Motor activity during simple syncope is common and may cause convulsive movements.

Hydrocephalus, Spina Bifida and Epilepsy

Presenting History

Two major ways in which a person can recognise themselves as having epilepsy:
- Blackouts or “absences” which are reported by eyewitnesses
- Episodes of abnormal uncontrollable movement of which the patient is aware

ACCESSORY SYMPTOMS may include sleepiness and confusion after the seizure

Ask the patient and a witness to the event to describe the patients behavior from beginning to end of the event.

Was the episode preceded by localized sensory or motor phenomena, nausea, or lightheadedness?
Any type of warning or aura = a focal-onset seizure
In contrast, generalized seizures have simultaneous onset in both hemispheres and are not associated with a warning. Nausea or lightheadedness is common before syncope

Did the patient lose consciousness?
NO? then it was a partial seizure or absence type generalized seizure.

If not, was consciousness altered?
  - simple partial seizures = normal consciousness,
  - complex partial seizures = altered consciousness.

If consciousness was altered but not lost, did the episode include staring and unresponsiveness?

Lip smacking? Picking at the clothes? Hand wringing? Motor manifestations?
- complex partial seizure = 30 to 90 seconds of unresponsive mindless automatism

Did the symptoms progress from unresponsiveness to unconsciousness?
- complex partial seizure, followed by secondary generalization.

Did the patient have generalized stiffness (tonic contraction) or rhythmic muscle movements (clonic contractions)?
A typical generalized tonic-clonic seizure is
  - loss of consciousness
  - a tonic phase, which consists of generalized stiffening of the body
  - then gradually merges with the clonic phase,
  - (progresses from high-frequency to low-frequency, rhythmic clonic jerks)
  - UNILATERAL INVOLVEMENT OF BODY = secondary generalized seizure.

Did the patient have a complete loss of muscle tone, followed by a fall to the ground?
= Atonic seizures begin with an abrupt loss of body tone
  THUS: drooping of head and/or collapse to the ground
  !! BUT !! atonic seizures are a childhood problem, and are associated with idiocy
  IN ADULTS such atonic collapse is probably a SYNCOPE

Was a transient neurological deficit (e.g., hemiparesis or aphasia) present after the spell ended?
  Transient weakness after motor seizure = Could be a partial seizure (Todds paresis)
  !! BUT !! a stroke, transient ischemic attack, or complicated (hemiplegic) migraine can also do this

How long did each component of the episode last?
- absence seizures usually last <15 seconds,
- partial and generalized seizures usually last ~30 seconds to 3 minutes,
- pseudoseizures often last >10 minutes.

How quickly did the patient return to normal after the spell ended?
Simple partial seizures and absence seizures = NOT CONFUSED AFTERWARDS
Complex partial seizures = postictal confusion and sleepiness (may be brief and not recalled)
GRAND MAL = stupor, confusion, and sleepiness that lasts minutes to hours.

Determine whether the patient had more than one spell, and if so, what was the frequency and/or interval between spells.
A patient who does not awaken between episodes may be experiencing status epilepticus
**Ask about possible risk factors and predisposing events**

**These are:**
- History of febrile seizures,
- Possible earlier auras or brief seizures not recognized as seizures,
- A family history of seizures.

**Possible predisposing events include**
- Prior head trauma,
- Stroke,
- Tumor,
- Vascular malformation,
- Sleep deprivation,
- Electrolyte or metabolic abnormalities,
- Acute infection,
- Alcohol,
- Use of either legal or illegal drugs.

**Differential Diagnoses**

- **Syncope** immediate precipitating factors (e.g., emotional distress), presyncopal nausea, pallor, posture (usually erect), and lightheadedness, plus no altered mental state afterwards
- **Stroke** (should have some focal neuro deficit and findings on CT or MRI)
- **Transient Ischaemic Attack** (no positive symptoms)
- **Hemiplegic Migraine**
- **Tumor causing seizures** (CT, MRI)
- **Intoxication or Withdrawal** (history findings and blood test)
- **Aneurysm** (will see on CT or MRI, and a focal deficit will usually accompany seizure; plus the aneurysm will be aggravated by exercise and increased blood pressure)
- **Pseudoseizure** (psychogenic, screaming or talking during the episode etc., and unlikely to damage self—more like a tantrum or anxiety attack; of course EEG will be normal.)

**Findings on Examination**

Look for signs of head and other trauma, alcohol or illicit drug use, chronic liver or renal disease.

**Cerebrovascular disease** signs eg. blood pressure, heart sounds, carotid arteries, peripheral vessels (scope that fundus!) may identify disorders that are associated with cerebrovascular disease.

**Signs of neoplasm that loves CNS metastasis** (e.g., melanoma, and lung and breast cancers)

**Adolescents and young adults:** examine the skin lesions suggestive of neurocutaneous syndromes.

- Café-au-lait spots or neurofibromas indicate neurofibromatosis;
- Depigmented areas, shagreen patches, or adenoma sebaceum indicate tuberous sclerosis;
- Facial port-wine stain indicate Sturge-Weber syndrome.

Perform a thorough neurological examination focused on finding deficits suggesting a cerebral lesion. THIS MEANS cranial nerve exam, higher cortical and motor function.

**Tests and Investigations**

**Skull CT** (if stroke is suspected) or MRI (modality of choice for any other sort of lesion) to rule out stroke, tumour and vascular abnormality;

- **Carotid Angiography** if aneurysm is suspected—do not step lightly into this 19th century measure;
- **Blood Biochemistry** if drug withdrawal or intoxication

**Idiopathic vs. Symptomatic:**
- **Idiopathic** means without underlying pathology
- **Symptomatic** means there’s something obviously wrong and the seizures are the result of this pathology, eg. tumor or stroke
EEG (electroencephalogram) is the diagnostic gold standard and WILL DIAGNOSE THE SUBTYPE OF EPILEPSY.

Electrodes are positioned at specific sites (international 10-20 system of scalp electrode placements) the EEG traces, or channels, are arranged in groups of 4 in an anterior to posterior fashion, odd numbers for the left side of the head, even for the right. Thus, the first 4 channels record from the left frontotemporal electrodes and then next 4 from the right frontotemporal electrodes. The last two traces represent midline electrodes.

2 things to look for:
- Interictal spikes of epileptiform activity (interictal meaning those that have no effect on the patient’s state)
- A recording of an actual seizure is the most accurate diagnostic finding.

How is this diagnosis made?
...by EEG and by elimination of every other possible cause of the symptoms.

Disease Definition (from the glorious mouthpiece of medicine, Harrisons.)
EPILEPSY = repeated paroxysmal events due to abnormal, excessive, hypersynchronous discharges from an aggregate of central nervous system (CNS) neurons; = a result of a shift in the normal balance of excitation and inhibition within the CNS.

CLASSIFICATION:

- Although we can recognize a number of well described clinical epilepsy syndromes, we do not know the actual cause of the epilepsy in about 60-70% of patients.

TYPES OF SEIZURE:
- Generalized tonic-clonic seizures, AKA grand mal, First a few seconds of sudden tonic sustained-extension posturing involving all muscles (including respiratory muscles - possibly contributing to an expiratory scream), followed by brief repetitive clonic muscular jerks that gradually slow down and usually stop after 1 to 3 minutes. Postictally, patients are initially unresponsive until they gradually awaken and return to normal mental functioning in minutes to hours.
- Tonic seizures and clonic seizures contain only one phase or the other of a generalized tonic-clonic seizure.
- Myoclonic seizures consist of a single lightning-like jerk, typically of the upper extremities, ictal EEGs often show generalized epileptiform discharges correlating with the myoclonic jerk.
- Atonic seizures, or drop attacks, involve complete momentary loss of all body tone, resulting in unprotected falling to the ground.
Absence seizures, previously termed petit mal, - staring unresponsiveness with few other manifestations, - automatisms can occur when seizures are prolonged. - These seizures typically occur many times per day. During absence seizures an EEG demonstrates characteristic generalized spike and slow wave discharges recurring at a rate of 3 per second.

Atypical absence seizures - may be associated with muscle relaxation and slower spike wave discharges on the EEG. - These seizures occur more often in mentally retarded patients.

Infantile spasms, also termed salaam attacks because patients appear to be bowing, - consist of sudden brief flexor or extensor spasms of the trunk - associated with a characteristic interictal EEG pattern of hypsarrhythmia.

SYNDROMES:
most common adolescent-onset epilepsy syndrome is juvenile myoclonic epilepsy; the most common adulthood-onset epilepsy syndrome is temporal lobe epilepsy.

Childhood absence epilepsy, juvenile absence epilepsy, and juvenile myoclonic epilepsy - typical absence seizures, classic examples of idiopathic generalized epilepsies. - a strong genetic (autosomal dominant) component, - Intercital EEGs in childhood and juvenile absence epilepsy show typical generalized 3 cycles per second (cps) spike and wave discharges, with or without clinical absence seizures, whereas in JME generalized 4.5 cps multiple spike and wave bursts are more likely.

Childhood absence epilepsy - is characterized by onset of typical absence seizures in school-aged children - Absence seizures occur many times per day. - Rarely, it is also associated with generalized tonic-clonic seizures. - Response to ethosuximide or valproate is excellent, - the seizures abate by age 14 years in 70% of patients

Juvenile absence epilepsy - is similar to the childhood type, but it starts in adolescence. - generalized tonic-clonic seizures are more common, - seizures more often persists into adulthood.

Autosomal dominant nocturnal frontal lobe epilepsy - uncommon but significant, because it represents the first inherited partial epilepsy in which the gene was located and the gene product identified - Seizures often arise at night and may consist of bizarre behavior and bilateral dystonic posturing. - EEG findings are normal, even during the seizure, as is typical of frontal lobe seizures. - The symptoms are often initially misdiagnosed as a sleep disorder.

Temporal lobe epilepsy is the most common identifiable specific epilepsy syndrome in adults. - often a history of febrile seizures in childhood. - Routine EEGs may show spikes in the temporal regions [ - MRI may show abnormalities in a temporal lobe. - The most common cause is mesial temporal sclerosis (neuronal loss and gliosis of the hippocampus and adjacent structures) that has a characteristic appearance of hippocampal atrophy and increased T2 signal on MRI - Benign tumors and developmental malformations are less common causes of temporal lobe epilepsy. - In 30% of cases, temporal lobe epilepsy is refractory to AEDs; these refractory patients are often excellent candidates for epilepsy surgery.

<table>
<thead>
<tr>
<th>Name</th>
<th>Age of onset</th>
<th>Seizure types</th>
<th>EEG features</th>
<th>Positive family history</th>
<th>Natural history</th>
</tr>
</thead>
<tbody>
<tr>
<td>West syndrome</td>
<td>6-24 mo.</td>
<td>Infantile spas</td>
<td>Hypsarrhythmia</td>
<td>Uncommon</td>
<td>Often evolves to Lennox-Gastaut syndrome</td>
</tr>
<tr>
<td>Lennox-Gastaut syndrome</td>
<td>2-5 y</td>
<td>Tonic, atomic, atypical ABS</td>
<td>Generalized slow spike-wave (&lt;3 cps)</td>
<td>Uncommon</td>
<td>Persists, difficult to control</td>
</tr>
<tr>
<td>Benign tonic clonic epilepsy (BECTS)</td>
<td>5-10 y</td>
<td>CPS (motor), CPS</td>
<td>Centro-temporal spikes</td>
<td>As above</td>
<td>Resolves by age 14</td>
</tr>
<tr>
<td>Childhood absence epilepsy</td>
<td>4-10 y</td>
<td>ABS, GTC</td>
<td>3 cps generalized spike-wave</td>
<td>As above</td>
<td>Resolves by age 14 in 70% of cases</td>
</tr>
<tr>
<td>Juvenile absence epilepsy</td>
<td>10-17 y</td>
<td>ABS, GTC</td>
<td>As above</td>
<td>As above</td>
<td>Persists more often than CAE</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>12-19 y</td>
<td>MYO, GTC</td>
<td>Generalized 4.5 cps multiple spike-wave</td>
<td>AD probable, variable penetrance</td>
<td>Persists, but usually well-controlled</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>3-40 y</td>
<td>CPS, 2 gen</td>
<td>Temporal spikes</td>
<td>Rarely AD</td>
<td>Persists</td>
</tr>
<tr>
<td>Nocturnal frontal lobe epilepsy</td>
<td>5-20 y</td>
<td>Frontal lobe CPS</td>
<td>Normal</td>
<td>Sporadic, AD</td>
<td>Often well controlled</td>
</tr>
<tr>
<td>Frontal lobe epilepsy (various causes)</td>
<td>Any age</td>
<td>CPS (95%), 20 gen (80%)</td>
<td>Often normal</td>
<td>Not applicable</td>
<td>Often poorly controlled, 50% surgical success rate</td>
</tr>
<tr>
<td>First generalized tonic-clonic seizure (idiopathic)</td>
<td>12-50 y</td>
<td>GTC</td>
<td>Often normal</td>
<td>Uncommon</td>
<td>Spontaneous remission in 70%</td>
</tr>
<tr>
<td>Seizures after stroke</td>
<td>&gt;50 y</td>
<td>SPS, GTC, CPS (combinations vary)</td>
<td>Varies</td>
<td>Not applicable</td>
<td>Usually well controlled, spontaneous remission in 50%</td>
</tr>
</tbody>
</table>

* Not a complete list.

ABS, absence; AD, autosomal dominant; BECTS, benign epilepsy of childhood with centrotemporal spikes; CAE, childhood absence epilepsy; CPS, complex partial seizure; cps, cycles per second; GTC, generalized tonic-clonic; MYO, myoclonic; SPS, simple partial seizure; 2 gen, secondarily generalized.
Management: WITH DRUGS

An epileptic focus may arise in the brain from
- an excess of neuronal excitation,
- a deficiency of neuronal inhibition
- or both.

Thus antiepileptic therapy is directed at
- limiting the firing frequency of neurones
- decreasing neuronal excitation or
- increasing neuronal inhibition.

Antiepileptic therapy is often directed at
GLUTAMATE and GABA.

**THUS: you can**

**LIMIT FIRING RATE OF NEURON**

Phenytoin limits the frequency of nerve impulse conduction;
Binds preferentially to to inactive (closed) Na channels, thus LOCKING THEM;
the poor Na channels cannot return to resting (also closed) state which they must enter in order to open again.

No drug is known that can decrease the synthesis or storage of glutamate in a therapeutically useful manner.

**REDUCE RELEASE OF EXCITATORY NEUROTRANSMITTER**

Phenobarbitone and barbiturates reduce the neuronal release of glutamate, as does
Carbamazepine via its action on presynaptic adenosine receptors;

**ENHANCE INHIBITORY RECEPTOR ACTIVITY**

Diazepam enhances the activation of some GABAA receptors by GABA;
barbiturates enhance the activation of most GABAA receptors by GABA and
in addition have a direct agonist action on these receptors

**REDUCE EXCITATORY RECEPTOR ACTIVITY**

NMDA glutamate receptor antagonists act as anticonvulsants:

**REDUCE RE-UPTAKE OF INHIBITORY TRANSMITTER thus increasing its synaptic dwell-time**

A range of inhibitors of GABA uptake related to nipecotic acid are in clinical trials as anticonvulsants; and
Sodium valproate and vigabatrin inhibit the metabolism of GABA
... thus increasing the levels of GABA in the brain.

Doses need to be individualised in many cases and may need to be changed over time.

Antiepileptic therapy should be kept as simple as possible, ideally using only one drug at a time.

**!! EFFECTIVE DOSE IS VERY CLOSE TO DANGEROUS DOSE !!**

**THUS: routinely monitor drug concentration;**

Therapeutic drug monitoring (TDM) is not used for all antiepileptic drugs, but is mainly of help with phenytoin, carbamazepine and sodium valproate.

(epecially phenytoin, because it saturates liver enzymes and ends up not being metabolised.

The value of drug level measurement depends upon
- when the sample was collected in relation to the dosing interval;
- whether the patient is “steady-state” after any recent dose adjustment;
- whether the dosing history from the patient is correctly documented.

---

**The major targets of pharmacological intervention in neuronal transmission include**

1. the conduction of nerve impulses,
2. transmitter synthesis and storage,
3. transmitter release,
4. transmitter action,
5. transmitter uptake and
6. transmitter metabolism.

---

<table>
<thead>
<tr>
<th>DRUG</th>
<th>USE</th>
<th>MECHANISM OF ACTION</th>
<th>OTHER INFORMATION</th>
<th>SIDE EFFECTS</th>
</tr>
</thead>
</table>
| Phenyltoin (Dilantin) | Partial | Limit firing frequency of neurons | Rate of met 
8 varies interindividually | Headache, tremor, nausea, dizziness, gum hypertrophy, acne, greasy skin, coarsening of facial features, hirum, rash, blood dyscrasias, lymphadenopathy, SLE |
| | Tonic clonic | | | |
| Barbiturates e.g. phenobarbitone | Partial | Activate & enhance activity or GABA Rs | Much more sedative than phenyltoin & carbamazepine | Cerebellar symptoms (ataxia, sedation, ataxia), drowsiness & hyperkinesia (in children) |
| | Tonic clonic | Inhibit GABA release | Tolerance occurs | |
| Benzodiazepines e.g. diazepam | Tonic clonic | | | |
| | Absence | Enhance the action of GABA at Rs | Very sedative | |
| | | | Tolerance occurs | |
| Carbamazepine | Partial | Enhance action of GABA at Rs | Active metabolite – anticonvulsant & neurotoxic activity | Nausea, headache, drowsiness, diplopia, ataxia, anulocystosis (rare), rash, blood dyscrasias |
| | Tonic clonic | Activate adenosine Rs | Potent inducer | |
| | Absence | | | |
| Na Valproate (Epilim) | Partial | Enhance action of GABA at Rs | = sedative | Mild = nausea, weight gain, bleeding tendencies, transient hair loss, occasional (idiosyncratic) hepatic toxicity |
| | Tonic clonic | Inhibit GABA met | Wide spectrum of activity | |
| | Absence | | | |
| Ethosuximide | Absence | | Only effective in absences & myoclonic seizures | |
| Vigiabatrin | | Inhibit GABA metabolism | “Suicide” substrate for GABA transporter (once bound = uptake GABA, GABA ~ 10x) | Retinal damage (visual field constriction), psychological change |
| Tegabamine | Partial | Inhibit GABA uptake | Newer agents, not as frequently used (other newer agents include lamotrigine) | |
| Gabapentin | Tonic clonic | GABA, R antagonist? | | |

**Prognosis**
- IDIOPATHIC epilepsy is something you have for the duration of your LONG NORMAL LIFE
- SYMPTOMATIC epilepsy prognosis is related to the pathology which causes it

**Epidemiology**
approximately 5 to 10% of the population will have at least one seizure during their lifetime, the highest incidence occurs in early childhood and late adulthood. Using the definition of epilepsy as two or more unprovoked seizures, the incidence of epilepsy is approximately 0.3 to 0.5% in different populations throughout the world, and the prevalence of epilepsy has been estimated at 5 to 10 persons per 1000.

**Basic Sciences: Action Potential Propagation**

**A cell:**
- lots of POTASSIUM INSIDE
- lots of SODIUM OUTSIDE (thanks to Na+/K+ ATPase)
- Plus chlorine and calcium are also kept outside

NORMAL AP:
- The neuron cruises normally at rest, with about –70 millivolts difference (inside to outside)
- Something (whatever) activates some kind of Na+ channels. (ligand-gated or mechanical)
- Na+ surges into the cell along its concentration gradient
- Thus, the inside becomes more POSITIVE, closer to the threshold, i.e. DEPOLARISES
- The reaching of threshold activates VOLTAGE-GATED Na+ CHANNELS further down the axon
- Thus, they also depolarise that bit of axon
- AND SO ON
- The Na+ channels will not be available until the cell gets back to –70mV (repolarises)
- THEN, and only then will they be able to open again;
- THIS IS THE REFRACTORY PERIOD
- Repolarisation is achieved by actively pumping K+ BACK OUT of the cell.

In some human neurons, the refractory period lasts only 0.001-0.002 seconds. This means that the neuron can transmit 500-1000 impulses per second.

HYPERPOLARISATION: making the cell more negative; opening of the Cl- or K+ channels increases the membrane potential by
- letting negatively-charged chloride ions (Cl-) IN and
- positively-charged potassium ions (K+) OUT
binding to GABA_A receptors opens chloride channels in the neuron.
binding to GABA_B receptors opens potassium channels.

@ myelinated neurons, the nodes of Ranvier are the only sites with Na+ channels; thus the AP leaps between Schwann cells

**Epileptogenesis**
The normal brain is capable of having a seizure under the appropriate circumstances, and there are differences between individuals in the susceptibility or threshold for seizures.

**BUT:**
There are a variety of conditions that have an extremely high likelihood of resulting in a chronic seizure disorder. Eg. penetrating trauma = 50%risk
Partial seizure activity can begin in a very discrete region of cortex and then spread to neighboring regions, i.e., there is a seizure initiation phase and a seizure propagation phase
INITIATION PHASE:

The initiation phase is characterized by two concurrent events in an aggregate of neurons:

- **High-frequency bursts**
- **Hypersynchronisation**

**1. High-frequency bursts of action potentials**

- Starts with DEPOLARISATION:
  - Influx of extracellular Ca++ ions
  - Voltage gated ion (Na+) channels open and admit MUCH Na+
  - MASSIVE INFLUX of Na+

- Followed by a similarly massive HYPERPOLARISATION via
  - K+ EFFLUX along concentration gradient
  - GABA-mediated ion channel Cl- INFLUX along concentration gradient

The above results in a characteristic EEG spike -
- IF MANY NEURONS DEPOLARISE SIMULTANEOUSLY
  - THE SPREAD OF SUCH A BURST IS USUALLY LIMITED BY GROUPS OF INHIBITORY NEURONS
  - But: if the excitation is sufficient, surrounding neurons become recruited by increasing [K+] in the ECF.
  - And: inhibitory interneurons are limited by their stores of GABA which eventually become depleted

  (these interneurons don’t have inexhaustable supplies)

- With repetitive depolarisations, the extracellular K+ concentration rises;
- This happens during the refractory period, when the cell is letting K+ out of itself to repolarise
- THUS the concentration gradient becomes less and less steep until there’s nothing to drive repolarisation, and the cell gets stuck in a permanently depolarised state
- PLUS so much Ca++ overfills the cell that the Neurotransmitter vesicles are always releasing more neurotransmitters, which in turn causes further Ca++ to enter the cell, and so on and so forth.
- DEAD AXONS which pass near dendrites of nearby cells often get refilled by a new axonal growth - which may not attach the same way: MAY ATTACH TO THE DENDRITE INSTEAD thus exciting something that shouldn’t be getting excited;
- THIS sort of crosstalk can lead to excitation of whole groups of neurons

**HYPERSYNCHRONISATION**

**These two events result in a focus of seizure activity which is measured on EEG**

The PROPAGATION phase is mediated in part by the above events, in part by abnormalities in channels, and in part by aberrant neural networks (which may exclude normally present interneurons out of the loop)

The recruitment of a sufficient number of neurons leads to a loss of the surrounding inhibition and propagation of seizure activity into contiguous areas via local cortical connections, and to more distant areas via long commissural pathways such as the corpus callosum.

POSSIBLE MECHANISM
Biochemistry and Cell biology: NEUROTRANSMITTERS

2 types: fast and slow

FAST: ion channels: milliseconds
- GLUTAMATE
- GABA
- Glycine
- Serotonin
- Acetylcholine

SLOW: METABOTROPIC, i.e G-protein coupled; eg. smell, taste receptors
- GABA
- Glutamate
- Serotonin
- Dopamine
- NorAdrenaline
- Acetylcholine
- 30 or so Neuropeptides

Inhibitory: allow influx of Cl- ions, thus HYPERPOLARISE
Excitatory: allow influx of Na+ ions, thus DEPOLARISE

Action Potential:
- Reaches the cell: INFLUX of Ca+
- Ca+ triggers release of neurotransmitter from vesicles

Glutamate:
1. Binds to AMPA receptor
2. AMPA receptor allows SOME K+ to escape and LOTS of Na+ to enter
3. Na+ triggers a TRANSIENT DEPOLARISATION
4. This sudden shift of polarity UNCORKS THE NMDA RECEPTOR
   (the “cork” is a manganese (Mg++) ion)

The NMDA receptor NEEDS TO BE PRIMED with Glycine which is always bound to the receptor, ready and waiting
ONCE OPEN the NMDA receptor acts as an ion channel, allowing MUCH Na+ and Ca++ to enter the cell, therefore causing DEPOLARISATION PROPER

Ischaemia: causes Na+/K+ gradients to collapse (no ATP, so who’s powering the Na+/K+ATPase?)
No gradients means no glutamate resorption pump

Too Much Glutamate leads to EXCITOTOXICITY: so much Ca++ is bad for the neurone and may lead to APOPTOSIS
After its release, the glutamate is slowly mopped up by the neurone and the surrounding glia.
Power for transport of glutamate back into the cell is derived from 3 Na+ molecules being shuttled back in.

DRUGS:
- KETAMINE (NMDA-r. blocker)
- Glycine levels can be manipulated, (less glycine means less excitation)

![Diagram of glutamate and NMDA receptors]

GABA: predominantly metabotropic;
G-protein is usually attached to a K+ or Cl- channel, (GABA-A = Cl-; GABA-B = K+)
…plus it triggers Adenylate Cyclase which in turn kicks of numerous cellular events;
EFFECT DEPENDS ON THESE SECONDARY PATHWAYS.
**Behavioural science: Stigma of Epilepsy**

Epilepsy is the classic example of a condition where patients feel concern about being labelled and stigmatised. Up to a point the term stigma and discrimination could be used interchangeably, at least in the mind of the person with epilepsy. There are 3 subsets of this problem:

- **Legal discrimination**: where people with epilepsy are not allowed to be airline pilots, drive buses, etc. These are common sense matters.
- **Real stigma**: where a person with epilepsy is, for example, refused a job in a bank just because they have epilepsy.
- **Perceived stigma**: where the person with epilepsy perceive that they are "different", thus others will see them as such and will treat them differently. MC exemplifies this very well. Whilst perceived stigma may seem quite illogical to the outside observer, it is very real to and painful for the sufferer.

For most people with epilepsy it is "the having of seizures" which is the problem, rather than the "having of epilepsy". This means that the "labelling" is not that important, but being seen to have a seizure may be a very real issue. In turn this is because whilst having a seizure, the person is "out of control", as if mad - hence the incorrect association with mental illness. Although this association is incorrect, what people do during seizures is not what most of us do; hence it is abnormal at that particular time. This may be seen as unreliable or unpredictable as a result.

**Real stigma is in fact quite uncommon.** Perceived stigma is much more common and is associated with non-disclosure of the epilepsy. This leads to hiding the epilepsy, which in turn means avoidance of social contacts, reclusiveness and enhanced perceived stigma. This is a very destructive process and perceived stigma is much more damaging than real stigma. It is something which should be looked for in a clinical setting and should be "treated", just as much as the seizures. Disclosure which means having accepted one's epilepsy is the only path to a healthy psychosocial outcome. Some people with epilepsy will achieve this and others, unfortunately, will not. Doctors should participate actively in this process.

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**Genetics of Epilepsy**

straight out of Harrissons

- all of the mutations identified to date cause rare forms of epilepsy
- many of the inherited, idiopathic epilepsies are due to mutations affecting ion channel function.
- These syndromes are therefore part of the larger group of "channelopathies" causing paroxysmal disorders such as cardiac arrhythmias, episodic ataxia, periodic weakness, and familial hemiplegic migraine

In contrast, gene mutations observed in symptomatic epilepsies (i.e., disorders in which other neurologic abnormalities, such as cognitive impairment, coexist with seizures) are proving to be associated with pathways influencing CNS development or neuronal homeostasis.
Spina bifida and hydrocephalus

**Spina bifida:**
- A midline bony defect of the vertebrae, usually the lumbosacral vertebrae.

**Spina bifida cystica**
- Also involves nerve tissue defects
  - Myelomeningocele is the most common form of spina bifida cystica
  - Exists over several lumbosacral vertebrae
  - Has cystic structure containing
    - Meninges,
    - Nerve roots
    - Dysplastic spinal cord tissue.
  - There may be a defect in the skin so that the neural tissue is exposed.
  - Meningocele is a less serious defect
    - Herniation of the meninges through the bony defect to produce a cystic lesion.
    - Cystic cavity does not contain nerve roots or spinal cord tissue but the underlying spinal cord may be abnormal, dysplastic.

**Spina bifida occulta**
- Bony defect is present without herniation of the meninges
- Usually some clue to its presence in the form of a dimple, pigmented skin lesion (naevus), dermal sinus, palpable lipoma or tuft of hair.
- The underlying spinal cord may be malformed.

**Less common spinal cord malformations with spina bifida:**
- Myelocystocele or syringomyelocele
  - Expansion of central spinal canal into a cyst
- Myelocele
  - Sack-like outpouching of the spinal cord through a defective vertebral column
- Lipomyelomeningocele
  - Growth of fatty tissue that tethers the spinal cord usually at is distal (towards the tailbone) end.
  - Tethering of the cord leads to compromise spinal cord blood supply and possibly lead to progressive neurologic deficit
- Anencephaly
  - No brain, instead “area cerebrovasculosa” of disorganised tissue
- Encephalocele
  - Brain herniating through gaping skull (occipitally)
- Chiari malformations frequently occur in association with spina bifida.
  - A benign structural problem affecting the cerebellum
  - Extra cerebellum crowding the outlet of the brainstem/spinal cord from the skull on its way to the spinal canal.
  - This crowding will commonly lead to headaches, neck pain, funny feelings in the arms and/or legs, stiffness, and less often will cause difficulties with swallowing or gagging.

**Mechanism:**
The critical disturbance = @ 4th week of gestation
 failure of closure of the posterior neuropore
  - Subsequent failure of development the overlying skeletonmuscular and epithelial elements.
The extent of the defect relates to the timing of the disruption: Myelomeningoceles are produced by earlier defects than meningoceles, the latter occurring after the posterior neuropore has closed and the spinal cord has formed.

**Clinical manifestations of spina bifida**
- Cystic lesion in the lumbosacral region.
  - (may be leaking CSF through a torn membrane)
  - Over 90% of spina bifida cystica are myelomeningoceles
  - And are associated with a variety of neurological deficits depending upon the exact level of the defect with respect to the spinal cord and corda equina.
  - Bladder and bowel involvement is almost always present.
  - The clinical neurological examination is used to reveal the extent of motor and sensory deficits in the lower limbs and bladder and bowel dysfunction.
  - Important secondary orthopaedic deformities, renal abnormalities may develop in infancy and childhood.
  - Myelomeningoceles are frequently associated with a disturbance of the anatomy of the cerebellum and posterior fossa in the form of the Chiari II malformation.

  - Is frequently associated with the development of obstructive HYDROCEPHALUS
  - Brainstem dysfunction may occur with bulbar paresis and vocal cord paralysis.
**Anatomy of the ventricular system:**

**General Flow of CSF:**

**LATERAL VENTRICLES → FORAMEN OF MONROE → THIRD VENTRICLE → CEREBRAL AQUEDUCT → FOURTH VENTRICLE**

- **CSF IS:**
  - A clear colourless ultrafiltrate of plasma
  - The same osmolality (295 mosm/l) but
    - Slightly higher magnesium
    - (2.3 mmol/l compared with 1.7 mmol/l)
    - Slightly higher chloride
    - (119 mmol/l compared with 102 mmol/l)
    - Slightly lower calcium (2.1 mmol/l compared with 4.8 mmol/l).
    - The protein content is only 0.5% that of serum
    - The maximal number of white cells is 5/microlitre.

- **Lateral ventricles (25mls),**
- **Third and fourth ventricles (5mls),**
- **Craniocerebral subarachnoid space (25mls),**
- **Spinal subarachnoid space (75mls),**

**Normal total volume of 130mls.**

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**VENTRICLE DEVELOPMENT**

- **Lined with Ependymal cells**
- The 4th variety of glial cell
- Origin from the cavity of the cephalic neural tube
- At its rostral end the neural tube cavity evolves into two laterally placed telencephalic vesicles that give origin to the left and right cerebral hemisphere and within these, the left and right lateral ventricle. The cavity contained within the diencephalon evolves into the future third ventricle. The communication between each laterally placed lateral ventricle and the midline third ventricle becomes the interventricular foramen. The cavity of the rhombencephalon is the primordial fourth ventricle. The cavity within the mesencephalon does not enlarge in size to the extent of the other cavities but continues to act as a conduit for CSF from the third ventricle to the fourth ventricle as the midbrain (cerebral) aqueduct.

**3rd Month:**

1. The median aperture (Magenid)
2. Then the two lateral apertures of Luschka allowing the primordial fourth ventricle to communicate with the primordial subarachnoid space.
PATHWAY OF CSF CIRCULATION

**Subarachnoid space**

- freely communicating space containing CSF
- communicates with fourth ventricle via
  - two lateral (Luschka) apertures
  - one midline (Magendie) aperture.

**Boundaries: Pia and Arachnoid membranes**

The arachnoid membrane is **loosely anchored to the pia**
by numerous weblike arachnoid extensions
- **cisterns** are large spaces between the arachnoid and pia.
Apart from CSF these cisterns at the base of the brain contain the Circle of Willis.

**THUS:**

You're a CSF droplet. You start in the lateral ventricle, go down through the Foramen of Monroe into the Third Ventricle, drop down through the Cerebral aqueduct, leave though Luschka's openings into the PONTINE CISTERNS
Or through Magendie's opening into the CISTERNA MAGNA

The cranial dura mater is composed of an **endosteal** superficial layer (functioning as periosteum) and a deeper **meningeal** layer. These 2 layers are separated only by the **dural venous sinuses** over the brain.
Specialised organs of CSF production

80% of CSF produced by CHOROID PLEXUS: made of MODIFIED EPENDYMAL CELLS
DIFFERENT TO NORMAL Blood-Brain Barrier ARRANGEMENTS:
- Capillaries are FENESTRATED
- Choroid Ependyma bound to each other by tight junctions (normally they are not)
- CONTAIN CARBONIC ANHYDRASE: produces WATER from protons and carbonate ions
  (can be blocked by carbonic anhydrase blocking drug acetazolamide)

The choroid plexus is found in each of the cerebral ventricles
BUT not in the aqueducts
(it extends through the lateral apertures of the fourth ventricle into the subarachnoid space).
20% of production comes from the non-choroidal capillaries of the CNS (both brain and spine).

The formation rate of all sources of CSF is 20mls/hr.
This rate is constant over normal cerebral blood pressure.

Increased production sponsored by:
  - sympathetic denervation
  - cholinergic stimulation
  - cholera toxin application (increased cAMP)

Decreased production sponsored by:
  - sympathetic stimulation
  - ventriculitis (an infection of the ventricles)
  - acetazolamide.

Interaction of the subarachnoid space with the cerebral venous drainage
REABSORPTION OF CSF = THROUGH UNIDIRECTIONAL VALVES
between venous sinuses and subarachnoid space.

These valves are called arachnoid villi
  = organised into visible clumps called arachnoid granulations.
  = aneurysmal outpouchings of the subarachnoid space into the lumen of the large venous sinuses.
AT THEIR APEX:
  a layer of endothelium with tight junctions
  continuous with the inner surface of the venous sinus.
THUS: unidirectional flow of CSF from the SAS to venous sinus
when the hydrostatic gradient between the two reaches 20-50 mm of water.
Transport = passive PINOCYTOSIS
(requiring no other mechanism other than that of the hydrostatic pressure gradient)

Secondary sites of CSF absorption are located in the cranial and spinal nerve root sleeves into lymphatics.
This system is relatively unimportant but may become so at higher pressure.
PATHOGENESIS OF NEURAL TUBE DEFECTS

Lack of FOLATE

Competition for FOLATE TRANSPORTER
By Valproate and Carbamazepine (risk = 1-2%, danger outweighed by danger from maternal epilepsy)

NEURAL TUBE DEFECT

24 days: ANACEPHALY

26 days: SPINA BIFIDA

Lack of Cholesterol Or TRISOMY 13
\[\rightarrow\] depressed Sonic Hedgehog
\[\rightarrow\] HOLOPROSENCEPHALY
(failure to develop bilateral symmetry)

SPINA BIFIDA OCCULTA:
Weeks 5-12
The vertebral arches never joined up, but spinal cord is intact and covered by tissue
MENINGOCELE:
weeks 5 to 12
Sack-like outpouching of meninges, but spinal cord still intact

Chiari Cerebellar malformation:
Type 1 = cerebellar tonsils sticking through the Foramen magnum
Type 2 = (Arnold-Chiari) = extension of cerebellar vermis through the foramen magnum.

Myelomeningocele: 90%
Sack of meninges with spinal cord sticking out;

Foetal protein in the amniotic fluid:
!! WHATS IT DOING THERE ??
means the FOETUS IS LEAKY

Myelomeningocele: 90%
Sack of meninges with spinal cord sticking out;

Natural Maturation:
The vertebral column elongates but the spinal cord does not;
IF the spinal cord is AFFIXED eg. by surgical repair of myelomeningocele, the cord pulls the brainstem down into the vertebral canal and THUS PLUGS THE HOLE through which the CSF would normally travel

Obstruction of CSF flow causes HYDROCEPHALUS
Communicating:
Ventricles can communicate, but no CSF can travel though to the subarachnoid space
Non-communicating:
The blockage is between the ventricles, i.e the ventricles cant communicate

!! COMMONEST CNS MALFORMATION !!
1 in 1000 births
= Absence of Calvarium, Meninges and Brain.
Absurd tissue on top of head is “Area Cerebrovasculosa” = totally disorganised
MAY STILL BE ABLE TO BREATHE and maintain circulation… but not much else

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