalosporin
   ii. otic or metastatic lung abscess
      • high incidence of GIT pathogens, ∴gentamicin 3.5 mg/kg/d added to above
   iii. traumatic / post-surgical
      • commonly *Staph. aureus*
      • ∴use flucloxacillin or vancomycin, plus rifampicin
b. surgical drainage
c. prophlactic ***antiepileptic*** therapy
d. ***steroids*** only if significant cerebral oedema, otherwise should be avoided

Meningitis

	Adult Cases %	Paediatric %	Neonatal - type
Strep. pneumoniae	**30-50**	10-20	group B streptococci
Neisseria meningitidis	10-30	30-45	gram negative aerobes
H. influenzae[1]	1-3	**40-60**	*Listeria monocytogenes*

[1] this figure is prior to the introduction of HIB inoculation

• most commonly blood-borne infection
• remaining ~ 20% result from,

a. *Staph. aureus* | *epidermidis*
b. anaerobic & microaerophilic *Streptococci*
c. *Enterobacteriaciae*
d. Pseudomonas

• rarely *Listeria monocytogenes* or other agents in severely debilitated patients

- ***Investigation***

1. FBE, EC&U
2. blood cultures x 3
3. urinary latex Ag screening
4. CT scan * ***with*** contrast
   - should be performed ***prior*** to LP
5. ***lumbar puncture***
   - ↑ pressure
   - ↑ total protein > 450 mg/l
   - pleocytosis ~ 5,000-20,000 PMNs / mm^3
   - ↓ CSF:blood glucose ratio < 0.3
   - positive culture > 75%
6. CXR, SXR, sinus XRay

NB: in the paediatric subset especially, LP should not be performed where there is evidence of raised ICP, or where the diagnosis is obvious

- ***Aseptic Meningitis***

a. viral infection
b. other infective organisms with negative culture
   - syphilis, toxoplasmosis, leptospirosis, cryptococcosis, nocardia, TB
c. cerebral abscess
d. Lyme disease
e. relapsing fever
f. SLE
g. metastatic carcinoma

- ***Management***

a. pneumococcal or meningococcal
   - penicillin G ~ 16-24^{MU} /70kg/day

b. *Haemophilus influenzae* or, patients allergic to penicillin
   or, ***empirical therapy***
   - ***cefotaxime*** ~ 200 mg/kg/day
   - or chloramphenacol

c. *Staph. aureus*
   - flucoxacillin ~ 12 g / 70kg/day

d. other organisms per culture sensitivity

e. dexamethasone ~ 0.15 mg/kg prior to antibiotics
   - ***children only*** results in reduction of neurological and auditory sequelae

f. prophylaxis
   - all household contacts for *meningococcal* or *Haemophilus influenzae* infection
   - incidence of infection in this group ~ 500-800x general population
   - rifampicin ~ 600 mg q12h for 2 days in adults
     ~ 10 mg/kg q12h in children
     ~ 5 mg/kg q12h in infants < 12 months

g. vaccination
   - meningococcal vaccination of little routine use
   - may be given for high risk groups - post-splenectomy
     - low CH_{50}

Viral Encephalitis

- ***Aetiology***

1. HSV-1
2. EBV
3. measles, mumps, rubella, varicella
4. echoviruses, coxsackie, poliovirus, arbovirus, rabies

- ***herpes simplex*** is the most common sporadic viral encephalitis
- most cases are due to activation of latent infection
- in 90% of cases 1 or both ***temporal lobes*** are involved
- onset is typical of a generalized viraemia, followed by,

a. decreased CNS state

b. focal sensory & motor neurological deficits

c. convulsions & coma

- ***Investigation***

a. CT scan | MRI scan | isotope brain scan
   - often demonstrate characteristic temporal lobe abnormalities
   - ↑ contrast of white matter around basal ganglia
   - if done early, CT is most often ***normal***

b. LP
   - clear, or slight turbidity
   - normal or slightly elevated pressure
   - mild pleocytosis ~ 50-500 PMNs/mm^3
   - mild elevation of protein

c. serum | CSF serology
   - > 4x rise in specific Ab titre
   - polymerase chain reaction amplification of DNA extracted from CSF allows early detection of the HSV genome & is ***highly specific***

d. brain biopsy

- ***Management***

a. supportive

b. seizure prophylaxis

c. acyclovir ~ 10 mg/kg q8h

- ***Poliomyelitis***

- may present as a generalised viraemia, without CNS signs, or as an ***aseptic meningitis***
- a small percentage of patients, after 5-10 days develop,

a. meningeal signs

b. assymetric flaccid paralysis ± bulbar paralysis
   ± respiratory paralysis

c. urinary retention may occur

d. sensation is normal

- weakness may recur or worsen 15-45 years following the illness

→ ***progressive poliomyelitis muscular atrophy***

EPILEPSY

Def'n: ***epilepsy*** denotes any disorder caracterised by ***recurrent seizures***,

a ***seizure*** is a transient disturbance of cerebral function due to an abnormal paroxysmal neuronal discharge in the brain

Essential Features

1. recurrent seizures, accompanied by EEG changes
2. mental status abnormality, or focal neurological symptoms / signs
   - these may persist for a period of several hours post-ictally

Classification: Seizures

1. ***partial*** seizures
   - involve, or begin in only one part of the brain
   - causes include cerebral structural lesions (neoplasia, infarction, abscess)

   i. simple partial - no LOC

   ii. complex partial - associated disturbance of consciousness
   - predominantly a ***temporal lobe*** disorder

2. ***general*** seizures

   i. absence seizures - *petit mal*

   ii. atypical absence

   iii. myoclonic seizures

   iv. tonic-clonic - *grand mal*

   v. tonic, clonic, or atonic

Aetiology: Common Causes

1. idiopathic - onset most commonly 5-20 yrs
2. infective
3. traumatic
4. anticonvulsant withdrawal
5. drug related - alcohol
   - induced | withdrawal

- ***Aetiology***

a. ***idiopathic***

b. ***focal lesions***

i.	1° CNS disease	- multiple sclerosis, leucodystrophies, tuberose sclerosis
ii.	1° dementias	- Alzheimer's
iii.	trauma	- post-traumatic / postoperative scarring - subdural, extradural haematoma
iv.	tumour	- especially ***meningioma***
v.	cerebrovascular	- angioma, AV malformation - thrombotic/embolic CVA, SAH, subdural - hypertensive encephalopathy - TTP, SLE, PAN, cerebral arteritis
vi.	infectious	- meningitis, encephalitis (esp. HSV-1) - abscess, tuberculoma, hydatid cyst - neurosyphilis, cysticercosis

c. ***metabolic***

i. hypoxia, hypoglycaemia

ii. rapid or severe ↓↓ - osmolality, Na^{+}, Ca^{++}, Mg^{++}, $HPO_4^{=}$

iii. severe alkalosis

iv. uraemia, dialysis disequilibrium

v. hepatic encephalopathy

vi. pyridoxine deficiency

vii. hyperthermia - febrile convulsions

d. ***drugs***

i. analeptics - theophylline, caffeine, cocaine, amphetamines

ii. direct toxicity
- local anaesthetics
- penicillins, imipenem
- phenothiazines, tricyclic antidepressants, lithium, lead
- possibly - enflurane, propofol, ether

iii. side-effects
- insulin - hypoglycaemia
- isoniazid - pyridoxine deficiency

iv. withdrawal
- anticonvulsants
- alcohol, barbiturates, benzodiazepines, other sedatives
- corticosteroids
- opioids - ?? not according to HPIM

e. ***other causes***

i. electrocution

ii. electroconvulsive therapy

- ***Common Causes: Children***

1. febrile convulsion
2. anticonvulsant withdrawal
3. CNS infection - meningitis, encephalitis
4. traumatic
5. metabolic - hypo-Na^{+}
   - hypo-Ca^{++}
6. cerebral palsy

- ***Common Causes: Neonate***

1. perinatal hypoxia / ischaemia
2. hypoglycaemia
3. intracerebral haemorrhage - days 1-3
4. electrolyte disturbance (Na^{+}, Ca^{++}, $HPO_4^{=}$) - days 3-8
5. meningitis, encephalitis
6. inborn-errors of metabolism (pyridoxine def.)

Investigations

- ***Adult***

1. serum biochemistry - EC&U, Ca/P, LFT, BSL
2. AGA's
3. drug screen
4. drug levels - known epileptic
5. ECG
6. echocardiogram
7. CT | MRI scan
8. LP
9. EEG

- ***Neonate***

a.	biochemistry	- Na^+, K^+, Ca^{++}, Mg^{++}, $HPO_4^=$ - LFT's, urea and NH_3
b.	FBE	- WCC, platelets
c.	TORCH screen	- toxoplasmosis, rubella, CMV, HSV, other
d.	micro	- blood & urine for culture, Ag testing
e.	LP	- MC&S - glucose, protein & electrolytes, cells
f.	AA and organic acid screen	

Treatment *Status*

1. resuscitation / ABC
2. IV access & check serum chemistry
3. diazepam ~ 0.1 mg/kg to 0.3 mg/kg
4. phenytoin ~ 13-18 mg/kg @ 50 mg/min = 1000 mg/20 min
   - achieves full effect in 10-15 minutes
   - rapid admininstration may result in AV block & hypotension
   - requires co-admininistration of a rapidly acting agent
5. thiopentone ~ 5-10 mg/kg over 10 min
~ 2-7 mg/min
6. $MgSO_4$ ~ 10-15 mmol stat
~ 4 mmol/hr
   - recent large RCT showed more effective than phenytoin in ***eclampsia***

- ***Adverse Effects***

1.	phenytoin	- nystagmus, ataxia, dysarthria - dysmorphic effects (gum hypertrophy, acne, hirsutism) - lymphadenopathy, peripheral neuropathy, rash, hyperkeratosis - vit.K antagonism, vit.D antagonism (osteomalacia) - folic acid antagonism (competes for GI transport)
2.	carbamazepine	- metabolism induced by self & other agents, variable $t_{½\beta}$ - drowsiness, dizziness, diplopia, nystagmus, ataxia, N&V - rash, anaemia, granulocytopaenia, oedema - SIADH, complete heart block, hepatotoxicity
3.	Na-valproate	- hepatotoxicity, thrombocytopaenia, hypofibrinogenaemia - pancreatitis, alopecia, N&V, weight gain
4.	vigabatrin	* inhibits ***GABA-aminotransferase*** $\rightarrow$ $\uparrow$ CNS GABA levels

Myoclonic Seizures / Jerks

a.	myoclonic epilepsy	
b.	withdrawal syndrome	- alcohol - barbiturates - benzodiazepines
c.	metabolic encephalopathies	- uraemia - hepatic encephalopathy - hyponatraemia - porphyria - thyrotoxicosis - hypoglycaemia - pyridoxine deficiency - phenylketonuria
d.	hypoxic encephalopathy- post-anoxia	- respiratory failure - CO poisoning - rarely CVA
e.	septic encephalopathy	- especially gram (-)'ve
f.	CNS infections	- abscess - encephalitis (viral, parasitic) - rarely meningitis
g.	other rare causes	- lipid storage diseases - Jacob-Creutzfeld disease - SSPE

AUTONOMIC NEUROPATHY

- ***Classification***

  a. primary or secondary

  b. hyporeflexic or hyperreflexic types

- ***Primary Autonomic Neuropathy***

  a. pure ANS disease
     - idiopathic ***postural hypotension***
     - familial dysautonomia (Riley-Day)

  b. with CNS involvement
     - i. Shy-Drager — postural hypotension & parkinsonian features
     - ii. Holmes-Adie
       - tonic dilated pupil
       - parasympathetic lesion distal to ciliary ganglion

- ***Secondary Autonomic Neuropathy***

  a. ***central***
     - poliomyelitis
     - tetanus
     - multiple sclerosis
     - Parkinson's d.

  b. ***spinal***
     - trauma
     - transverse myelitis
     - syringomyelia

  c. ***peripheral***
     - i. afferent
       - tabes dorsalis
       - Guillain-Bárre
     - ii. efferent
       - diabetes
       - amyloidosis
       - ? alcohol
     - iii. mixed

  d. ***mixed*** → multiple sites of action
     - i. drugs
     - ii. porphyria
     - iii. chronic renal failure

Hyporeflexic Autonomic Neuropathy

a.	***diabetes mellitus***	- commonest ≤ 40%
b.	other metabolic	- Wernicke's encephalopathy - alcohol associated polyneuropathy
c.	primary	
	i. idiopathic postural hypotension	
	ii. Riley-Day	- familial dysautonomia
	iii. Shy-Drager syndrome	- progressive disease of unknown aetiology - ANS, then CNS disease, esp. Parkinsonism
	iv. Holmes-Adie's	- tonic pulpillary response to near vision
d.	drug-induced	- sympathectomy (local anaesthetic, pharmacological) - malignant neuroleptic syndrome - ganglionic blocking agents, α/β blockers
e.	infectious	- Guillain-Bárre syndrome (?) - tetanus - poliomyelitis - syphilis
f.	other	- acute spinal cord trauma - MS - amyloidosis

- ***Clinical Features***

a.	CVS	- postural hypotension - abnormal Valsalva response, no reflex ↑ or ↓ HR - loss of sinus arrhythmia
b.	GUS	- impotence - frequency / incontinence - retention
c.	GIT	- acute gastric dilatation - ileus, constipation, occ. diarrhoea
d.	skin	- anhydrosis
e.	respiratory system	- stridor
f.	pupils	- anisocoria, Horner's syndrome
g.	metabolic	- blunted response to hypoglycaemia - poikilothermia
h.	CNS	- extrapyramidal signs, Parkinsonian - cerebellar signs

- ***ICU / Anaesthetic Problems***

a.	exaggerated hypotension	- IPPV - drugs - hypovolaemia - postural change - spinal/epidural anaesthesia
b.	denervation hypersensitivity	- adrenergic & cholinergic
c.	impaired response to	- hypoglycaemia - hypovolaemia, hypervolaemia - changing anaesthetic depth
d.	bradyarrhythmias	? ischaemia - hypersensitivity
e.	GIT	- acute gastric dilatation, reflux/regurgitation - ileus
f.	hyperpyrexia	
g.	urinary retention	

- ***Treatment***

a.	treat primary cause	
b.	CVS	- avoid rapid postural changes, heat, alcohol, high CHO - increase fluid intake - elastic stockings, antigravity suits
c.	drugs	- 9-α-fluorohydrocortisone - ephedrine, dihydroergotamine - indomethacin - metoclopramide, ? cisapride - desmopressin - caffeine
d.	GIT	- metoclopramide, ? cisapride - high-fibre diet - codeine
e.	urinary frequency	- cholinergics

- ***Investigations***

a.	CVS	- response to standing up - head-up tilt 45° - Valsalva - isometric exercise - hyperventilation
b.	sweating	- intradermal ACh - increase core temp by 1°C
c.	bladder	- urodynamics, IVP
d.	GIT	- gastric emptying

Hyper-Reflexic Autonomic Neuropathy

1. chronic spinal cord trauma > T_8
2. severe essential hypertension
3. phaeochromocytoma
4. thyrotoxicosis
5. malignant hyperthermia
6. head injury
   - diencephalic fits
   - midbrain lesions
7. tetanus
8. strychnine poisoning

Blindness Sudden

a. trauma
b. cerebrovascular accident, TIA
c. vitreous haemorrhage - eg. diabetics*
d. retinal detachment*
e. acute glaucoma*
f. temporal arteritis*
g. retinal artery embolus
h. retinal vein thrombosis
i. acute migraine
j. post-vertebral angiogram
k. drug toxicity
   - methanol
   - quinine
   - tobacco
   - severe B_{12} deficiency
l. acute hydrocephalus
m. retrograde spread of LA via epidural veins
n. hysteria

Carpal Tunnel Syndrome

a. idiopathic
b. pregnancy, OCP, pre-menstrual
c. myxoedema
d. acromegaly
e. rheumatoid arthritis
f. scaphoid fracture
g. intermittent trauma
h. mucopolysaccharidosis type V

- ***Differential Diagnosis - CTS***

a. cervical spondylitis
b. syringomyelia
c. motor neurone disease

PERIPHERAL NEUROPATHIES

• these may be characterised on the basis of structure primarily affected,

a. axonal degeneration - normal conduction velocity
- EMG shows ***denervation***

b. paranodal demyelination

c. segmental demyelination - slowed to completely blocked ***conduction***
- no EMG signs of denervation

NB: differentiation may be made on ***nerve conduction studies*** and ***EMG***

- ***Classification***

1. ***idiopathic***
   - i. acute idiopathic demyelinating polyneuropathy - GBS / AIDP
   - ii. chronic idiopathic demyelinating polyneuropathy - CIDP
2. ***hereditary*** neuropathies
   - i. Charcot-Marie-Tooth - HMSN I & II
   - ii. Dejerine-Sottas - HMSN III
   - iii. Refsum's disease - HMSN IV
   - iv. Friedreich's ataxia
3. ***metabolic*** & systemic disorders
   - i. diabetes mellitus
   - ii. uraemia
   - iii. chronic liver disease
   - iv. alcoholism / nutritional - B_{12}, folate, pryidoxine, thiamine
   - v. paraproteinaemias
   - vi. porphyria - 3 types
4. ***infectious*** & ***inflammatory*** disease
   - i. leprosy, Lyme disease
   - ii. AIDS
   - iii. sarcoidosis, PAN, rheumatoid arthritis
5. ***toxic*** neuropathies
   - i. industrial agents & pesticides - organophosphates, solvents
   - ii. heavy metals
   - iii. drugs - amiodarone, perhexiline, phenytoin, isoniazid
     * A COLD DAMP MIST (see over)
   - iv. diphtheria toxin
6. ***paraneoplastic***

- mechanisms of nerve injury include,
    1. idiopathic inflammatory polyneuropathy - GBS
    2. connective tissue disorders
    3. vasculitidies
    4. direct trauma / compression
    5. tumours - von Recklinghausen's
    6. metabolic
    7. radiation
    8. infiltration
    9. paraneoplastic
    10. hereditary

Drugs Causing Peripheral Neuropathy	
Condition	Treatment
A • alcohol	**A** • disulfuram
C • cancer **O** • other (HIV, HT) **L** • leprosy **D** • deficiency	**C** • vincristine, cisplatin, taxol **O** • didanosine, hydrallazine **L** • dapsone (motor) **D** • pyridoxine, thiamine
D • dysrhythmia **A** • angina **M** • microbial **P** • psychotic	**D** • amiodarone **A** • perhexiline **M** • metronidazole, nitrofurantoin, chloramphenicol **P** • lithium, tricyclics
M • malaria **I** • inflammatory **S** • seizure **T** • TB	**M** • chloroquine **I** • gold, colchicine **S** • phenytoin **T** • isoniazid, ethambutol

- ***Neuropathy: Acute***

1. Guillain-Bárre
2. "critically-ill" polyneuropathy
3. carcinoma, lymphoma
4. drugs, chemicals
5. tetanus
6. traumatic
7. infectious mononucleosis
8. botulism
9. diphtheria
10. acute intermittent porphyria

- ***Neuropathy: Chronic***

1. diabetes mellitus
2. alcoholism
3. malignancy
4. collagen / vascular diseases - PAN, SLE
5. uraemia
6. amyloidosis
7. sarcoidosis
8. myxoedema
9. multiple myeloma
10. drugs, toxic neuropathy

- ***Neuropathy: Drugs, Toxins/Chemicals***

1. bacterial - botulism, tetanus
2. heavy metals - lead, mercury, arsenic
3. trichlorocresyl $PO4^{=}$
4. organophosphates
5. nitrofurantoin
6. vincristine, vinblastine
7. isoniazid
8. amiodarone, phenytoin

GUILLAIN-BÁRRE | LANDRY-STROHL SYNDROME

- ***Essential Features***

1. progressive ***symmetrical ascending*** weakness → LMN-type, > 1 limb
2. diminished or ***absent reflexes***
3. CSF cell count < 50 monocytes & 2 polymorphs / mm^3
   ↑ protein → ***cytoalbuminologic dissociation***

- ***Supporting Features***

1. progression over days/weeks, with ***relative symmetry***
2. mild ***sensory*** signs or symptoms - paraesthesia, neuritic pain, rarely muscle pains
   ~ 50% mild sensory loss
3. ***cranial nerve*** involvement ~ **50%**, starting with CN's in ~ 5%
4. ***autonomic*** dysfunction ~ 20%
5. ***absence*** of fever
6. CSF: - elevated ***protein*** after 1 week (normal earlier)
   - may have ↑ cells in ***HIV seropositive*** patients with GBS
7. EMG: - slow ***conduction*** velocity
   - prolonged F waves (distal latency)
8. onset: ~ 2-8 weeks after - URTI ~ 45%
   - GIT ~ 20%
9. epidemiology: - isolated cases
   - well-developed nations
10. incidence - 1.7 per 100,000
11. pathophysiology: - perivenular inflammation
    - myelin degeneration ± axonal degeneration (rarely)

- ***Aetiology***

a. post-infectious ~ 50% are sero-positive for ***Shigella***
   - adenovirus, influenza A&B, EBV, CMV, herpes zoster, parainfluenza 3, measles, chickenpox, mycoplasma
   - axonal cases reported following ***C.jejuni*** (PEN-19)

b. post-vaccination * 1976 USA National Influenza Immunization Program
   - Inf. A / New Jersey / 76 (swine) vaccine, > 1000 cases ~ 5-6 x ↑ incidence

c. involves CMI ? myelin neuritogenic protein
   - anti-GM_1-Ab (*C.jejuni*)

- ***CSF Findings***

1. normal pressure
2. clear
3. ≥ 90% have ***increased protein*** ≥ 400 mg/l → mainly ***albumin***
4. cell count / mm^3 < 50 lymphocytes
   < 2 PMN's
   - ≤ 10% have mild lymhpocytosis

- ***Monitor***

a. signs of ***respiratory failure*** - RR, HR
   - PEFR, VC
   - P_{aO2}, P_{aCO2}

b. effectiveness of ***cough*** - VC < 15 ml/kg
   - bulbar palsy

c. extent and severity of neurological deficit

d. nerve conduction studies

- ***Indications for Ventilation***

1. diminished VC < **15 ml/kg**
   - or, clinical / CXR signs of sputum retention & getting worse
2. loss of airway reflexes - bulbar palsy
3. imminent respiratory failure ***(late signs)*** - P_{aO2} < 60 mmHg on 60%
   - P_{aCO2} > 60 mmHg, or rapidly rising

- ***Clinical Variants***

a. Miller-Fisher variant
   i. ophthalmoplegia
   ii. ataxia
   iii. areflexia

b. severe ***sensory loss*** with muscle ***pain***

c. presence of a ***temperature*** at onset

d. extensor plantar responses - ie., ***UMN signs***

e. unreactive ***pupils***

- ***Differential Diagnosis***

1. severe limb weakness with ***normal cranial nerves***
   - i. Guillain-Bárre
   - ii. critically-ill polyneuropathy
   - iii. spinal cord disease
     - transverse myelitis
     - ant. spinal artery syndrome
     - cord trauma, oedema, tumour, malformation
     - cervical spondylitis
   - iv. motor neurone disease - amyotrophic lateral sclerosis
   - v. dermatomyositis, polymyositis
   - vi. endocrine / metabolic
     - familial periodic paralysis - hypokalaemic | hyperkalaemic
     - severe hypo/hyperkalaemia, hypermagnesaemia
     - steroids
     - hyperthyroidism
2. weakness usually ***including***, or mainly ***cranial nerves***
   - i. myasthenic crisis
   - ii. botulism
   - iii. poisoning
     - shellfish, tick paralysis
     - organophosphates, hexacarbons
   - iv. drugs - nitrofurantoin, perhexiline, dapsone
   - v. acute intermittent porphyria
   - vi. infections
     - poliomyelitis
     - diphtheria
     - infectious hepatitis
   - vii. pontine disease - infarction, central pontine myelinolysis
   - viii. polyarteritis nodosa - mononeuritis multiplex
   - ix. metabolic myopathies - high muscle enzymes
   - x. malignancy
     - Eaton-Lambert syndrome
     - mainly limb girdle
3. ***differentiating features***
   - i. sensory signs
   - ii. muscle enzymes
   - iii. CSF cells
   - iv. EMG
   - v. nerve conduction studies

- ***Plasmapheresis***

NB: ***all*** patients with severe disease, ie. unable to walk unaided
preferrably ***early*** in the disease course, ie. before 2 weeks;
currently some use ***immunoglobulin*** instead | with pheresis

1. shortens the duration of ventilation - mean from 48 to 24 days
2. shortens time to walk unaided - mean from 85 to 53 days
3. may halt progression of the disease
4. more effective if commenced ***prior*** to onset of respiratory failure

• ***corticosteroids*** are ***not recommended*** in uncomplicated GBS, as they,

1. delay the onset of recovery
2. negate the beneficial effects of plasmapheresis

• however, they may be useful in 2-3% who progress to ***chronic relapsing polyneuropathy***

- ***Signs of Poor Outcome***

a. dense ***quadriplegia***

b. prolonged time to ***recovery onset***
   - weakness usually ceases to progress > 2 weeks in 50%
     > 3 weeks in 80%
     > 4 weeks in 90%
   - recovery usually begins ~ 1-2 weeks after progression stops

c. ***axonal damage*** on nerve conduction studies ? *C.jejuni* infection cases

NB: 19-28% of this group in most series have a residual motor deficit at 1 year
mortality even in large teaching centres **~ 10%**

• factors ***not predictive*** of outcome

a. CSF protein levels

b. ? duration of ventilation

- ***Causes of Death***

a. respiratory failure

b. aspiration / nosocomial pneumonia

c. nosocomial infection / sepsis

d. pulmonary embolus

e. cardiac arrhythmia

CRITICALLY-ILL POLYNEUROPATHY

Def'n: the ***syndrome*** of "critically-ill polyneuropathy" includes,

1. the development of generalised weakness at the peak of illness, which is often ***sepsis***
2. ***flaccid*** weakness in all limbs with preserved ***or*** absent deep tendon reflexes
   - weakness disproportionate to muscle wasting → ***amyotrophy***
3. similar in features to Guillain-Bárre but ***characteristic EMG***
   i. ***normal*** conduction velocity
   ii. 'denervation-type' pattern, with ***axonal degeneration***
   → fibrillation potentials & sharp waves
   iii. reduced sensory and motor CAP's
   - later may be ***polyphasic*** suggesting associated primary ***myopathy***
4. pathophysiology
   - patchy axonal degeneration ± muscle involvement
   - histology shows ***no*** evidence of inflammation, cf. inflammatory neuropathies
   - muscle biopsy shows scattered, atrophic fibres, typical of acute ***denervation***
   - occasional scattered muscle fibre necrosis, suggesting a 1° myopathy 2° to sepsis
5. CSF normal ± raised protein

f. aetiology ***unknown***
   - multiple regression analysis of 43 cases by Witt *et al.* showed significant relationship to time in ICU, plasma glucose and albumin levels
   - suggested by Bolton to be secondary to altered microcirculation to the peripheral nerve, within the CNS

7. ***no*** association with,
   i. nutritional deficiency
   ii. antibiotics, or drug toxicity
   iii. other known causes of neuropathy §see over
8. incidence ~ **20%** in patients septic for > 2 weeks
   - may occur in £ **70%** of severely septic patients (Witt *et al.* Chest 1991)
9. course - spontaneous recovery usual
   - recovery in 1 month in mild forms
   - 3-6 months in severe forms
10. mortality - ***high***, due to primary illness

- in setting of sepsis syndrome, encephalopathy may occur early & may be severe
- as this is resolving, difficulty in ***weaning*** from ventilation is frequently observed, with clinical signs of polyneuropathy being absent in > 50% of these patients
- sensory testing is unreliable, ∴ ***electrophysiological testing*** is essential
- responses to pain may help differentiate between prolonged effects of NMJ blockers & CIP, due to the sparing of cranial nerves in the later

• §recent number of reports which implicate ***neuromuscular blockers*** and ***steroids*** as causes of neuropathy, myopathy and prolonged NMJ blockade
• Bolton *et al.* ICM 1993 believe these to be two relatively distinct syndromes,

1. patients with ***sepsis & MODS*** are given NMJ blockers
   - following discontinuation signs of quadriplegia appear
   - electrophysiology supports 1° axonal degeneration & denervation atrophy
   - repetitive nerve stimulation studies ***do not*** show a defect of NMJ transmission
   - the ***predominant factor*** is CIP, probably unmasked by NMJ blockade but the possibility of an additive toxic effect cannot be excluded
2. patients with ***severe acute asthma*** requiring NMJ blockade & high dose steroids
   - some cases have suggested a motor neuropathy, others 1° myopathy
   - nerve stimulation studies may, or may not, show a defect of NMJ transmission
   - CPK levels may be significantly elevated
   - muscle B_X shows central structural loss, especially thick myosin filaments
   - these morphological changes are similar to those seen experimentally with denervated muscle plus high dose steroids

NB: therefore, they describe 3 types of polyneuropathy in the critically ill:
classical CIP, plus 1 & 2 above

• to these are added the ***primary myopathies*** which are commonly,

1. cachexic or disuse atrophy
   - EMG and CPK levels are normal
   - biopsy shows type II fibre atrophy
2. panfascicular muscle fibre necrosis
   - marked ↑ CPK, rarely myoglobinuria
   - needle EMG may be normal early, but later is consistent with fibre necrosis
   - biopsy shows an inflammatory reaction and fibre necrosis

■ ***Usual Manifestations CIP***

a. difficulty weaning
b. EMG: - characteristic pattern of ***axonal degeneration***
   needle EMG: - positive sharp waves and fibrillation potentials
c. reduced or absent deep tendon reflexes
d. limb weakness with relative ***cranial nerve sparing***
e. CSF: - usually ***normal***, or slightly elevated ***protein***
f. important ***negative features***
   i. no cranial nerve, autonomic or sensory (?) involvement
   ii. CSF usually normal

Condition	Illness	Clinical Features	Electro-physiology	Morphology	Ma
CIP	Sepsis	Absent, or mainly motor neuropathy	1° axonal degeneration	1° axonal degeneration + denervation atrophy of muscle	Rx
Neuropathy & NMJ Blockers	Sepsis	Acute quadriplegia	NMJ transmission defect, ± axonal motor neuropathy	Normal, or denervation atrophy on B_X	No
Myopathy & NMJ Blockers & Steroids	?? Sepsis	Acute quadriplegia	NMJ transmission defect, ± myopathy	Thick myosin filament loss	No
Panfascicular Muscle Fibre Necrosis	Infection, Trauma	Muscle weakness, ↑ CPK	Positive sharp waves, fibrillation potentials	Panfascicular muscle fibre necrosis	No ? C my
Cachetic Myopathy	Severe illness, Prolonged immobility	Diffuse muscle wasting	Normal	Type II fibre atrophy	Ph Nu

- ***Leijten, et al. JAMA 1995***

• hypothesis that prolonged motor recovery after long-term ventilation may be due to polyneuropathy
• cohort study, 50 patients < 75 years, IPPV > 7 days over an 18 month period

a. polyneuropathy was identified by EMG
b. end point was defined as return of normal muscle strength and ability to walk 50 m
c. EMG diagnosis of polyneuropathy → 29/50 patients **~ 60%**
   - higher ICU ***mortality*** - 14 vs 4 (p = .03)
   - multiple organ failure - 22 vs 11 (p = .08)
   - aminoglycoside treatment of suspected gram-negative sepsis -17 vs 4 (p = .05)
   - ***axonal polyneuropathy*** with conduction slowing on EMG indicated a poor prognosis

• 9 patients with delays > 4 weeks,

a. 8 had polyneuropathy
b. 5 of whom had persistent motor handicap after 1 year

• polyneuropathy in the critically ill,

1. is related to multiple organ failure and gram-negative sepsis
2. is associated with higher mortality
3. causes important rehabilitation problems
4. EMG recordings in the ICU can identify patients at risk.

Guillain-Bárre Syndrome	
Aetiology	• post-infectious • adenovirus, influenza A&B, parainfluenza 3, mycoplasma, herpes zoster, EBV, mumps, measles, CMV, chickenpox, ***C.jejuni***
	• post-vaccination (Influenza A/New Jersey/76 swine vaccine)
Epidemiology	• isolated cases, usually well developed nations
Incidence	• 1.7:100,000
Pathophysiology	• perivenular inflammation, ? cell mediated immunity • autoantigen ? ***myelin neuritogenic protein*** • myelin degeneration ± axonal degeneration
Onset	• ~ 2-8 weeks post URTI ~ 45% GIT ~ 20%
Motor signs	• progressive, ascending ***symmetrical*** paralysis
Cranial nerves	• **~ 45%** involvement • virtually always with limb signs
Tendon reflexes	• decreased or absent
Sensory symptoms	• ***paraesthesia*** **~ 50**% • cramps (rare)
Sensory signs	• none, or mild loss
Autonomic involvement	• Yes ~ 20%
Meningismus	• No
CSF: pressure cells protein	• ~ normal • < 50 lymphocytes/µl, < 2 PMN's/µl • ***increased*** ↑ rise after 1 week
EMG: conduction velocity distal latency sensory/muscle AP's	• reduced • increased • normal
Prognosis	• **~ 85%** full recovery
Treatment	• supportive • ***plasmapheresis*** ± ***immune globulin***
Mortality	• low
Permanent weakness	• < 10%

Poliomyelitis	
Aetiology	• poliomyelitis enterovirus
Epidemiology	• epidemics • under-developed countries
Incidence	• rare ± paralysis ~ 5%
Pathophysiology	• α-motor neurone • bulbar & spinal ± axonal degeneration
Onset	• ~ 2-3 weeks
Motor signs	• ***asymmetrical*** paralysis
Cranial nerves	• ~ 25% involvement
Tendon reflexes	• diminished
Sensory symptoms	• muscle cramps common
Sensory signs	• ***none***
Autonomic involvement	• Yes
Meningismus	• Yes
CSF: pressure cells protein	• normal • 25-2,000/µl ~ 80% PMN's early, then ***monocytes*** • ***increased***
EMG: conduction velocity distal latency muscle AP's sensory AP's	• normal • normal • decreased ∝ denervation • normal
Prognosis	• high incidence of permanent disability • scoliosis, limb girdle weakness
Mortality	• low with supportive R_X
Treatment	• supportive, physiotherapy • prophylactic vaccination

Critically Ill Polyneuropathy	
Aetiology	• unknown • ? toxic/metabolic
Epidemiology	• severe sepsis • MODS
Incidence	• **~ 20%** of severe sepsis (< 70%)
Pathophysiology	• patchy ***axonal degeneration***
Onset	• ~ 1-14 days
Motor signs	• flaccid paralysis • failure to wean from IPPV
Cranial nerves	• usually ***not involved***
Tendon reflexes	• normal, decreased or absent
Sensory signs	• probable but unexaminable
Autonomic involvement	• ***No***
Meningismus	• No
CSF: pressure cells protein	• normal • normal • normal ± slight increase
EMG: conduction velocity distal latency muscle AP's sensory AP's	• normal • normal • decreased • decreased
Prognosis	• ***poor*** = underlying disease
Treatment	• underlying disease, support
Mortality	• high
Permanent weakness	• low incidence

Botulism	
Aetiology	• *Clostridium botulinum* ***exotoxin*** A,B, or E
Epidemiology	• food-borne, adult intestinal • wound • infantile
Incidence	• rare
Pathophysiology	• exotoxin inhibits ***presynaptic*** ACh release
Onset	• 6 hrs - 8 days • prodrome - ingested exotoxin • sore throat, GIT, fatigue
Motor signs	• ***descending symmetrical*** flaccid paralysis
Cranial N. involvement	• ***early***, most cases
Tendon reflexes	• normal, sometimes decreased
Sensory symptoms	• none
Sensory signs	• none
Autonomic involvement	• mydriasis, ileus, dry mouth • ie. anticholinergic
Meningismus	• none
CSF: pressure cells protein	• normal • normal • normal ± slight increase
EMG: conduction velocity distal latency muscle AP's sensory AP's	• normal • normal • decreased + ***post-tetanic facilitation*** • decreased
Prognosis	• good with treatment
Treatment	• supportive
Mortality	• high
Permanent weakness	• nil

Neuropathies - Miscellaneous

- ***Lead Neuropathy***

1. history of ingestion
2. radial nerve palsy → ***wrist drop***
3. arm weakness, rarely shoulder girdle
4. anaemia with ***basophilic stipling***
5. colicky abdominal pain, constipation
6. dementia
7. encephalopathy in children
8. raised urinary Pb^{++}, and coproporphyrins

- ***Beri-Beri***

1. acute ***thiamine deficiency*** resulting in ***axonal degeneration***
   - always malnourished
   - common in chronic alcoholics
2. sensory loss
   - progressive ***symmetrical*** distal paraesthesia, "glove & stocking"
   - diminished proprioception, vibration ± touch
3. ***LMN weakness*** - loss of reflexes
4. ***no*** cranial nerve involvement
5. occasionally ***autonomic dysfunction***
6. normal CSF
7. associated CVS changes, ***cardiomyopathy***
8. abnormal rbc ***transketolase***

Subacute Combined Degeneration of the Cord

1. vitamin B_{12} deficiency
2. spinal postero-lateral column degeneration
3. bilateral, usually symmetrical posterior column loss
   i. joint position & vibration loss
   ii. ataxic gait
   iii. positive Romberg sign
4. ***upper motor neurone*** signs in the legs
   - usually exaggerated, but occasionally absent, knee reflexes
   - clonus, up-going plantars
   - but, absent ankle reflexes
   - reflexes may be diminished or absent due to sensory dysfunction
5. associated findings
   i. optic atrophy
   ii. peripheral sensory neuropathy
   iii. dementia

NB: R_X **B_{12}** & ***folate***

MULTIPLE SCLEROSIS

- ***Essential Features***

1. ***episodic*** symptoms including,
   i. blurred vision
   ii. sensory abnormalities
   iii. motor weakness, ***with or without spasticity***
   iv. sphincter disturbances
2. patient age usually **< 55** ***years***
3. clinical findings ***cannot*** be explained by a ***single*** pathological lesion
4. multiple CNS focal lesions, best shown by MRI

- ***Clinical Features***

a. commonest demyelinating disease
b. episodic course with ***relapses & remissions***
c. varied symptomatology, mimics many other diseases
d. usually starts in ***young adults*** ~ 30 yrs age
   ~ 60% females
e. young adults frequently present with ***ocular***, or ***UMN motor*** features
f. elderly tend to get progressive spastic paraparesis
g. ***localising signs*** → probably ***not*** MS

- ***Clinical Symptoms***

a. visual change - scotomata, blurring
   - diplopia
b. ocular pain - optic neuritis
c. vomiting, vertigo, ataxia
d. limb weakness
e. paraesthesia
f. GUS
   i. early - urinary frequency & urgency
   ii. late - urinary retention
   - reflex emptying

- ***Clinical Signs***

a. eye
- nystagmus → ***abduction*** > adduction
- internuclear ophthalmoplegia (III, IV)
- papilloedema, later optic atrophy

b. limbs
- spasticity, UMNL lesion
- hypo- or areflexia
- cerebellar signs

c. speech
- staccato, scanning speech

d. personality
- emotional lability
- intellectual impairment

- ***CSF Findings***

1. elevated total protein - rare
2. increased Ig's
3. mild lymphocytosis

Poor Prognostic Features	**Better Prognostic Features**
1. young age	1. older age
2. male > female	2. complete recovery
3. incomplete, or no remissions	3. ↑ duration between recurrences
4. early recurrence	4. type of initial lesion
5. type of initial lesion	• retrobulbar neuritis
• motor, brainstem, or cerebellar	• sensory, no motor involvement

Treatment

a. physiotherapy and supportive
- minimise 2° complications - infection, pressure sores, etc.

b. ***steroids***
- relapses → Dexamethasone 2mg q8h for 5 days
- hastens recovery, but ***no change*** in long term disability or relapse rate

c. cyclophosphamide / azathioprine
- may be beneficial in long-term management, currently being trialled

d. interferon - may help if relapsing disease
- trials being done

e. plasmapheresis - ***no benefit*** in MS

MOTOR NEURONE DISEASE

- group of disorders, characterised by ***weakness*** and ***variable wasting***, without sensory changes
- infantile/childhood variants include Wernig-Hoffman disease
- the disease variably involves,
    a. cranial nerve motor neurones
    b. spinal motor neurones
    c. pyramidal tract motor neurones

NB: → progressive ***bulbar palsy*** or ***limb weakness***

- ***Classification***

1.	progressive ***bulbar palsy***	- motor nuclei of cranial nn.
2.	***pseudobulbar palsy***	- bilateral corticobulbar disease - UMN lesions of the cranial nn.
3.	progressive ***spinal muscular atrophy***	
4.	primary lateral sclerosis	- purely UMN deficits in the limbs
5.	***amyotrophic lateral sclerosis***	- mixed UMN/LMN lesions of the limbs - associated with dementia, parkinsonism, etc.

- ***Clinical Features***

a. in at least ***3 extremities***, a combination of,
    i. LMNL in arms → ***progressive muscular atrophy***
        - ***fasciculation***, weakness, atrophy & loss of reflexes
    ii. UMNL in legs → ***amyotrophic lateral sclerosis***
b. LMNL lower cranial nerves - bulbar palsy
c. reflexes variable - hyperactive (UMN), or lost early (LMN)
d. absence of sensory signs and upper cranial nerve involvement
e. sphincters generally spared
f. CSF examination normal

- ***Differential Diagnosis***

a. Guillain-Bárre
b. high cervical cord lesion
c. syphilis
d. paraneoplastic syndrome

PHRENIC NERVE PALSY

- ***Unilateral***

  a. idiopathic / congenital

  b. trauma - cervical
     - surgical
     - post-CABG

  c. mediastinal tumour

  d. local anaesthetics - interpleural, interscalene
     - stellate ganglion

  e. features
     i. asymptomatic - in the absence of other cardiorespiratory disease
     ii. small fall in VC
     iii. elevated hemidiaphragm on CXR
     iv. no movement on ***double-exposure*** CXR

- ***Bilateral***

  a. congenital

  b. cervical cord damage

  c. motor neurone disease

  d. polyneuropathies

  e. poliomyelitis

  f. mediastinal tumour

  g. "cryoanaesthesia" of phrenic nerves during open-heart surgery

  h. features
     i. paradoxical respiration
     ii. respiratory failure
     iii. small VC
     iv. failure to wean from IPPV after CABG

CENTRAL PONTINE MYELINOLYSIS

- pontine myelinolysis should be suspected on the following criteria,
    a. progressive neurological deficits resulting in ***"locked-in" syndrome***,
        i. flaccid quadriplegia
        ii. pseudobulbar palsy - inability to speak or swallow
        iii. facial weakness
        iv. upper cranial nerves ***spared***
        v. impaired pain response
    b. risk factors,
        i. severely malnourished alcoholic
        ii. severe hyponatraemia
        iii. hepatic encepalopathy - only 25% are hyponatraemic
        iv. inappropriate hydration of a patient at risk
            - too much water, or too rapid correction
            - correction to ***hypernatraemic*** levels (animal studies ~ 150 mmol/l)
    c. development over days
    d. diagnosis by CT/MRI
        - only ~ 15-20% of presumptive CPM is positive by MRI criteria

- the pathology → ***central*** and ***symmetrical*** demyelination at the base (ventral) of the pons
- the major differential diagnosis is from,
    a. critically-ill polyneuropathy
    b. severe hyperkalaemia

NB: also termed ***osmotic demyelination syndrome***

Cerebellar Lesions

a. alcohol[§]
b. tumour[§]
c. CVA[§]
d. Friedrich's ataxia[§]

[§]common causes of ***cerebellar signs***

e. multiple sclerosis
f. drugs - phenytoin
- barbiturates, alcohol
g. ischaemia - vertebrobasilar disease
h. paraneoplastic syndrome - eg. bronchial Ca.
i. hypothyroidism
j. Arnold-Chiari malformation
k. other brainstem and cerebello-pontine angle tumours

Friedrich's Ataxia

• a familial disorder, of autosomal ***dominant*** inheritance, with a usual age of onset **~ 5-15 years**
• characterised by ***dorsal*** and ***lateral spinal column*** degeneration, affecting pyramidal, spinocerebellar and sensory tracts

- ***Clinical Features***

1. upper motor neurone lesion in legs
   - lower limb weakness and ***extensor plantars***
   - sensory involvement → depressed or absent knee jerks
2. cerebellar ataxia - first in the lower limbs, then upper limbs
3. ***cardiomyopathy*** - arrhythmias & sudden death
4. optic atrophy
5. pes excavatum
6. scoliosis

NB: ie. lower limb findings similar to SACD, differentiated by other findings & I_x

Headache

a. tension headaches
b. migraine - common
- neurological
c. cluster headache, migrainous neuralgia
d. meningeal irritation - infection
- blood
e. intracerebral tumour
f. intracranial haematoma
g. raised ICP - any cause
h. temporal arteritis

Facial Pain

NB: common causes - sinusitis, dental problems, fractures

- ***Differential Diagnosis Severe Pain***

a. trigeminal neuralgia
b. post-herpetic neuralgia
c. atypical facial neuralgia
d. Costen's syndrome - temporomandibular joint arthritis
e. Tolosa-Hunt syndrome - temporal / facial arteritis, orbital pain
f. Raeder's para-trigeminal syndrome - organic compression of trigeminal ganglion
g. migrainous neuralgia
h. rare neuralgias - supraorbital, infraorbital
- sphenopalatine, ciliary

Holmes-Adie Syndrome

a. myotonic pupil - dilated
- reacts sluggishly to light
b. autonomic hyporeflexia - postural hypotension
c. absent tendon jerks

Horner's Syndrome

1. ptosis - SNS supplies upper eyelid ***smooth muscle***
2. miosis - unopposed PNS action
3. anhidrosis * all ***unilateral***
4. enophthalmos - probably ***not*** in man, or if so very minor

- ***Aetiology***

a. brain-stem vascular disease
   - lateral medullary syndrome
   - PICA syndrome

b. demyelinating diseases
   - MS
   ? GBS

c. syringomyelia, syringobulbia

d. carcinoma of the bronchus - Pancoast tumour

e. cervical sympathectomy & stellate ganglion block - chemical, surgical

f. secondary carcinoma in cervical nodes

g. traumatic

h. aneurysm
   - aortic
   - carotid
   - ophthalmic

Limb Pain - Causes

i. trauma
ii. cellulitis
iii. lymphangitis
iv. osteomyelitis
v. superficial or deep venous thrombosis
vi. arterial occlusion
vii. AV fistula
viii. cramps
ix. erythromelalgia
x. sympathetic dystrophy
xi. nerve entrapments
xii. erythema nodosum
xiii. varicose veins
xiv. ischaemic compartment syndromes

MYASTHENIA GRAVIS

Def'n: a neuromuscular disorder resulting in weakness and fatiguability of skeletal muscle, due to an ***autoimmune*** mediated decrease in the ***number***, and ***functional integrity*** of ACh receptors at the neuromuscular junction;

"the prototype of antibody mediated autoimmune disease"

1. ***degradation*** of AChR's at an accelerated rate due to cross-linking
2. effective ***junctional blockade*** due to receptor occupancy by antibodies
3. damage to the postsynaptic membrane due to ***complement activation***

▪ ***Essential Features***

a. muscular ***weakness***
- external ophthalmoplegia ≥ 90%
  * may be assymetrical
- facial weakness
- bulbar muscle involvement * risk of aspiration
- respiratory failure

b. easy ***fatigability***

c. recovery with ***rest*** or ***anticholinesterases***

Myasthenia Grades[§]	
I	• extraocular muscle involvement only • good response to anticholinesterases
IIA	• generalised mild muscle weakness • ***no*** respiratory involvement • good response to anticholinesterases and steroids
IIB	• generalised moderate muscle weakness, and/or bulbar dysfunction • ***may*** involve respiratory muscles • more severe, rapidly progressive
III	• acute, fulminating presentation, and/or respiratory dysfunction • rapid deterioration over ≤ 6 months • high mortality
IV	• late, severe, generalised myasthenia gravis • incidence ~ 1:20,000 • females > males • 80% > 20 yrs • progression from types I & II

[§] Osserman and Genkins (1971)

- ***Anti-ACh-Receptor Ab's***

a. all grades ~ 85-90% (+)'ve * virtually diagnostic if present

b. grade I ~ 50% (+)'ve

c. AChR-Ab (-)'ve patients have mild or localised myasthenia

d. **IgG** predominantly against the a ***-subunit*** of the endplate receptors

e. individual patients have ***heterogenous*** populations of AChR antibodies

f. there is limited sharing of idiotypes between patients

g. T-cells become sensitised against ***thymic myoid cell*** AChR's during maturation

h. ***T-cell dependent,*** B-cell antibody production results in circulating Ab's

NB: clinical effects appear when muscle is unable to synthesise new receptors faster than the rate of destruction

- ***Presentation***

a. ***transient neonatal myasthenia***
- **~ 15-20%** of neonates born to myasthenic mothers
- pregnancy may result in remission or exacerbation of maternal myasthenia
- *no correlation* between the severity of maternal disease and neonatal occurrence
- *no correlation* between the level of maternal AChR-Ab's and neonatal occurrence
- spontaneous remission usually in 2-4 weeks

b. ***congenital or infantile myasthenia***
- ***not*** autoimmune, possibly autosomal recessive inheritance
- rare in the absence of maternal myasthenia
- comprises a number of genetically determined abnormalities of the AChR or the post-synaptic membrane

c. ***juvenile myasthenia***
- ~ 4% onset before 10 years and ~ 24% before age 20 years
- marked female predominance ~ 4:1
- pathologically identical to the adult disease, though, thymoma ***is not*** a feature

d. ***adult myasthenia***
- prevalence ~ 1:20,000 * F:M ~ **3:2** overall
  - F:M ~ 2:1 < 50 years
  - F:M ~ 1:1 > 50 years
- males tend to have more severe & rapidly progressing disease
- hyperplasia of the thymus in > 70%, ***thymoma*** in 10-15%
- distribution, severity & outcome are determined by the course within the first 2-3 years following onset, suggesting most ACh receptor damage occurs early
- ~ 15% remain localised to the extraocular muscles, 85% becoming generalised
- spontaneous remission rate ~ 20% in first 2 years, but rarely complete

- ***Clinical Features***

1. muscle groups
   i. eye muscle weakness ~ 80%
   ii. bulbar palsies ~ 30%
   iii. facial muscles
   iv. shoulder girdle, neck & respiratory muscle weakness
      - trunk and limb muscles less frequently involved
   v. tendon reflexes are ***brisk*** and sensation is normal
2. clinical picture
   i. restricted ocular disease ~ 25%
   ii. ocular, bulbar, mild-moderate generalised weakness ~ 50%
   iii. acute fulminating disease + respiratory involvement ~ 10%
   iv. late chronic muscular atrophy

- ***Complications***

a. myasthenic crisis - severe life-threatening relapse
b. cholinergic crisis
c. respiratory failure - aspiration, infection, weakness
d. "Mary Walker phenomenon"
   → acute muscle weakness following exercise∝ ***lactic acidosis***
e. ***cardiomyopathy***
f. associated diseases making weakness worse
   - hyper / hypothyroidism, SLE, RA, polymyositis, pernicious anaemia

- ***Differential Diagnosis***

1. myasthenic syndrome - Eaton-Lambert
2. acquired myopathies - hyperthyroidism, hyperparathyroidism, Cushing's d.
   - polymyositis / dermatomyositis
3. botulinism, Guillain-Barré, motor neurone disease
4. organophosphonate poisoning
5. envenomations - tick paralysis, snake bites
6. neurasthenia
7. progressive post-poliomyelitis muscular atrophy
8. familial periodic paralysis
9. intracranial mass lesions

- ***Investigation***

1. ACh-R ***antibodies***
   - all grades ~ 85-90%
   - grade I ~ 50%
   - essentially diagnostic if present
2. anticholinesterase tests
   - ***edrophonium*** is commonly used due to rapid onset (< 30s) and short duration of action (~ 5 mins), resulting from freely ***reversible*** binding with ACh-E
   - objective assessment of one of the unequivocally weak groups of muscles,

   i. initial dose 2 mg IV

   ii. improvement (+)'ve - test is terminated

   iii. no improvement (-)'ve - further dose of 8 mg

   iv. small initial dose due to unpleasant side-effects
      - nausea, diarrhoea, salivation, fasciculations and rarely syncope
      - atropine (0.6 mg) should be available for administration

   v. false positives - amyotrophic lateral sclerosis
      - placebo-reactors

   - some cases may be better assessed with a long acting anticholinesterase agents, such as neostigmine
3. electrodiagnositic testing
   - ***fade***, train of five (3Hz) > 10% decrement 1 → 5
   - ***post-tetanic facilitation***
4. CT of thoracic inlet/mediastinum
5. other serology

   i. thyroid function studies ~ 5% of myasthenics

   ii. ANF, RF
6. other auto-Ab's

   i. anti-striated muscle Ab's ~ 90% of myasthenics with ***thymoma***

   ii. ANA, DNA, extractable nuclear Ag

   iii. smooth muscle, islet cell, parietal cell, intrinsic factor, adrenal

Myasthenic Crisis

Def'n: sudden, severe life-threatening relapse

1. may last weeks - months
2. risk factors
   - introduction of steroids
   - increasing age
   - pregnancy
   - infection
   - surgery, trauma
3. drugs
   - aminoglycosides, tetracyclines
   - class Ia antiarrhythmics
   - narcotics, volatile anaesthetics
   - muscle relaxants

- ***Clinical Features***

a. rapid deterioration

b. ***positive*** tensilon (edrophonium) test

c. NM stimulation → tetanic fade
post-tetanic facilitation

Cholinergic Crisis

Def'n: muscular weakness 2° to excessive doses of anticholinesterases

1. risk factors
   - recovery phase from any "stress"
   - following response to
     - steroids, immunosuppressives
     - thymectomy, plasmapheresis
2. differentiation from ***myasthenic crisis***

- ***Clinical Features***

a. ***negative*** Tensilon test

b. NM stimulation → depressed single twitch
absent fade & absent post-tetanic facilitation

c. signs of ***cholinergic toxicity*** may appear
   - miosis, lacrimation
   - tremor, anxiety, confusion, seizures
   - bradycardia, AV block
   - bronchospasm, bronchorrhoea, pulmonary oedema
   - abdominal cramps, N&V, diarrhoea, diaphoresis

Treatment

a. ***anticholinesterases***

- little benefit in severe cases with respiratory muscle involvement
- animal studies show long term administration results in changes in the AChR similar to those seen in myasthenia
- patient education regarding overdose (cholinergic) vs. underdose (myasthenic)

i. neostigmine 15 mg qid ~ 0.5 mg IV
~ 1.5 mg IM

ii. pyridostigmine 60 mg 6-8 hrly

b. ***immunosupression***

i. prednisolone 50-100 mg/day
- increases muscle strength & results in remission ~ 80%
- may result in ***increased*** weakness during first 7 days, especially high doses
- complete withdrawal is seldom possible

ii. cyclophosphamide, azathioprine

c. ***plasmapheresis***

- every 2-3 days for 2 wks → ~ 45% show marked improvement or ***remission***
- however, this only lasts 4 days to 12 weeks
- plasma compartment contains ~ 45% of total IgG,
  → ~ 70% of this being removed by total plasma exchange
  → **~ 30%** removal of IgG
- therefore, should always be accompanied by immunosuppressive therapy
- indications

i. myasthenic crisis, especially with respiratory failure

ii. respiratory failure

iii. preoperative (for thymectomy)

iv. refractory to drug therapy (steroids & anticholinesterases)

d. ***thymectomy*** *see over

- ***Thymectomy***

NB: should be performed on ***all*** adult patients with ***generalised*** disease, especially between puberty & 55 years;
there is also unanimity regarding resection of ***thymomas***, although, disease remission is ***less frequent***

a.	removal of thymoma	~ 10% of cases, most are benign - resection to prevent local spread
b.	therapeutic thymectomy	≤ 85% of patients improve ~ 35% achieve drug-free remission ~ 50% reduction in ***mortality*** in generalized disease

- thymus is abnormal in ~ 75% (65% hyperplasia + 10% thymoma)
- improvement may begin up to 1-10 years post-surgery !!
- usually lowers the AChR-Ab titre, which correlates well with clinical improvement
- there is ***no evidence*** that removal in ***childhood*** results in immunodeficiency
- operation ***is*** usually recommended for patients with only extraocular disease (Class I)
- the anterior, ***trans-sternal approach*** is superior, as even small remnants left during the transcervical approach will limit success

Anaesthetic Management

NB: use regional or local anaesthesia whenever possible

a.	***preoperative evaluation***	- age, sex, onset & duration of disease - presence or absence of thymoma, R_X - bulbar involvement, aspiration risk, CAL
b.	***optimisation of condition***	- steroids ± azathioprine (age > 15) - plasmapheresis ? anticholinesterases

- the use of anticholinesterases is debated
- they potentiate vagal responses & require the use of atropine
- decrease the metabolism of suxamethonium and ester local anaesthetics

c.	***premedication***	- avoid respiratory depressants ? atropine IM ± benzodiazepines
d.	***induction / maintenance***	- deep inhalational anaesthesia - balanced anaesthesia with muscle relaxants

- abnormal response to both ***depolarizing*** (↓) & ***non-depolarizing*** (↑) relaxants
- these responses are seen during remission & with localised extraocular disease
- ED_{95} for SCh may be 2-2.5 x normal, however ***type II blockade*** is readily produced
- conversely, the ED_{95} for the non-depolarising agents may be 10% of normal
- atracurium & vecuronium have short enough half-lives to allow titration to effect

e. ***postoperative management***
- neuromuscular monitoring should be continued into the postoperative phase
- few studies correlate tests of NMJ function with adequacy of ventilation

NB: the ***differential responses*** seen between peripheral versus bulbar muscles is further exaggerated in the myasthenic patient !

Elective Postoperative Ventilation		
Factor		Points
• long history of myasthenia	> 6 yrs	12
• moderate to severe CAL	- not 2° to MG	10
• high pyridostigmine dose	> 750 mg/day	8
• diminished vital capacity	< 2.9 l < 40 ml/kg	4

NB: total score **> 10 points** = post-operative ventilation for > 3 hours

NB: following transcervical thymectomy **~ 7.4%** of patients require prolonged (> 3 hrs) ventilation

- ***Outcome***

a. ***thymectomy*** benefits ~ 96% of patients, irrespective of preoperative status
   i. ~ 46% develop complete remission
   ii. ~ 50% are asymptomatic or improve on therapy
   iii. ~ 4% remain the same

b. thymectomy ***does not*** always result in a decrease the anti-AChR-Ab titre

NB: the anti-AChR sensitised T-cells survive long after thymectomy

Eaton-Lambert Syndrome

- acquired disorder of ***quantal release*** of ACh from motor nerve terminal
- usually males, aged 50-70 years, with a high association with ***small cell carcinoma*** of the lung
- disease predominantly of the ***limb girdle*** muscles, with weakness, aching and stiffness
- IgG-Ab to the ***presynaptic*** voltage-dependent Ca^{++} channels → ↓ ACh quantal release
- ACh content and acetyltransferase activity are normal
- decreased quantal release & decreased MEPP frequency
- ***tendon reflexes*** are depressed or absent, unlike myasthenia
- ***dysautonomia*** may occur

  → dry mouth, impaired accomodation, urinary hesitancy and constipation

- "characteristic" EMG →

  1. incremental response
  2. ***improvement*** with exercise / tetanic stimulation
  3. marked EMG deficit with "normal" clinical strength[§]

  NB: [§] this is in contrast to myasthenia,
  where the EMG abnormality is ***mild*** in the presence of marked clinical weakness

- weakness is ***not*** reliably reversed with anti-AChE agents
- however, 3,4-diaminopyridine increases ACh release & may be beneficial
- patients are sensitive to ***both*** depolarising and non-depolarising relaxants

MYOPATHIES

Classification

- ***Congenital***

a.	muscular ***dystrophies***	- Duchene - limb girdle, F-S-H, etc.
b.	***myotonias***	- dystrophica myotonica - myotonia congenita - paramyotonia
c.	***myopathies***	- central core - nemaline - microtubular
d.	glycogen storage diseases	
e.	familial periodic paralysis	

- ***Acquired***

a.	***alcohol***		
b.	***drugs***		- steroids - D-penicillamine - organophosphates
c.	***endocrine***		- thyrotoxic - diabetes - hypoparathyroid - hypopituitarism - Cushing's
d.	***infective***		
	i.	viral	- influenza A & B - Coxsackie B_5 - adenovirus, EBV, herpes - dengue, measles
	ii.	bacterial	- brucella - legionella - Staphlococcal - leptospirosis
	iii.	fungal	
	iv.	protozoal	- toxoplasmosis - trichinosis, worms

e. ***autoimmune*** - SLE, RA
- polymyositis / dermatomyositis
- polymyalgia rheumatica

f. ***NMJ*** - myasthenia gravis
- Eaton-Lambert
- organophosphates

g. ***metabolic***
   i. hypo - glycaemia / K^+ / Ca^{++} / $HPO_4^=$
   ii. hyper - Mg^{++} / K^+

h. chronic renal failure

i. nutritional

j. infiltrative - amyloid, tumour, fibrositis

k. disuse atrophy

l. rhabdomyolysis

Polymyositis / Dermatomyositis

- inflammatory diseases of skeletal muscle with ***lymphocytic*** infiltration and fibre damage
- dermatomyositis, in addition, has a ***heliotrope*** cyanosis & oedema from infiltration of the skin
- often associated with,

   a. ***malignancy*** *ovary, breast, GIT, lung and prostate

   b. collagen/vascular diseases - RA, SLE, scleroderma

   c. Raynaud's disease

   d. rheumatic fever

- clinical features,

   a. difficulty swallowing - bulbar palsy

   b. proximal, limb girdle weakness

   c. diminished reflexes - but always ***present***

   d. low grade ***fever***

   e. ↑ CPK, ESR, CRP

   f. tachycardia, rarely myocarditis

   g. positive ***muscle biopsy***

- management with steroids / azathioprine

Muscular Dystrophy

- ***Types***

a. x-linked recessive
   - i. Duchene's
     - onset 1-5 years, rapid progression
     - death within 15 years of onset
     - pelvic, then shoulder girdle
     - later respiratory muscles
   - ii. Becker's
     - slow progression, may have normal life-span
     - age of onset 5-25 yrs

b. autosomal recessive
   - i. limb girdle Erb's
     - onset 10-30 yrs
     - variable severity, mild & severe forms
     - pelvic or shoulder girdle

c. autosomal dominant
   - i. facio-scapulo-humeral - onset at any age, slow progression
   - ii. distal - onset 40-60 yrs, slow progression
   - iii. ocular
     - onset any age (usually 5-30)
     - may be recessive
   - iv. oculopharyngeal - same as ocular but involves pharyngeal mm.

Duchenne Muscular Dystrophy

- ***Principal Problems***

1. progressive ***muscle weakness***
   - i. ascending - lower limb girdle first
   - ii. restrictive respiratory defect
   - iii. dysphagia, dysphonia, risk of aspiration
2. increased sensitivity of ***respiratory drive*** to sedatives
3. muscle relaxants
   - i. suxamethonium → ***hyperkalaemia*** and rhabdomyolysis
   - ii. nondepolarisers → ↑ ***sensitivity***
4. cardiomyopathy
   - i. especially ***RV obstructive cardiomyopathy*** (PV outflow obstruction)
   - ii. ECG - RVH and "strain", conduction delays, VE's
   - iii. very sensitive to negative inotropes (eg. volatile agents)
5. possible association with ***malignant hyperthermia*** (probably not)

- ***Clinical Features***

a. ***x-linked recessive*** disorder, affecting almost exclusively ***males***

b. incidence ~ 13-33:100,000
~ 1:3,000-8,000

c. progressive, ***symmetrical*** weakness of the pelvic & shoulder girdles,
   i. onset by age 5 years
   ii. leg braces by 8-10
   iii. non-ambulatory by 12 years
   iv. survival beyond 25 years is rare

d. associated problems
   i. tendon and muscle contractures
   ii. progressive ***kyphoscoliosis***
   iii. impaired pulmonary function
   iv. ***cardiomyopathy***
   v. intellectual impairment ~ 33%

e. palpable enlargement of some muscles, resulting initially from ***hypertrophy*** and later from replacement with fat and connective tissue

f. laboratory findings

i.	***CK***, aldolase	- massive & early elevations - MM & MB bands - ***not*** BB (cancer, heart trauma, CPB, CT disorders)
ii.	EMG	- myopathic pattern
iii.	ECG	- tall R in V_1, deep Q in precordial leads - 'pseudo-infarct' pattern
iv.	***biopsy***	- necrotic fibres, phagocytosis, fatty replacement

g. carrier detection

i.	CK	~ 50% of female carriers show elevation
ii.	DNA probes	- abnormal gene coding for ***dystrophin*** - restriction fragment length polymorphisms (RFLP's)

h. complications

i.	respiratory	- respiratory failure - recurrent infections
ii.	CVS	- ***cardiomyopathy*** in almost ***all*** patients - CCF occurs rarely, only with major stress - arrhythmias occur but also uncommon * cardiac death is ***rare***
iii.	GIT	- acute gastric dilatation (may be fatal) - aspiration syndromes

Myotonic Dystrophy *Dystrophica Myotonica*

a. ***autosomal dominant*** ~ 1:10,000

b. onset - typically 2nd or 3rd decade
- affected individuals may remain asymptomatic

c. ***congenital myotonic dystrophy***
- occurs in infants of affected mothers with severe facial and bulbar palsy
- neonatal respiratory insufficiency may occur but is usually ***self-limiting***

d. clinical features
   i. manifests as an inability to relax muscles following strong contraction
   ii. initially muscles of face, neck and distal extremities
   iii. characteristic "hatchet" face
      - ptosis, temporal wasting, drooping of the lower lip and sagging of the jaw
   iv. cardiac involvement usually affects conducting tissue
      - 1st degree ***heart block*** is present in the majority
      - CHB may dictate pacemaker insertion
      - ***sudden death*** may occur, tachyarrhythmias & CCF are less frequent
   v. respiratory muscle weakness may be severe with minimal limb involvement
   vi. impaired ventilatory drive & extreme sensitivity to opioids etc.
   vii. central & peripheral ***sleep apnoea*** with chronic hypoxia may lead to ***cor pulmonale***, and this is the usual cause of CCF in these patients

e. characteristic ***facial features***
   i. ptosis
   ii. atrophy of facial muscles & sternomastoid
   iii. frontal baldness & hyperostosis frontalis
   iv. posterior subcapsular cataracts

f. laboratory studies
   i. CK - normal or mildly elevated
   ii. EMG - characteristic myotonia & myopathic features
   iii. ECG - 1st degree HB ± CHB
   iv. ***biopsy*** - distinctive ***type I fibre atrophy***
   v. genetics - mutant gene long arm of $\mathbf{C_{19}}$
      * antenatal diagnosis possible

g. general management
- condition is seldom so disabling as to require treatment
- ***phenytoin*** is drug of choice
- antimyotonia agents, quinidine & procainamide, may ***worsen*** cardiac conduction

h. treatment of ***myotonic contractures*** - hydrocortisone
- dantrolene
- procainamide

- ***Myotonic Contracture Triggers***

1. cold, shivering, stress
2. trauma, exercise, mechanical stimulation
3. tourniquets, hyperkalaemia
4. ***drugs*** - suxamethonium
   - halothane
   - anticholinesterases

- ***Other Complications***

1.	respiratory muscle weakness	- respiratory failure
2.	myotonic contracture	- chest wall rigidity - difficult to ventilate
3.	cardiomyopathy	± cor pulmonale
4.	***endocrinopathy***	- hypothyroidism - diabetes mellitus
5.	gastrointestinal disease	- pharyngeal weakness - aspiration risk
6.	gonadal atrophy	
7.	intellectual impairment	
8.	hypersomnia / sleep apnoea syndrome	
9.	possible association with MH	* abnormality on C_{19}
10.	drugs	- contractures - respiratory depression

- ***Treatment of Myotonic Contractures***

1. hydrocortisone
2. phenytoin
3. dantrolene
4. procainamide, quinidine - may worsen intracardiac conduction

Myotonia Congenita

a. occurs as autosomal dominant and autosomal recessive forms

b. those with the ***recessive*** form may develop slight weakness,
those with the dominant form do not

c. there is no other significant organ involvement

d. respond well to antimyotonia agents
- quinine, procainamide, tocainide
- phenytoin
- acetazolamide

Miscellaneous Muscular Dystrophies

1. oculopharyngeal dystrophy
2. congenital muscular dystrophy
3. distal muscular dystrophy
4. scapuloperoneal dystrophy

Congenital Myopathies

NB: 1. these are rare disorders, distinguished from the ***muscular dystrophies*** by the presence of ***specific histochemical*** & ***structural*** abnormalities in muscle
2. a ***non-progressive*** course is common but not invariable
3. pectus excavatum, kyphoscoliosis, hip dislocation & pes cavum are common

▪ ***Central Core Disease***

- the first congenital myopathy described, by Shy & Magee in 1956
- ***autosomal dominant*** inheritance but sporadic cases occur
- weakness of muscles of the face & legs is usually mild
- serum CK and EMG may be normal
- diagnostic biopsy with "central cores" in fibres, devoid of oxidative enzymes

NB: almost ***definite*** association with ***malignant hyperpyrexia***

▪ ***Nemaline Myopathy***

- usually autosomal dominant, may be recessive or sporadic
- infantile hypotonia is present & often severe leading to respiratory failure
- serum CK may be normal, EMG usually shows myopathy

▪ ***Myotubular Myopathy***

- multiple patterns of inheritance plus sporadic cases
- similar to above but distinguished by external ophthalmoplegia
- CK is normal or slightly elevated, the EMG abnormal

▪ ***Congenital Fibre Disproportion***

- hypotonia, weakness, delayed motor milestones, skeletal deformities as above
- biopsy shows increased number of small type I fibres, with normal or hypertrophied type II fibres

THERMAL SYNDROMES

Regulation of Body Temperature

NB: balance between heat generation and heat dissipation

a. heat production / gain
   i. basal VO_2
   ii. muscular activity
   iii. SDA of food
   iv. non-shivering thermogenesis
   v. gain from the environment

b. heat loss
   i. radiation ~ 40%
   ii. convection ~ 30%
   iii. evaporation ~ 29%
   iv. conduction, feces/urine ~ 1%

NB: ***respiratory losses*** ~ **10%** → humidification ~ 8%
convection ~ 2%

- ***Sensory Systems***

a. cutaneous thermoreceptors **~ 15%** of input
   i. cold receptors < 24°C
   ii. heat receptors > 44°C

b. deep/core thermoreceptors **~ 85%** of input
   i. ***anterior hypothalamus***
   ii. spinal cord
   iii. hollow viscera

- ***Central Integration***

• some processing in the spinal cord, majority in the ***posterior hypothalamus***
• "central thermostat" regulated by,

1. diurnal rhythm, age, sex, hormones
2. endogenous pyrogens - IL-1 → PGE_2
3. drugs
4. neurotransmitters (? 5HT)
5. exercise

- ***Effector Systems***

1. higher control centres
   i. posture, avoidance behaviour
   ii. apetite/hunger
   iii. clothing
   iv. level of activity → voluntary muscle metabolism
   ↑ BMR ≤ 1000% with exercise
2. ***cutaneous blood flow***
   - especially the extremities
   - may decrease skin blood flow to ~ 5% of normal & heat loss to ~ 12%
   - first line of defence activated against heat loss
3. ***shivering thermogenesis***
   - involuntary incoordinate muscular activity ~ 50 Hz
   - may ↑ VO_2 ~ 200-500%
   - may ↑ core temperature ~ 2-3 °C/hr
   - requires ↑ VO_2 ~ 100% / ↑1°C
4. ***nonshivering thermogenesis***
   - increased combustion of FFA's and glucose, regulated by,
   i. sympathoadrenal outflow → fast response - noradrenaline
   ii. thyroid function → slow response - adrenaline & T_4
   - liver and skeletal muscles in adults ~ 25% ↑ BMR
   - ***brown fat*** in neonates ~ 100% ↑ BMR
     ~ 25% of total CO
5. ***sweating***
   - direct or reflex stimulation of the spinal cord, medulla, hypothalamus or cortex
   - provides only coarse control of temperature
6. horripilation / piloerection - minimal effects in man cf. animals

NB: usual order of activation,

i. behavioural modification
ii. vasoconstriction
iii. nonshivering thermogenesis
iv. shivering thermogenesis

Heat Stroke

- above 37°C, for each 1°C rise,
  a. HR ↑ 8-10 bpm
  b. CI ↑ 1.8 l/m/m^2

- results predominantly from a reduced ability to ***dissipate heat***
- commonly occurs in susceptible patients, exposed to high environmental temperatures
  a. elderly patients
  b. CCF
  c. alcoholics
  d. patients on anticholinergic medication

Exertional Heat Injury

a. extreme exercise
b. thyroid storm
c. status epilepticus
d. delerium
e. drug induced
   i. overdosage - TCA's, MAOI's, theophylline, salicylates
      - PCP, cocaine, LSD, MDMA
   ii. withdrawal - alcohol, opioids, barbiturates

NB: cf. heat stroke patients, this group is usually ***sweating*** freely

- ***MH Susceptibility***

a. diseases almost certainly related → ***central core disease***

b. diseases possibly related
   i. King-Denborough syndrome ? RDM says certainly related
      - short stature, musculoskeletal deformities and mental retardation
   ii. Deuchenne muscular dystrophy
   iii. other myopathies
      - Schwartz-Jampel syndrome
      - Fukuyama muscular dystrophy
      - Becker muscular dystrophy
      - familial periodic paralysis
      - myotonia congenita
      - SR-ATP deficiency & mitochondrial myopathy

c. diseases coincidentally related
   i. SIDS
   ii. neuroleptic malignant syndrome
   iii. others
      - lymphomas
      - osteogenesis imperfecta
      - glycogen storage disease

d. triggerring agents
   i. volatile anaesthetic agents
   ii. depolarising muscle relaxants
   iii. anticholinesterases

Neuroleptic Malignant Syndrome

a. a rare complication of neuroleptic drugs

b. may occur at any age, or with any underlying disease

c. recent increase in dose, or introduction of a new drug

d. ***incidence*** ~ 0.4-0.5% of newly treated patients

e. sex ~ 66% males

f. drugs * often parallels the ***antidopaminergic*** activity of agent
   - haloperidol ~ 50%
   - chlorpromazine, metoclopramide
   - thioridazine, fluphenazine, MAOI's, L-Dopa withdrawal

g. onset ~ 1 hr - 65 days
   ~ *5 days* average

h. ***mortality*** **~ 22%**

i. association with MH controversial/unlikely

- ***Clinical Features***

1.	***fever***	- commonly ~ 40°C, but up to 42 °C
2.	***extrapyramidal*** reactions	- catatonia, akinesia & 'lead-pipe' muscular rigidity
3.	***autonomic*** dysfunction	- diaphoresis, hyper/hypotension, tachycardia
4.	mental state alteration	- agitation, dysarthria, stupor, coma

• may last up to 5 days after offending agent has been ceased
• not related to duration of exposure and usually occurs within ***therapeutic range***
• biochemical basis uncertain, but large ↓ dopaminergic activity & ↑ cytoplasmic Ca^{++}

- ***Complications***

a.	hyperthermia	
b.	dehydration	
c.	electrolyte disturbance	
d.	aspiration pnuemonitis	
e.	respiratory failure	
f.	rhabdomyolysis	
g.	renal failure	~ 16%

- ***Laboratory Findings***

a.	- ***CPK***	~ 92%
b.	***myoglobinaemia***	~ 75%
c.	leukocytosis	~ 70%
d.	normal	- LP/CSF - EEG

- ***Treatment***

1.	supportive / resuscitation	
2.	remove offending agent(s)	
3.	***bromocryptine***	~ 2.5-10 mg q8h
4.	dantrolene	
5.	NSAID's / paracetamol	

NB: regression may take from 4-40 days

Hypothermia

Def'n: ***core temperature*** **< 35°C**
homeotherms regulate core temperature ~ 36-37.5°C (T.Oh)
~ 37 ± 0.4°C (RDM)

1. mild > 33°C
2. moderate ~ 30-33°C
3. severe < 30°C

NB: demarcation is arbitrary, but effects more pronounced & ***loss of compensation***
lowest recorded core T in a survivor ~ 18°C

- ***Aetiology***

a. extremes of ***age***

b. debilitating ***illness***
   i. CNS - CVA, head injury, neoplasm
      - progressive mental deterioration
   ii. CVS - CCF, MI, PVD, PTE
   iii. infections - septicaemia from any cause, pneumonia
   iv. renal - uraemia

c. ***exposure*** - environment
   - IV fluids, irrigating fluids

d. ***drugs*** - alcohol
   - GA, barbiturates, benzodiazepines, etc.
   - antipyretics
   - vasodilators
   - chlorpromazine

e. ***endocrine*** - hypothyroidism
   - panhypopituitarism
   - Addisonian crisis, hypoglycaemia
   - diabetes, hyperosmolar coma, ketoacidosis (~ 20%)
   - protein / calorie malnutrition

f. ***spinal cord trauma***

g. ***skin diseases*** - burns
   - psoriasis, icthyosis, erythroderma

h. ***iatrogenic*** - induced hypothermia & inadequate rewarming

- ***Cardiovascular***

1. increased sympathetic tone - ↑ plasma NA/AD and FFA's
2. initially → vasoconstriction, tachycardia & ↑ CO
   later → bradycardia, hypotension & ↓ CO
3. cardiac output - ↓ CO ~ 30-40% at 30°C ∝ decrease in VO_2
   - mainly 2° to ***bradycardia***, SV well preserved
   - coronary perfusion well maintained
4. ECG changes - exacerbated by ***acidosis & hyperkalaemia***
   i. bradycardia / shivering artefact
   ii. prolonged PR, QRS, QT_C duration
   iii. J point elevation ≤ 33°C
   - delayed repolarisation of inferior heart surface
   iv. AF ~ 25-34°C (commonest arrhythmia)
   v. AV block 1° ~ 30°C
   3° ~ 20°
   vi. VF ~ **28°C**
   vii. asystole ~ 20°C
5. CPK & LDH levels are elevated
   - ? leakage from cells or microinfarction

- ***Central Nervous System***

- reasonably well preserved to 33°C, below this function deteriorates progressively,

1. initial confusion → coma at ~ 30°C with pupillary ***dilatation***
2. ↓ CBF ∝ ↓ C-VO_2 ~ **6-7% / °C**
   ~ similar change cf. whole body VO_2
3. progressive brainstem depression → ↓ HR & ↓ RR
4. ↓ ***temperature regulation*** → ↓ shivering ≤ 33°C
   → loss of temperature control ≤ 28°C
5. cerebral protection
   i. greater than achieved by metabolic depression
   ii. deep circulatory arrest
   iii. recovery from near drowning

- ***Pulmonary Changes***

1. central depression→ ↓ RR ≤ 33°C ~ 4 bpm ± respiratory arrest at 25°C
   ↓ CO_2 drive
   * no change in ***hypoxic drive***
2. impaired cough & gag reflexes → ***aspiration risk***
3. ↑ V/Q mismatch
   i. impaired hypoxic pulmonary vasoconstriction
   ii. ↓ FRC → atelectasis
   iii. decreased gaseous diffusion capacity
4. ↑ VO_2 with ***shivering*** → ↓ VO_2 ≤ 33°C
5. ↑ HbO_2 affinity / ***left shift*** → ↓ O_2 availability
6. increased ***gas solubility***
   i. ↑ αCO_2 / ↓ P_{aCO2} → ↑ pH (but, also ↑ neutral point of H_2O)
   ii. anaesthetic gases → ↓ rate of rise of F_A/F_I & elimination
   - halothane $MAC_{27°C}$ ~ 50% $MAC_{37°C}$

- ***Metabolic***

1. ↓ VO_2 ~ 6-7% / °C
2. severe ***acidosis*** → HbO_2 curve shifts to the ***right***
   i. respiratory ↓ CO_2 elimination due to hypoventilation
   ii. metabolic ↓ tissue perfusion
   ↓ hepatic lactate clearance
   ↓ renal tubular H^+ excretion
   iii. temperature correction of blood gas values offers ***no advantage*** in management
   → δ pH ~ -0.0147/°C
3. ***hyperkalaemia / hypokalaemia***
   • causes for expected rise in K^+
   i. decreased activity Na^+/K^+-ATPase → ↓Na^+ / ↑K^+
   ii. cellular hypoxia, membrane damage & acidosis
   • however, ***hypokalaemia*** is more commonly observed
   i. ? 2° diuresis
   ii. ICF shift
4. ***hyperglycaemia*** - ↓ insulin secretion & ↓ peripheral glucose utilisation
   - ? mild pancreatitis
   - hypoglycaemia may ensue in longstanding hypothermia
5. ↑ drug $t_{½\beta}$ ∝ ↓ hepatic blood flow & enzyme reaction rates
   → ***heparin, citrate & lactate***

- ***Renal***

1. ↓ GFR ∝ ↓ renal blood flow ~ 50% at 30°C
   ↓ drug clearance
2. ↓ tubular function
   i. cold diuresis - volume of urine initially increased or the same
   ii. hypoosmolar urine
   iii. glycosuria, kaluria → additional diuresis

- ***Neuromuscular Junction***

1. shivering occurs ~ 33-36°C
2. increased muscle tone → ***myoclonus*** ~ 26°C
3. increased sensitivity to ***both*** depolarising & nondepolarising with mild hypothermia

- ***Haematological***

1. ***coagulopathy***
   i. ↓ coagulation ↓ enzyme activity
   ii. thrombocytopaenia ↑ portal/splenic platelet sequestration
   ↑ bleeding time
2. increased blood ***viscosity*** - dehydration, haemoconcentration & ↑ Hct.
   - ↓ rbc deformability
   - ↓ microcirculatory blood flow
3. ***immunoparesis*** - ↓ WCC (sequestration) & function
4. marrow hypoplasia

- ***Immunological***

1. decreased neutrophils, phagocytes, migration, bactericidal activity
2. organ hypoperfusion & increased infection risk
3. diminished gag/cough reflexes
4. atelectasis

- ***Monitoring***

a. central - lower oesophageal & PA → heart
- tympanic membrane → brain

b. rectal - intermediate
- changes lag behind core/shell during cooling & warming

c. shell - skin/peripheral
- may estimate vasoconstrictor/vasodilator responses

NB: useful to measure both core & shell,
core-shell gradient → better assessment of overall body temperature
→ adequacy of rewarming & predicts "afterdrop"

- ***Management***

1. resuscitation
   - major hazard is peripheral vasodilatation & ***hypovolaemia***
2. monitoring
   i. routine BP, HR, RR, GCS
   ii. T°, ECG, U/Output
   iii. EC&U, AGA's, FBE
   iv. ***blood cultures***
3. rewarming
   i. ***passive*** ~ 0.5-1.0°C / hr in the absence of shivering
   ~ 0.5-2.0°C / hr with shivering
   - adequate for the vast majority of cases
   - only require active rewarming if haemodynamically unstable

   ii. ***active***
   - surface - 'Bear hugger' type
   - temperatures no greater than 40 °C, cease at ~ 35°C
   - core - CVVHD, CPB, PD
   - should be ceased at ~ 33°C
4. antibiotics - broad spectrum cover pending cultures

- ***Hypothermic Cardiac Arrest***

a. defibrillation virtually useless < 30°C
b. extracorporeal rewarming if possible
c. don't pronounce dead until T > 35°C
d. normally ***hypokalaemic***, if markedly hyperkalaemic then unlikely to succeed

Deliberate Hypothermia

- ***Surface Cooling***

• principally historical interest, main use currently is in the management of ***malignant hyperthermia***, or severe hyperthermia in septic ICU patients
• cold environment, ice bathing, especially groins & axillae
• problems of slow & uneven effects both during cooling and rewarming,

a. 2-6°C afterdrop when cooling / rewarming
b. uneven effects mean some tissues are still "at risk" for ischaemia

- ***Cardiopulmonary Bypass***

a. more rapid & even cooling / rewarming
b. more precise temperature regulation
c. maintenance of ***tissue perfusion*** despite ↓ CO / arrest
d. combined with ***haemodilution***
   i. offsets the effects on viscosity
   ii. "optimal Hct." ~ 18-22%

- ***Deep Hypothermia & Total Circulatory Arrest***

a. allows operation on still & bloodless heart
b. principally for correction of complex CHD
c. current operative times ~ 50-60 minutes at 18-20 °C
d. need for more thorough longterm outcome studies on CNS effects

NYSTAGMUS

a.	physiological	- optokinetic
b.	pharmacological	- alcohol - phenytoin, carbamazepine - barbiturates, benzodiazepines
c.	middle ear disease	- Meniere's syndrome - labyrinthitis
d.	brainstem lesion	- congenital - tumour - trauma - vascular - MS
e.	cerebellar disease	- congenital - tumour - trauma - vascular - MS

Nystagmus - Types

NB: the ***direction*** of nystagmus is taken as the direction of the ***fast component***, though, it is the ***slow component*** which is ***pathological***

a.	***pendular*** nystagmus	- macula lesion - albinism - cataract - optic atrophy - miners nystagmus - spamus mutans
b.	***jerk*** nystagmus	- physiological (optokinetic and caloric)
c.	***rotatory***	- midbrain or brainstem lesion
d.	***vertical***	- midbrain tectum lesion

Cranial Nerves

- ***Third Nerve Lesion***

1. clinical features
   - i. complete ptosis
   - ii. divergent strabismus → "down & out" gaze
   - iii. dilated pupil → unreactive to ***direct light*** & ***accomodation***
     consensual reaction in opposite eye intact
   - must exclude 4th nerve lesion when 3rd lesion present
     → look down & opposite side to lesion
     eye intorts * ***s***uperior oblique ***in***torts the eye (SIN)
2. aetiology
   - i. compressive lesions
     - aneurysm - PCA
     - tumour - cerebral, nasopharyngeal
     - basal meningitis
     - orbital lesions - Tolosa-Hunt (superior orbital fissure syndrome)
   - ii. ischaemia / infarction
     - diabetes
     - migraine
     - arteritis

NB: when due to midbrain lesions may involve both sides, as nuclei lie close together & may be incomplete, with ***partial ptosis*** & preservation of the light reflex

- ***Sixth Nerve Lesion***

1. clinical features
   - i. stabismus, failure of ***lateral gaze***
   - ii. diplopia
2. aetiology
   - i. bilateral
     - traumatic
     - Wernicke's encephalopathy
     - mononeuritis multiplex
     - ↑ ICP from any cause
   - ii. unilateral
     - idiopathic
     - traumatic
     - compression due to tumour, aneurysm etc.
     - ↑ ICP
     - vascular lesion, diabetes

Medial Longitudinal Fasiculus

- joins 3rd, 4th, and 6th cranial nuclei
- ***multiple sclerosis*** causes demyelination and nystagmus on ***abduction*** but not convergence
- may, or may not, result in weakness of adduction with lateral gaze, ie. a 4th nerve lesion

Seventh Nerve Lesion

1. clinical features
   - i. facial asymmetry
     - drooping of the corner of the mouth
     - loss of the nasolabial fold
     - smoothing of the forehead (UMN lesion only)
   - ii. decreased power
     - eye closure, eyebrow elevation, grinning
   - iii. Bell's phenomenon
     - present in ***all*** persons, though not visible
     - ***upward*** deviation of the eye on firm eyelid closure
   - iv. Ramsay-Hunt synd.
     - HSV-I vesicles located on the ***ear & palate***
2. aetiology
   - i. UMN lesion
     - vascular lesions
     - tumours
   - ii. LMN lesion
     - pontine
       - often associated with V & VI lesions
       - vascular lesions, tumours, syringobulbia, MS
     - posterior fossa
       - acoustic neuroma, meningioma
       - chronic meningitis
     - petrous temporal
       - idiopathic, ***Bell's palsy***
       - fracture, Ramsay-Hunt syndrome, otitis media
     - parotid
       - tumour, sarcoid
   - iii. bilateral "lesions"
     - GBS
     - bilateral parotid disease (sarcoid)
     - myasthenia gravis
     - myopathies
     - rarely mononeuritis multiplex

Argyll Robertson Pupil

Def'n: irregular small pupils
accommodation preserved but absent light reflex

- due to a lesion between the ***lateral geniculate body*** and the 3rd nerve nucleus
- common causes include,

1. diabetes mellitus*
2. syphilis - esp. tabes dorsalis*
3. chronic alcoholism
4. encephalitis
5. multiple sclerosis
6. midbrain lesions (vascular, tumour)

Opiate Receptors

- opiate receptor theory evidence,
  a. structure-activity relationship - common nucleus in all opiates
  b. stereospecificity → ***l-isomers*** most potent
  c. side-chain alterations change potency
  d. small doses highly effective
  e. agonist and antagonist drugs
  f. similar clinical effects from all opiates
  g. endogenous opiate compounds - endorphins, enkephalins, β-lipotropin
  h. tolerance, cross-tolerance, dependence

- ***μ - Receptor***

  a. sites
     - cortex (I,IV), thalamus, hypothalamus
     - periaqueductal grey, midbrain raphe
     - medullary centres (resp, vasomotor, vomiting, CTZ)
     - spinal cord (substantia gelatinosa)
     - gastrointestinal tract
  b. clinical
     - potent analgesia
     - respiratory depression
  c. most potent exogenous ligand - morphine (? lofentanyl)
  d. most potent endogenous ligand - metenkephalin ($t_{½\beta}$ ~ 30s)
  e. antagonist - naloxone

- *d-* ***Receptor***

  a. sites
     - cortex
     - limbic system, amygdala
     - pons, medullary centres
     - spinal cord (substantia gelatinosa)
  b. clinical
     - potent analgesia
     - respiratory depression
  c. most potent exogenous ligand - buprenorphine
  d. most potent endogenous ligand - leu-enkephalin
  e. antagonist - naloxone

- ***k* - Receptor**

  a. sites - limbic system
  - spinal cord (substantia gelatinosa)
  - ***not*** in vital medullary centres

  b. clinical - analgesia, vomiting
  - hallucinations
  - less respiratory depression

  c. most potent exogenous ligand - bremazocine, buprenorphine, ?fentanyl

  d. most potent endogenous ligand - dynorphin

- ***e* - Receptor**

  a. sites * widespread outside CNS
  - heart, liver
  - lung J receptors
  - carotid chemoreceptors
  - gut smooth muscle
  - neutrophils, lymphocytes

  b. most potent exogenous ligand ?

  c. most potent endogenous ligand - β-endorphin ($t_{½\beta}$ ~ 5-15 min)

- ***s* - Receptor**

  a. sites - limbic system
  - spinal cord (substantia gelatinosa)

  b. clinical - analgesia

  c. most potent exogenous ligand - phencyclidine, SKF 10047

  d. antagonist - ? n-allyl normetazocine

RETINAL PATHOLOGY

Diabetes Mellitus

- ***Background (Exudative) Retinopathy***

1.	hypertensive changes in vessels		
2.	microaneurysms		
3.	haemorrhages	- blot - flame	(deep) (superficial)
4.	exudates	- soft - hard	(deep infarct) (superficial oedema)

- ***Proliferative Retinopathy***

1. vessel proliferation
2. vitreous haemorrhages
3. retinal detachment
4. optic fibrosis

- ***Other Associated Eye Problems***

1. 3rd nerve palsy
2. cataract
3. glaucoma
4. optic atrophy

Papilloedema

1. engorged veins → ↓ A:V ratio
2. red discolouration of disc
3. blurred disc margin
4. loss of physiological cupping ± disc elevation
5. later haemorrhage and exudate

- ***Aetiology***

a. raised ICP
   i. space occupying lesion
   ii. hydrocephalus - obstructive
   - comunicating
   iii. benign intracranial hypertension - idiopathic
   - OCP, nitrofurantoin, tetracycline, etc
   - Addison's disease
   - head trauma
   iv. hypercarbia

b. central retinal venous obstruction

c. inflammation

d. hypertension - grade IV

e. oedema

Hypertensive Retinopathy	
Grade I	• silver wiring
Grade II	• A-V nipping
Grade III	• haemorrhages, exudates
Grade IV	• papilloedema

Optic Neuritis

Def'n: acute inflammation of the optic nerve resulting in,

1. acute ***visual loss***
2. pain
3. papilloedema
4. optic atrophy - later finding

Def'n: retrobulbar neuritis **:** "optic neuritis" *without* papilloedema

- ***Aetiology***

a.	demyelination	- MS ~ 30% - encephalomyelitis
b.	local inflammation	- meningitis - sinusitis - cellulitis - syphilis
c.	toxic	- ethambutol, chloroquine - alcohol, methanol - tobacco, nicotine - other drugs
d.	metabolic	- diabetes - B_{12} deficiency - hypoxia
e.	vascular	- temporal arteritis - ischaemia
f.	familial	- Leber's optic atrophy

- ***Optic Nerve - Anatomical Pathway***

1. retina
2. optic nerve
3. optic decussation at chiasma
4. lateral geniculate body in thalamus
   - fibres serving pupillary and ocular reflexes, ***bypass*** the geniculate body to reach the ***superior corpus quadrigeminum*** & the midbrain nuclei of III, IV & VI
5. optic radiation
6. calcarine cortex - occipital lobes

Optic Atrophy

1. chronic papilloedema | optic neuritis
2. optic nerve pressure | division
3. glaucoma
4. ischaemia
5. familial
   - retinitis pigmentosa
   - Leber's optic atrophy
   - Friederich's ataxia

Papilloedema	Papillitis
• optic disc swollen, no venous pulsation	• optic disc swollen
• normal visual acuity, unless chronic	• diminished ***visual acuity***
• large ***blind spot***	• large central scotomata
• peripheral constriction of visual fields	• ***pain*** on eye movement
• normal colour vision	• abnormal ***colour vision***, red desaturation
• usually bilateral	• usually sudden onset & ***unilateral***

Fundoscopy - Other

1. candidaemia
   - septic emboli
   - "puff balls" ± haemorrhagic centre
2. acute pancreatitis
   - "peeches" retinopathy
3. systemic tuberculosis
   - choroidal tubercles