Epilepsy for Medical Students

Said S. Dahbour, MD, FAAN
Professor of Medicine and Neurology
Faculty of Medicine – Jordan University
Amman - Jordan

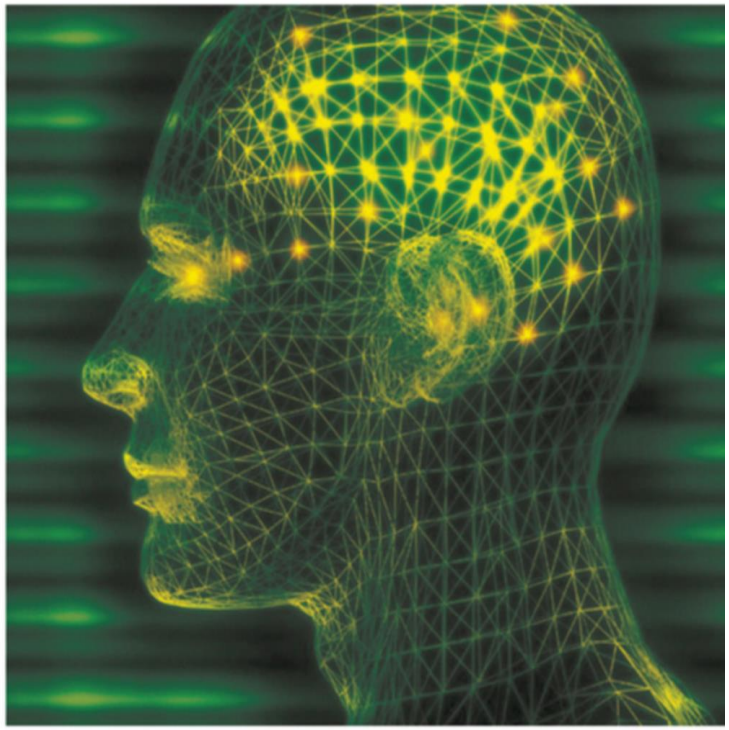
Outline

- General Aspects
- AED
- Epilepsy Surgery
- Drugs used for Status Epilepticus
- Conclusions

Neurology

LIONEL GINSBERG

9th edition



WILEY-BLACKWELL

Chapter 10

Epilepsy

Definitions

The physiological definition of epilepsy is unchanged from that provided by Hughlings Jackson in the nineteenth century:

> Epilepsy is the name for occasional, sudden, excessive, rapid and local discharges of grey matter.

Clinically, epilepsy is a paroxysmal disorder in which cerebral cortical neuronal discharges result in intermittent, stereotyped attacks of altered consciousness, motor or sensory function, behaviour or emotion.

A distinction must be drawn between an isolated seizure and the recurring tendency to seizures which is epilepsy.

Classification and causes

Epileptic seizures are broadly classified by whether their onset is focal (**partial**) or **generalized**. Partial seizures are further subclassifed as:

- **Simple partial seizures**, where consciousness is retained throughout the attack;
- **Complex partial seizures**, where consciousness is impaired at any stage.

Partial seizures may become **secondarily generalized**, the patient losing consciousness with clinical evidence of spread across the cerebral cortex, e.g. bilateral convulsive movements.

A more detailed classification of epilepsy within these broad categories, according to clinical and EEG characteristics, is given in Table 10.1.

Epilepsy may also be subdivided according to whether it is **idiopathic** (most patients) or **symptomatic**, i.e. where a cause can be found. Causes of symptomatic epilepsy are listed in Table 10.2. Idiopathic epilepsy frequently shows a strong inherited predisposition.

Epidemiology

Up to 1% of the general population suffer from active epilepsy, with 20–50 new patients being diagnosed per 100,000 per year. The approximate annual death rate for epilepsy is 2 per 100,000. Deaths may relate directly to seizures, for example when there is an uncontrolled series of seizures, the patient failing to regain consciousness between attacks (**status epilepticus** – Chapter 20), or when accidental injury has occurred. The phenomenon of sudden unexplained death in people with epilepsy is usually assumed to be related to seizure activity and possibly to associated cardiorespiratory dysfunction.

Lecture Notes: Neurology, 9th edition. By Lionel Ginsberg. Published 2010 by Blackwell Publishing.

Epilepsy and Genius:Some of Them

- Rulers and Worriers
  - Amenhotep IV
  - Drusus
  - Alexander the Great
  - Caligula
  - Julius Caesar
  - Peter the Great
  - William Pit
  - Napoleon Bonaparte
  - Louis XIII of France
  - Charles V of Spain
  - Archduke Charles of Austria
  - Alfred the Great
  - William III of England
- Philosophers, artists and scientists
  - Charles Dickens
  - Moliare
  - Pascal
  - Lord Byron
  - Dostoyevsky
  - Flaubert
  - Edward Lear
  - van Gogh
  - Alfred Nobel
  - William Morris
  - Isaac Newton
  - Leo Tolstoy

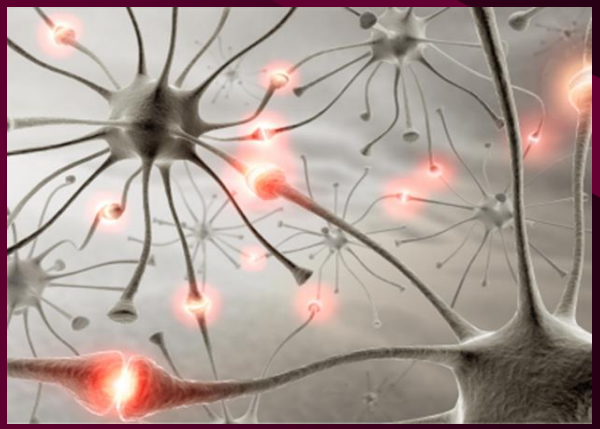
Seizures and Epilepsy

- **Seizure:** abnormal hypersynchronous electrical discharge form cerebral cortical neurons.
- **Clinical seizure:** the clinical manifestation of the electric seizure that depends on the site of onste and path of propagation
- **Epilepsy** =Recurrent Unprovoked Seizures

Definitions

- ♦ Seizure: the manifestation of an abnormal, hypersynchronous discharge of a population of cortical neurons

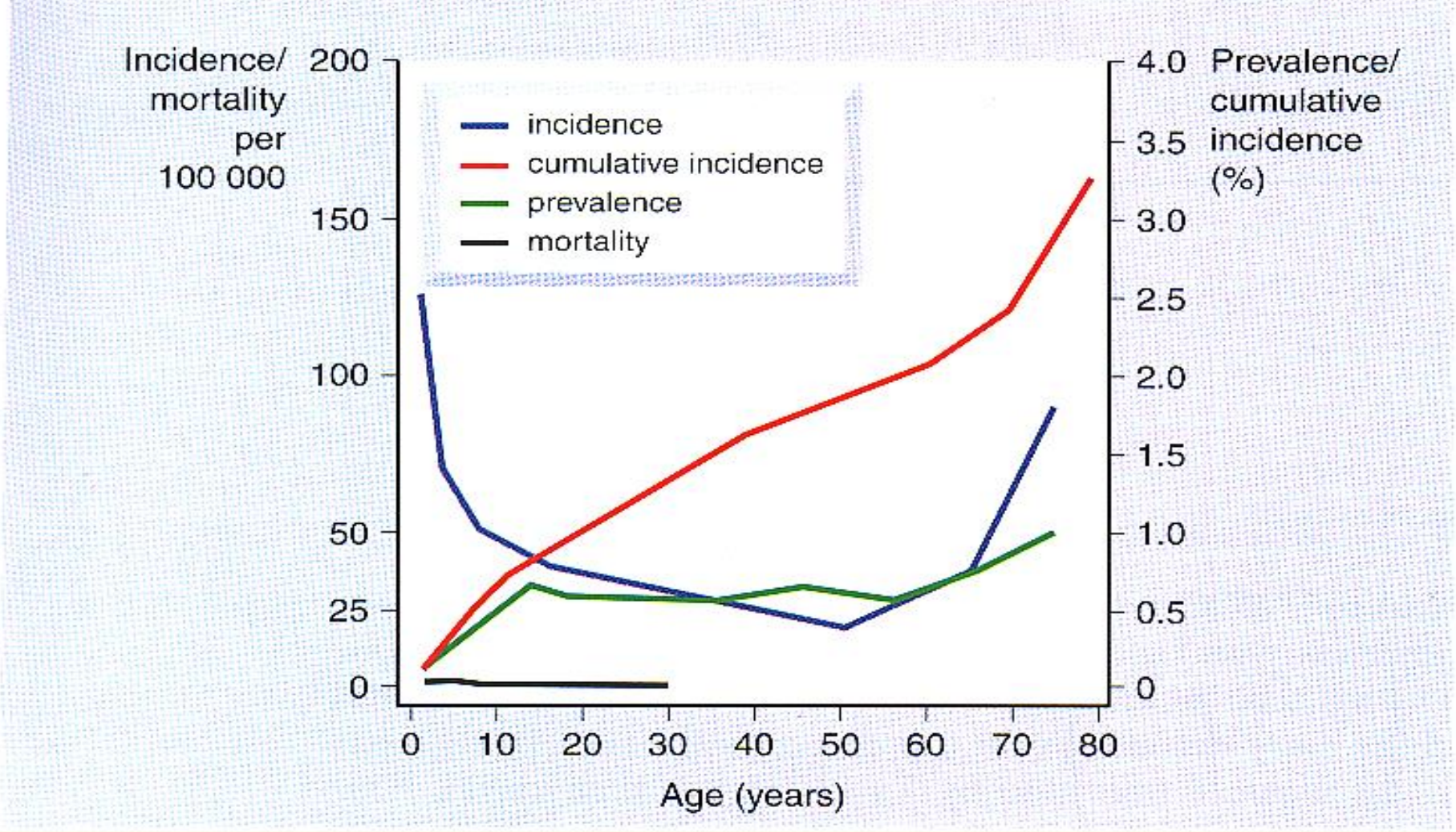
- ♦ Epilepsy: recurrent seizures (two or more) which are not provoked by acute systemic or neurologic insults



Epidemiology of Seizures and Epilepsy

- ♦ Seizures
  - Incidence: 80/100,000 per year
  - Lifetime incidence: 9% (1/3 febrile convulsions)

- ♦ Epilepsy
  - Incidence: 45/100,000 per year
  - Point prevalence: 0.5-1%
  - Cumulative lifetime incidence: 3%

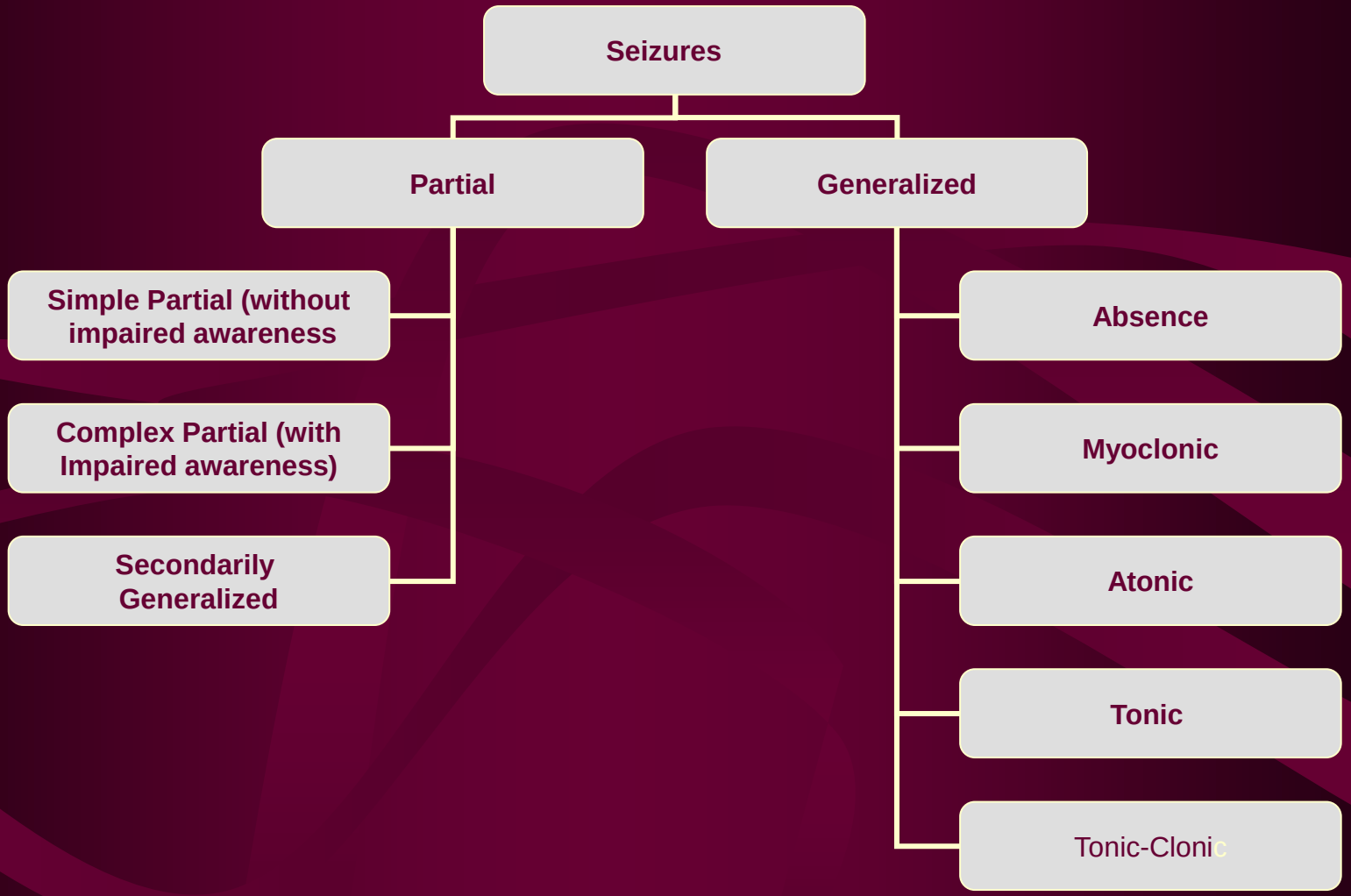


Rochester Minnesota Epilepsy Study (1935-1974)

Epilepsy Burden

- Epilepsy and seizures affect nearly 3 million Americans of all ages, at an estimated annual cost of $17.6 billion in direct and indirect costs.

ILAE Classification of Seizures



ILAE – International League Against Epilepsy

First unprovoked seizure – risk of seizure recurrence.

- 24-74 % in first 5 years.
  - Normal EEG and imaging studies – 24%
  - Abnormal EEG and imaging studies- 74%
- After 2nd unprovoked seizure – 80%

First unprovoked seizure

- Risk factors for seizure recurrence
  - Family history
  - Abnormal EEG
  - Abnormal neuroimaging.
  - Seizure in sleep.

First unprovoked seizure

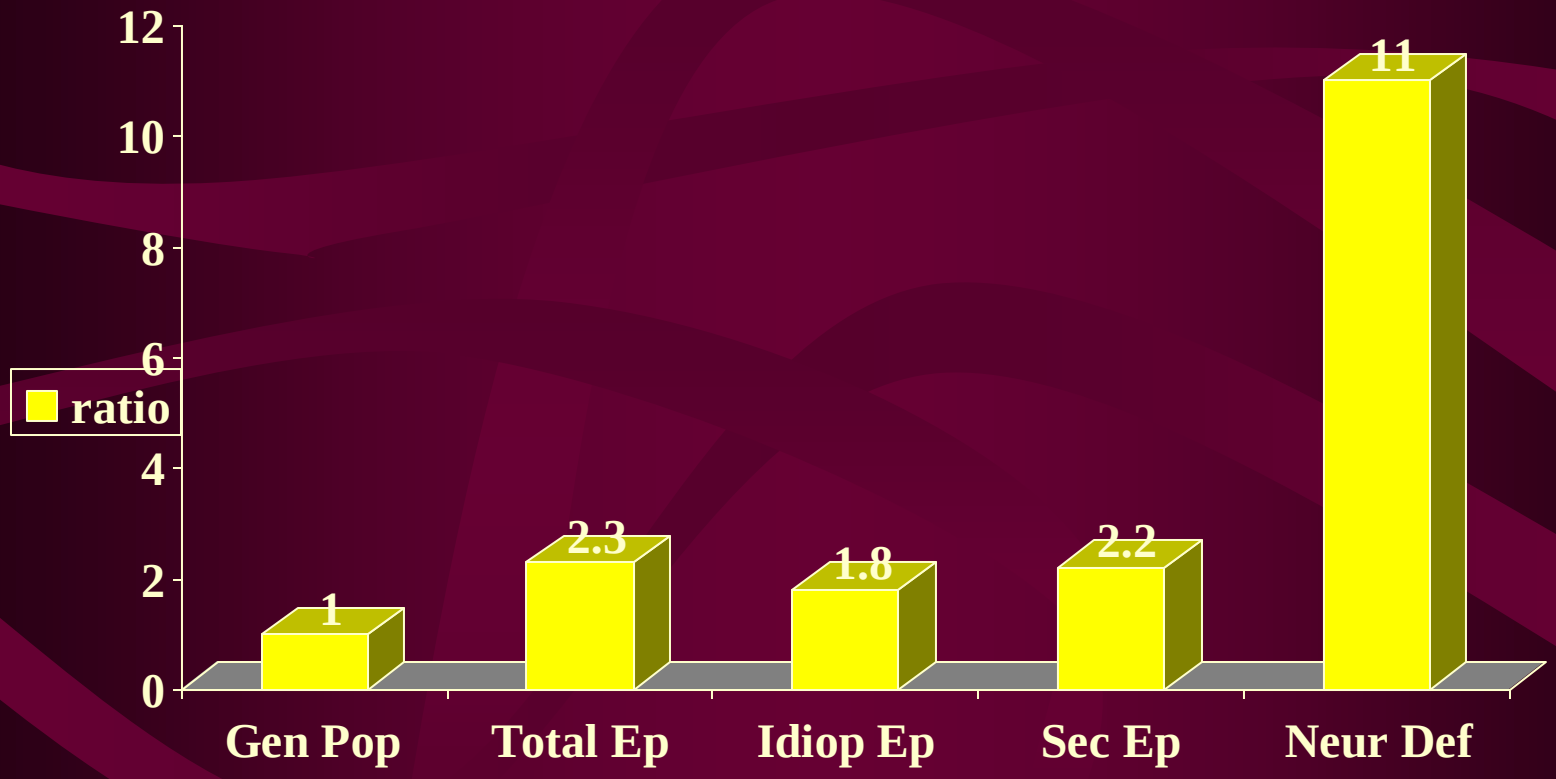
- 50 % seizures recur in the first year
- 80% with in two years.

First unprovoked seizure

- Current Guidelines
  - No antiepileptic drugs (AEDs) if
    - There are no other risk factors
    - Normal EEG.

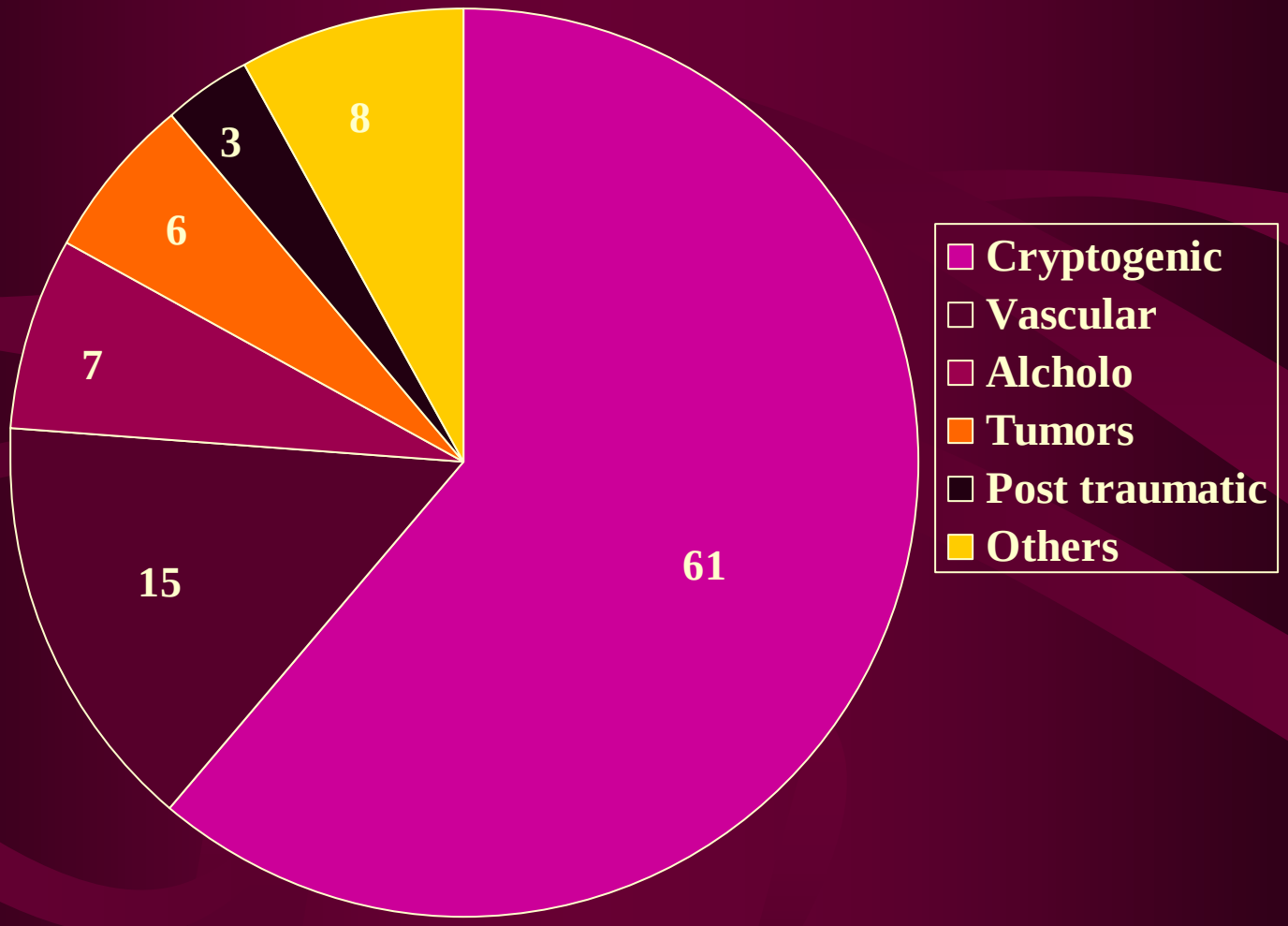
Standardized Mortality Ratios for Patients with Epilepsy

Rochester Study (1935-1974); Hauser Epilepsia 1980



Gen pop: general population, Ep epilepsy, idiop: idiopathic, sec: secondary, Neur def: neural deficit since birth

Etiology of Newly Diagnosed Epilepsy

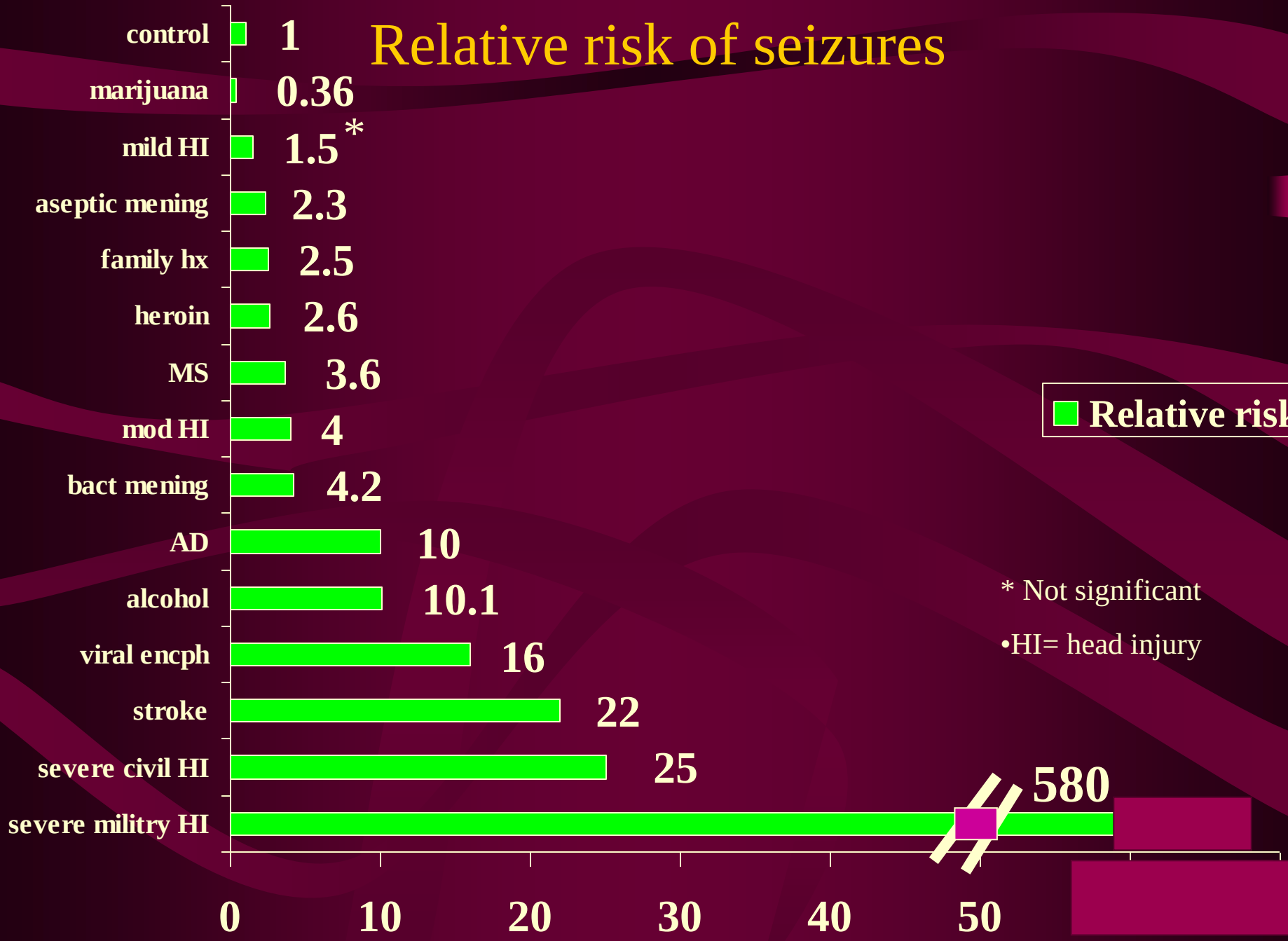


Causes of symptomatic epilepsy

Chapter 10: lecture notes neurology

- *Neonates*
  - Birth trauma
  - Intracranial haemorrhage
  - Hypoxia
  - Hypoglycaemia
  - Hypocalcaemia
- *Children*
  - Congenital anomalies
  - Tuberous sclerosis
  - Metabolic storage diseases
- *Young adults*
  - Head injury
  - Drugs and alcohol
- *Middle-aged adults*
  - Cerebral tumour
- *Elderly*
  - Cerebrovascular disease
  - Degenerative disorders (Alzheimer's, prion diseases)
- Not all the above causes are strictly age-specific; e.g. tumours may present at other ages .
- Some causes are not restricted to individual age groups:
  - Infection, e.g. meningitis, encephalitis, abscess, cysticercosis
  - Inflammation – multiple sclerosis (rarely), vasculitis
  - Metabolic encephalopathy

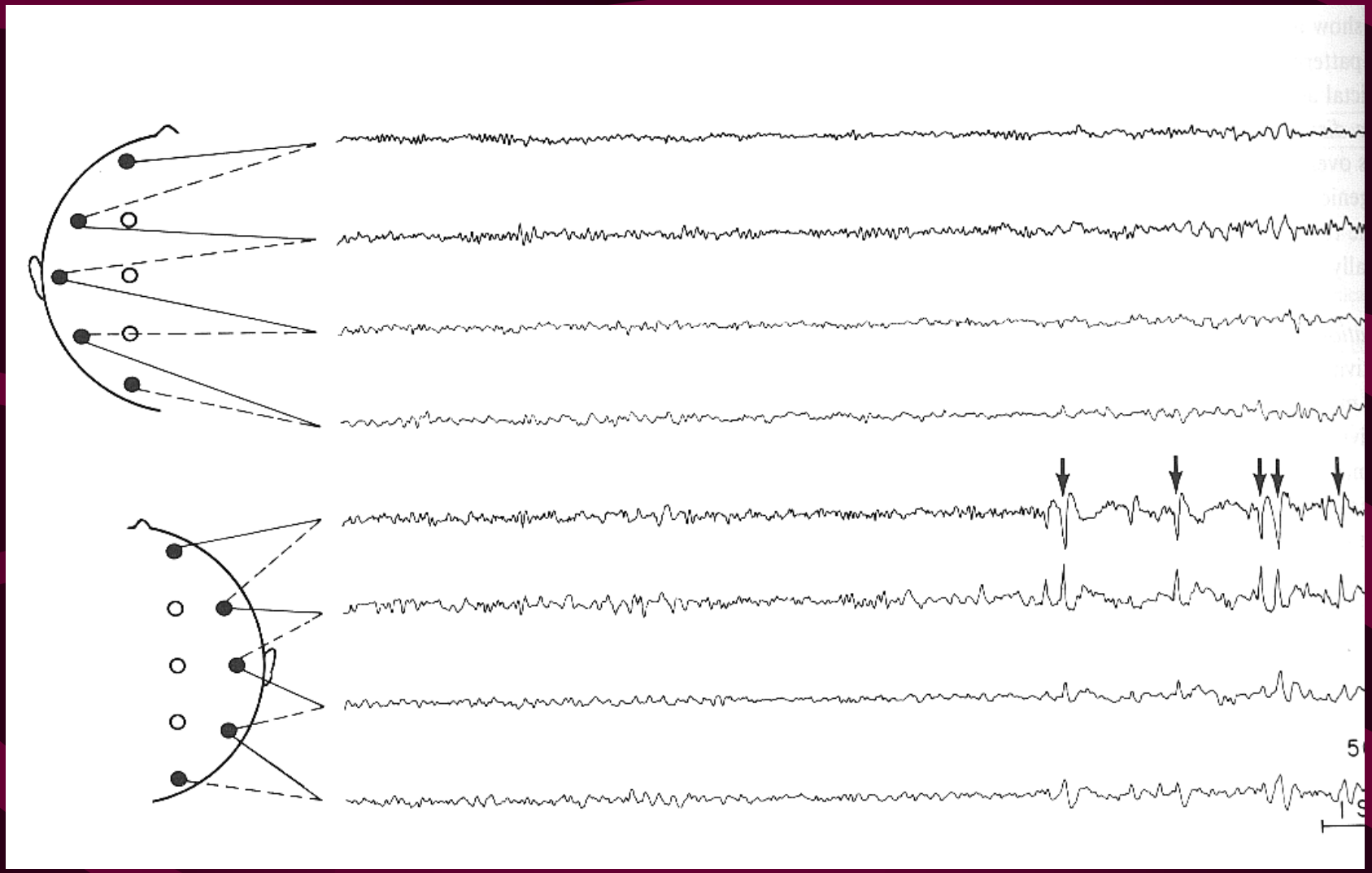
Relative risk of seizures



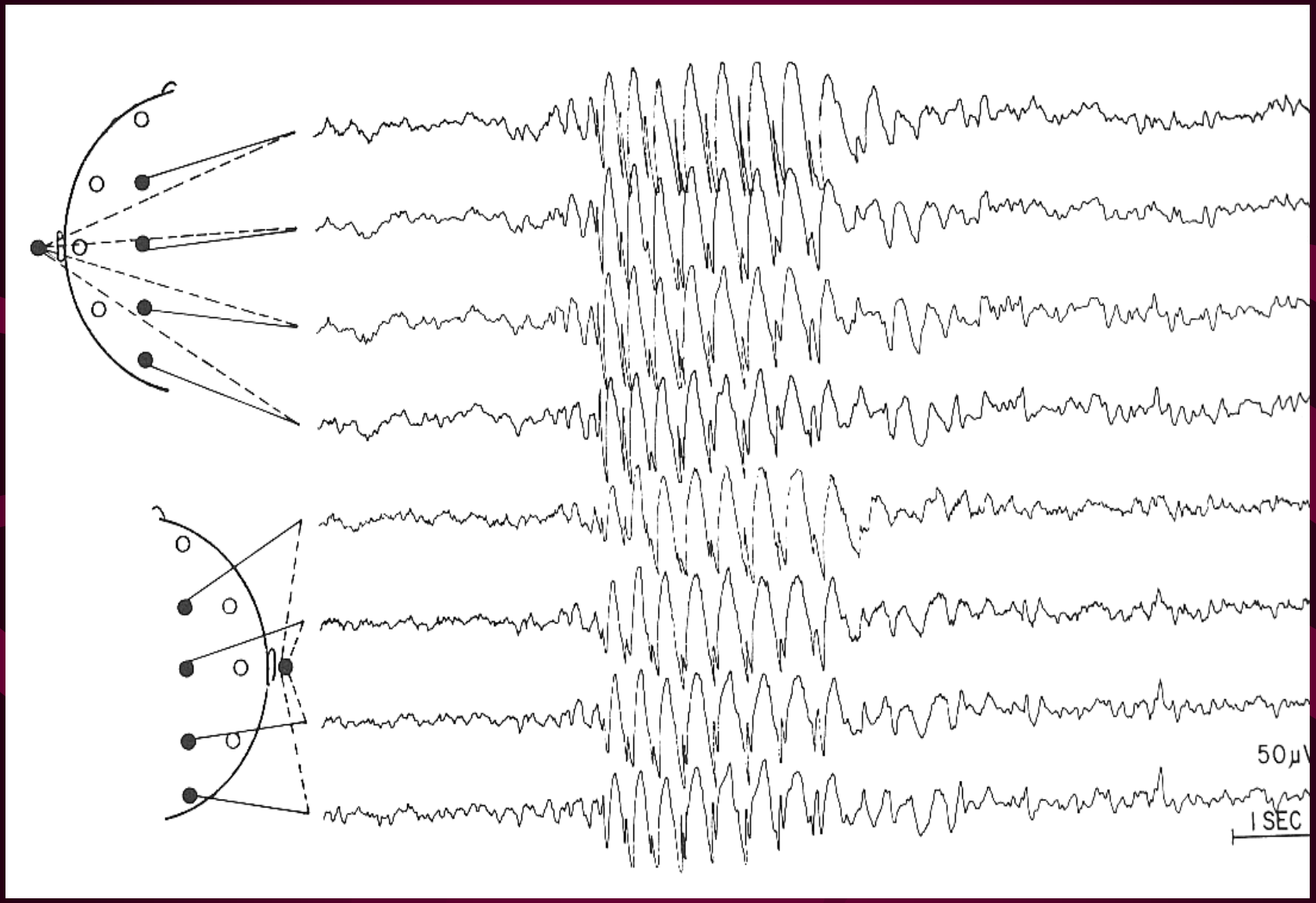
Epilepsy: Diagnosis

- History
- Physical examination
- EEG
- MRI
- Special testing

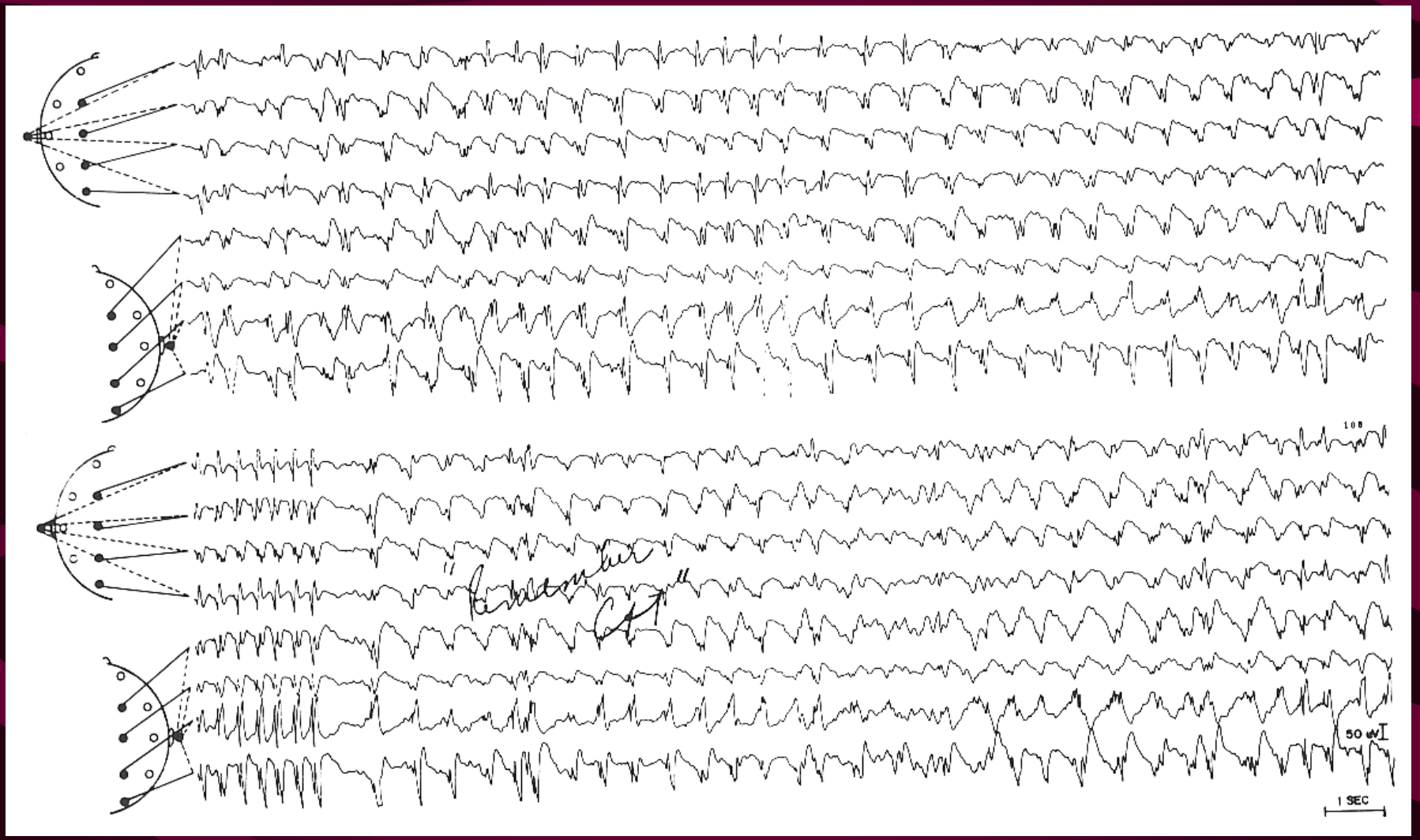
RIGHT ANTERIOR TEMPORAL SHARPS.



INTERICTAL GENERALIZED 3 HTZ SPIKE-WAVE DISCHARGE



GENERALIZED SEIZURE



Differential diagnosis of epilepsy.

Chapter 10: lecture notes neurology

- Syncope
- Cardiac dysrhythmia
- Pseudoseizures
- Hyperventilation/panic attacks
- Transient ischaemic attacks
- Migraine
- Narcolepsy
- Hypoglycaemia
- Vestibular disorders

Differential diagnosis of seizures in adults

- Vasovagal syncope
- Cardiogenic syncope
- Migraine
- TIA
- Psychogenic pseudosizures
- Panic attacks
- Rage attacks

Differential diagnosis of seizures in children

- Tics
- Infantile syncope
- Breath holding spells
- Night terrors
- Gastroesophegeal reflux
- Shudder attacks
- Benign sleep myoclonus

DIFFERENCES BETWEEN SYNCOPE AND SEIZURES

FEATURE	SYNCOPE	SEIZURUE
POSTURE	UPRIGHT	ANY POSTURE
PALLOR AND SWEATING	INVARIABLE	UNCOMMON
ONSET	GRADUAL	SUDDEN/ AURA
INJURY	RARE	NOT UNCOMMON
CONVULSIVE JERKS	RARE	COMMON
INCONTENENCE	RARE	COMMON
UNCONSIOUSNESS	SECONDS	MINUTES
RECORY	RAPID	OFTEN SLOW
POST ICTAL CONFUSION	RARE	COMMON
FREQUENCY	INFREQUENT	MAY BE FREQUENT
PRECIPITATING FACTORS	CROWDED PLACES, LACK OF FOOD, UNPLEASENT CONDITIONS	RARE

Features That Are Not Helpful in Differentiating Syncope from Seizure

- Incontinence
- Prolactin level
- Dizziness
- Fear
- Injury other than lateral tongue biting
- Eye movements (rolling back)
- Brief automatisms

Hirsch et al, Merritt's Textbook of Neurology, 2007

Migraine aura vs. occipital seizure

	Migraine	Occipital Seizure
Duration	5-20 min	0.5-5 min
Typical Content	Straight lines; slow spread	Color, round, variable spread
Laterality	Either side	Always same side (contralateral)
Associated Features		Altered awareness, automatisms

Hirsch et al, Merritt's Textbook of Neurology, 2007

Psychogenic Non-epileptic Seizures

- 10-45% of patients referred for intractable spells
- Females > males
- Psychiatric mechanism — dissociation, conversion
- Common association with physical, emotional, or sexual abuse
- Spells with non-epileptic etiology
- No obvious ictal eeg correlation

  (classically normal awake background during episode of impaired consciousness)

  Caveats: Diagnosis can be complicated
  - The majority of simple partial seizures have no EEG correlation
  - Frontal lobe seizures may have unusual semiology and no discernable EEG correlation

Psychogenic Non-epileptic Seizures

FEATURES SUGGESTIVE OF NONEPILEPTIC PSYCHOGENIC SEIZURES

- Eye Closure
- Pelvic thrusting
- Opisthotonus
- Side-to-side head shaking
- Prolonged duration (>4 minutes)
- Stopping and starting
- Suggestibility

Psychogenic Non-epileptic Seizures

Features suggestive of Non-epileptic seizures	**Important Caveats**
Thrashing, struggling, crying, pelvic thrusting, side-to-side rolling, wild movements	Bizarre complex automatisms can occur with frontal lobe seizures
Preserved consciousness with bilateral tonic or clonic mts	Frontal lobe seizures may have bilateral convulsive movements without impairment of consciousness
Lack of postictal confusion	Posti-ictal confusion is often absent after frontal lobe seizures
Postictal crying or shouting	Aggressive and emotional behavior can occur after epileptic seizures

Psychogenic Non-epileptic Seizures

- Represents psychiatric disease
- Once recognized, approximately 50% respond well to specific psychiatric treatment
- Epileptic and nonepileptic seizures may co-exist
- Video-EEG monitoring often required for diagnosis

Utility of epilepsy video/EEG monitoring units

Epilepsy Monitoring Unit (EMU):

- Inpatient unit with specialized personnel
- Continuous video and EEG recording
- Utility:
  - Differentiate between epileptic and non-epileptic spells
  - Identification of unrecognized seizures
  - Recording seizures for pre surgical evaluation

NAEC Guidelines for EMU evaluation:

- Treatment failure of 1 year
- Failure of 2-3 AEDs

Utility of epilepsy video/EEG monitoring units: Non-epileptic spells

- Study of 213 EMU admissions
  - 21% had purely nonepileptic events
    - Treated as if epilepsy for a mean of 9 yrs
    - Half treated w/ ≥3 AEDs
  - EMU yielded definitive diagnosis in 88%

Smolowitz et al. American Journal of Medical Quality. 2007;22(2):117–122.

ADVERSE PROGNOSTIC FACTORS IN EPILEPSY

- Symptomatic etiology.
- Partial onset seizures.
- Atonic seizures.
- Late onset or first year epilepsy
- Additional mental or motor handicap.
- Long duration prior to therapy.
- Poor initial response to therapy.

Medical Rx of Epilepsy

- General measures:
  proper and adequate sleep/ nutrition/ relaxation / adherence to medications
- 1st line drugs
  - Phenytoin
  - Carbamezapine
  - Valproic acid
  - Phenobarbital

Medical Rx of Epilepsy

- Second line drugs
  Lamotrigine
  Topiramate
  Gabapentin
- 3rd line drugs
  Leviteracetam
  Lacosamide
  Perampanil

Antiepileptic drugs and epileptic syndromes
Chapter 10: lecture notes neurology.

Seizure type	Drugs of choice
Partial	Carbamazepine Sodium valproate Phenytoin Lamotrigine
Absence	Ethosuximide Sodium valproate Lamotrigine
Myoclonic	Sodium valproate Clonazepam Lamotrigine
Generalized tonic-clonic	Sodium valproate Phenytoin Carbamazepine Lamotrigine

Major antiepileptic drugs.

Chapter 10: lecture notes neurology.

Drug	Mode of action	Pharmacokinetics	Side effects	
			Dose-related	Allergic
Carbamazepine	'Membrane stabilizer' Limits repetitive firing of action potentials	Initial low dosage Controlled-release preparation permits twice-daily regime Blood levels limited value	Giddiness Nausea Drowsiness	Rashes Leucopenia
Sodium valproate	Uncertain – multiple	Controlled-release preparation permits twice-or even once-daily regime Blood levels little value	Tremor Confusion Chronic toxicity: alopecia, weight gain	Hepatitis
Phenytoin	'Membrane stabilizer'	Once-daily regime Narrow therapeutic range Blood levels useful	Drowsiness Ataxia Chronic toxicity: gum hypertrophy, acne, hirsutism, coarsening of facial features, folate deficiency	Rashes Lymphadenopathy
Lamotrigine	'Membrane stabilizer'	Half-life prolonged by sodium valproate Dosing schedule depends on concomitant drug treatment	Nausea Dizziness Tremor Headache	Rash Fever Arthralgia Lymphadenopathy Eosinophilia Stevens–Johnson syndrome

Other antiepileptic drugs.
Chapter 10: lecture notes neurology.

Older anti-epilepsy drugs retaining specific uses

Phenobarbitone (and primidone)

Many patients with long-standing epilepsy remain on these drugs

Primidone is metabolized to phenobarbitone

Withdrawal seizures are likely if phenobarbitone is stopped abruptly

Phenobarbitone retains a role in the management of status epilepticus (Chapter 20)

Ethosuximide

Used in childhood absence epilepsy (petit mal)

May exacerbate tonic-clonic seizures

Clonazepam

Effective in myoclonic and absence epilepsy

May be administered intravenously in status epilepticus

Clobazam

Add-on therapy in tonic-clonic and partial seizures, especially if perimenstrual

Newer drugs used predominantly as add-on therapy for partial seizures

Vigabatrin

Also used as monotherapy for infantile spasms (West's syndrome)

Avoid in patients with a psychiatric history

Associated with irreversible peripheral visual field defects in about one-third of patients

For this reason nowadays only used in exceptional circumstances outside the context of West's syndrome

Gabapentin

Also used in the management of neurogenic pain

Unlike many other anti-epilepsy drugs is eliminated by the renal route rather than hepatic metabolism

Topiramate

Also used as adjunctive treatment for primary generalized tonic-clonic seizures

Avoid in patients with a history of renal stones

Tiagabine

Oxcarbazepine

Similar indications to carbamazepine, probably has a better side effect profile

Levetiracetam

Increasingly used as monotherapy

May cause behavioural and mood change

Pregabalin

Useful in patients with epilepsy and generalized anxiety disorder

Zonisamide

Risk of renal calculi

Lacosamide

Anti epileptic Drugs

- 1850 : Bromides
- **1910: Phenobarbital**
- **1940: Phenytoin**
- 1950: Ethosuximide
- **1958: ACTH**
- 1954: Primidone
- **1968: Carbamazepine**
- **1975: Clonazepam**
- **1978: Valproic acid**

1990/2000s: Newer AEDs were developed.

- **Gabapentin 1993(Neurontin)**
- Felbamate 1993(Felbatol)
- **Lamotrigine 1994 (Lamictal)**
- **Levetiracetam 1999 (Keppra)**
- **Topiramate 1996 (Topamax)**
- **Oxcarbazepine 2000 (Trileptal)**
- Zonisamide 2000 (Zonegran)
- **Pregabalin 2004 (Lyrica)**
- **Lacosamide 2008 (Vimpat)**
- Rufinamide 2008 (Banzel)
- **Vigabatrin 2009 (Sabril)**
- Clobazam 2011 (Onfi)
- Ezogabine 2011 (Potiga)
- **Perampanel 2012 (Fycompa)**
- Eslicarbazepine 2013 (Aptiom)
- Brivaracetam 2016 (Briviact®)

- Good efficacy,
- Fewer toxic effects,
- Better tolerability

Intractable Epilepsy

- Impairment of quality of life due to Seizures &/ or Drugs
- 20-30% of epileptics are intractable
- Patients failing 2 drugs are likely to be intractable
- 30-40% newly diagnosed partial epilepsy will not attain a seizure remission with pharmacotherapy.

Intractable Epilepsy

- Treatment options

  New AED

  surgery

  Vagus nerve stimulation

  special diets in children

FACTS:

- 50 % of patients fail to achieve the goal of treatment. (1985) NEJM
- 1/3 of patients treated 1984-1997 failed to become seizure free in the first year of treatment. (2000) NEJM

Potential benefits of AED related seizure control

- Reduced social stigma
- Reduced negative cognitive effects from frequent seizures.
- Reduced risk of status epilepticus (if compliant)
- Reduced risk of physical injury
- Improve employment likelihood
- Helps maintain driving privileges

Risks of AED related adverse effects

- Behavioral problems
- Cognitive impairment
- Idiosyncratic reactions
- Systemic toxicity
- Teratogenicity
- Expense

Ideal Antiepileptic Drug

- Antiepileptogenic
- Complete Seizure Suppression
- Minimal Side Effects

Possible Advantages of New AED

- More effective
- Better tolerated
- Safer
- Better for women
- Less interaction
- Broader spectrum

New AED: common concern

- High cost
- Dose related toxicity
- Pharmacodynamic interactions
- Drug levels of limited use

New AED : how they compare

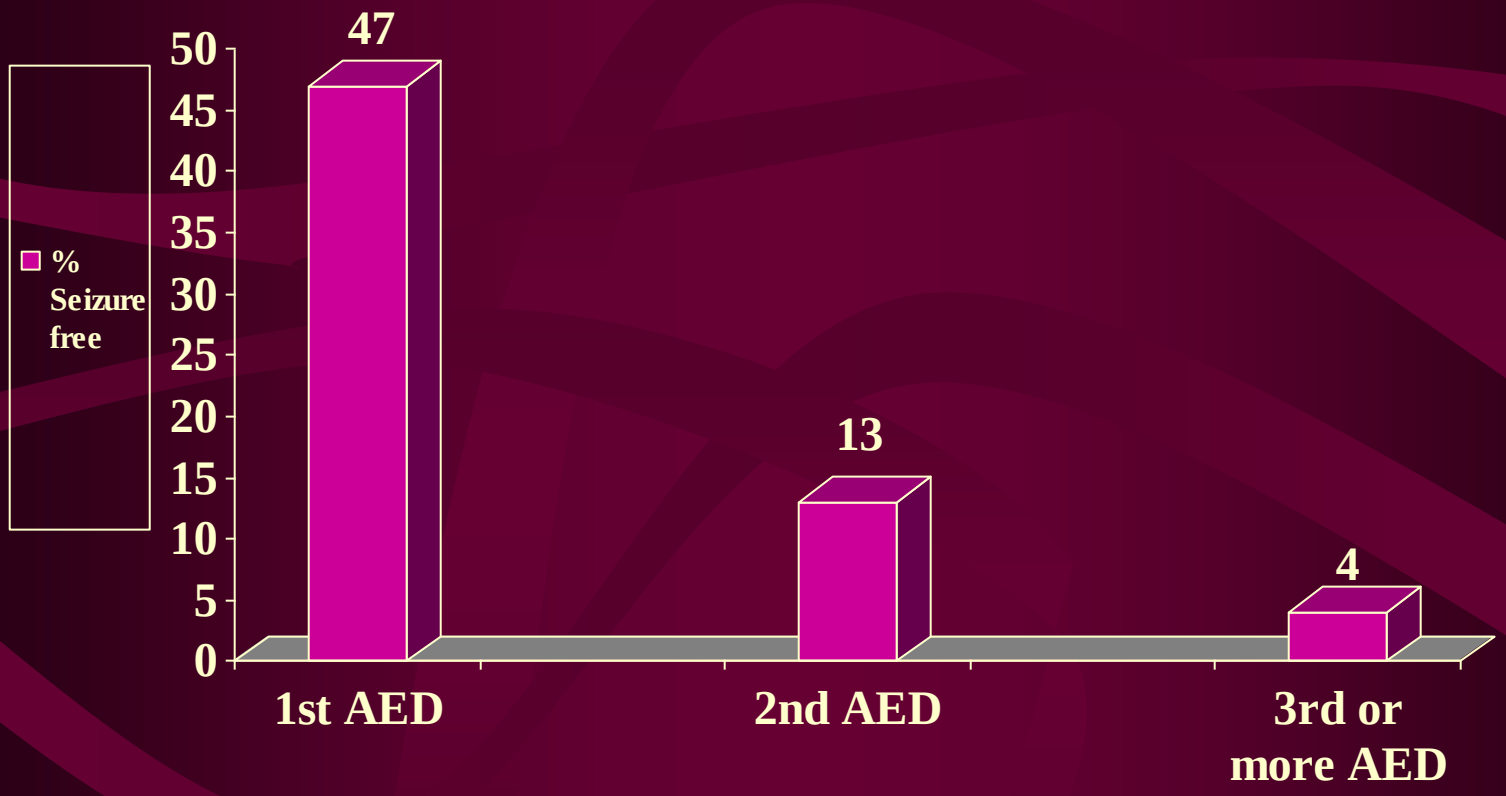
- Similar in :
  - Responder rate ≈ 40%
  - Seizure free rate < 10%
- Differ in :
  - Adverse effects
  - Pharmacokinetic profile
  - Efficacy for seizure type(s)

Epilepsy Surgery

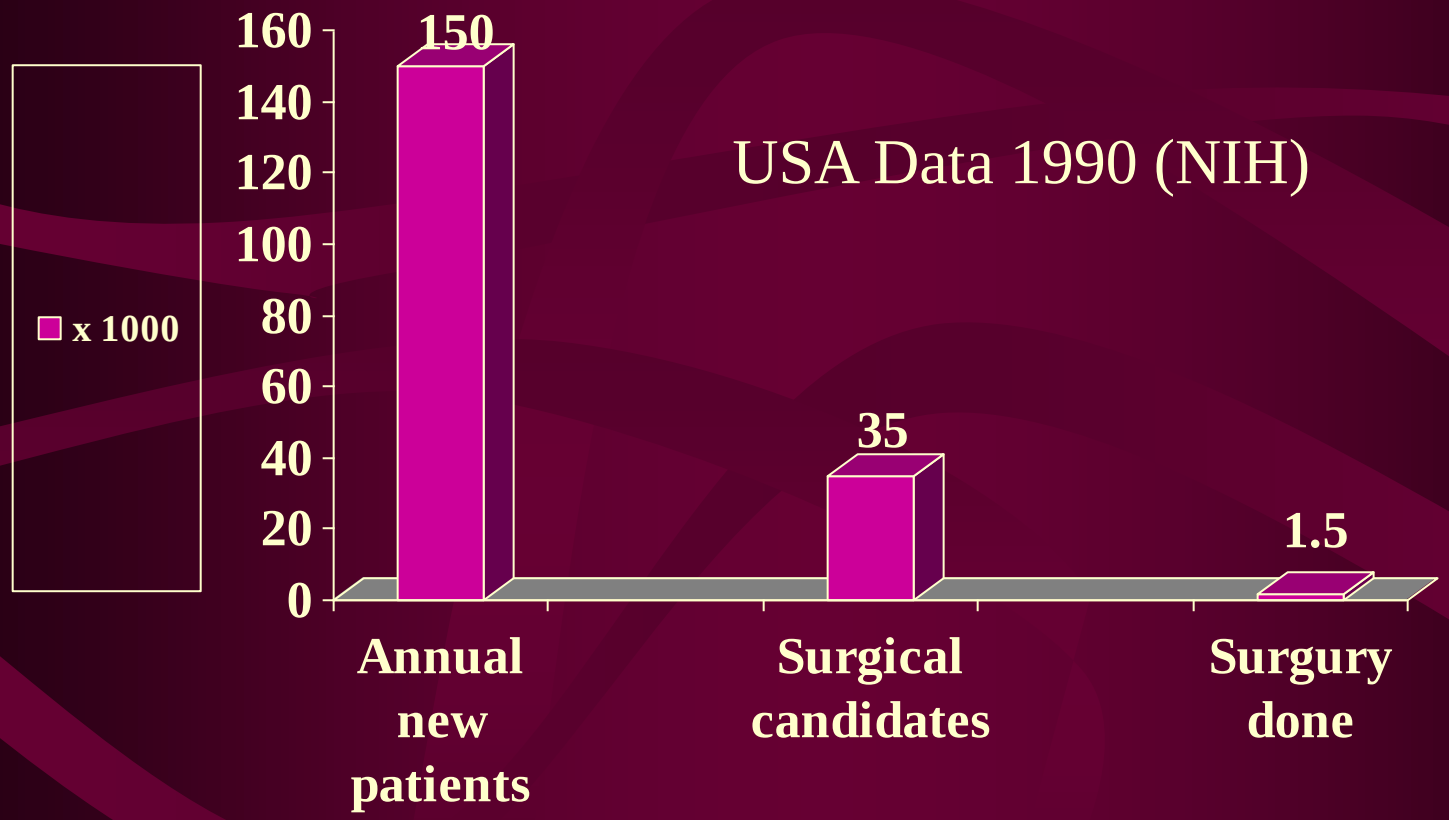
Surgical Candidates

- Medically refractory seizures
- Physically, socially disabled
- Localization-related epilepsy
- Low risk of morbidity
- Potential for rehabilitaiion

Response to AED in newly diagnosed epileptics. Kwan et al NEJM, 2000



Epilepsy surgery : quite under used



Epilepsy Surgery: Types

- Medial temporal lobe epilepsy: MTS
  - Most common
  - Most successful
- Lesionectomy:
  - Tumor
  - Vascular anomaly
  - Cortical malformation
- Hemispherectomy: Rausmusen's encephalitis
- Corpus callosotomy: LGS
- Vagal nerve stimulation: intractable, not surgical candidates
- Multiple subpial transection: elequent areas

CONTRAINDICATIONS TO EPILEPSY SURGERY

- Absolute:
  - Primary generalized epilepsy
  - Minor seizures that do not impair quality of life

- Relative:
  - Progressive medical or neurological disorders
  - Behavioral problems that impair post op rehabilitation
  - Serious medical disorder that may increase surgical mortality
  - Poor memory function in the opposite hemisphere
  - Active psychosis not related to peri-ictal period

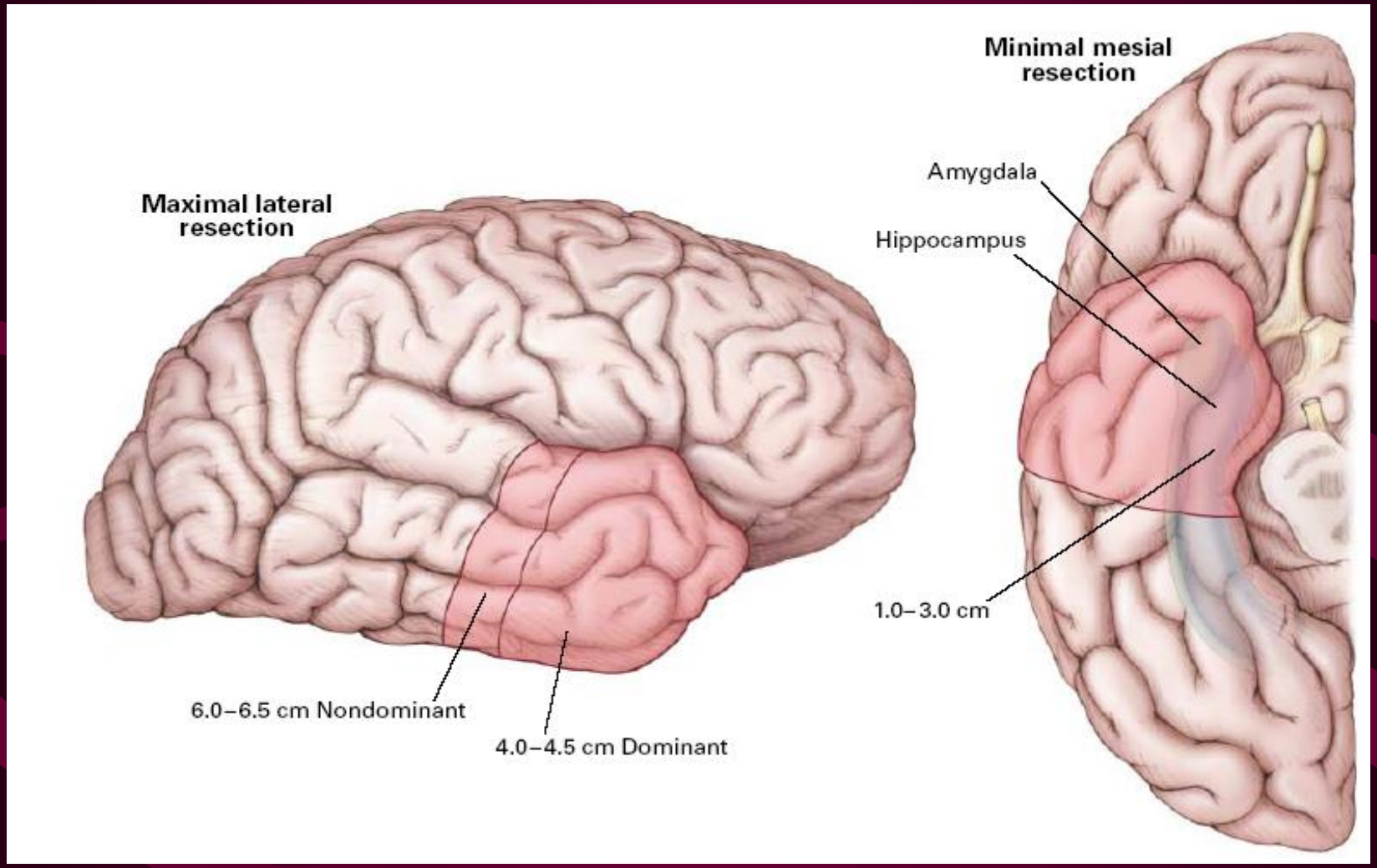
Pre surgical evaluation

- Routine EEG
- Brain MRI (seizure protocol)
- Long term video EEG monitoring
- Visual perimetry
- Neuropsychometry
- Sodium amobarbital test

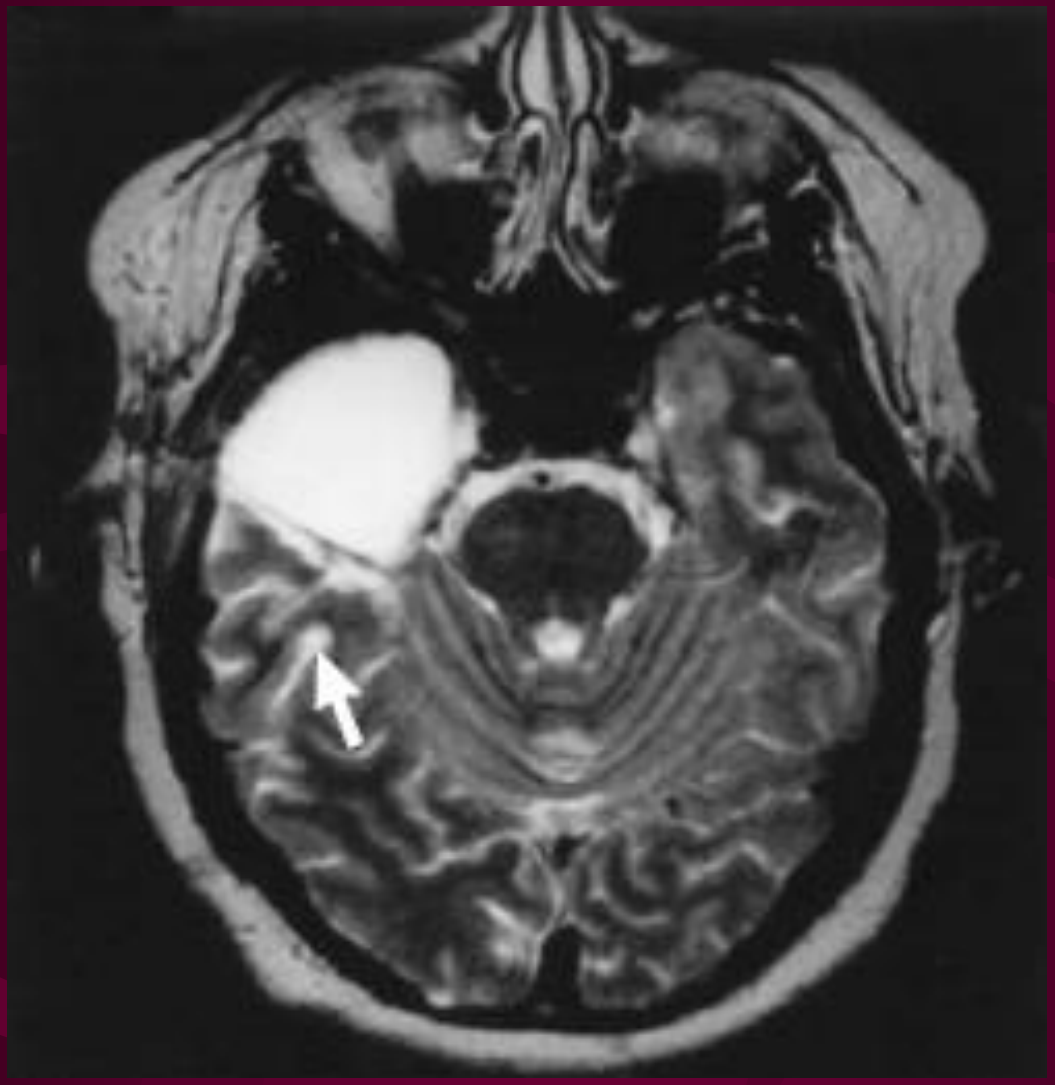
Epilepsy surgery : Risks

- Visual field loss < 10% (temporal lobectomy)
- Any surgical complication < 5%
- Death or serious complication <0.5%
- Memory or cognitive deterioration (predictable)
- Aphasia 1% (reversible)
- Psychosis or depression 5% (treatable)
- Most serious adverse outcomes occur when surgery is unsuccessful controlling seizures

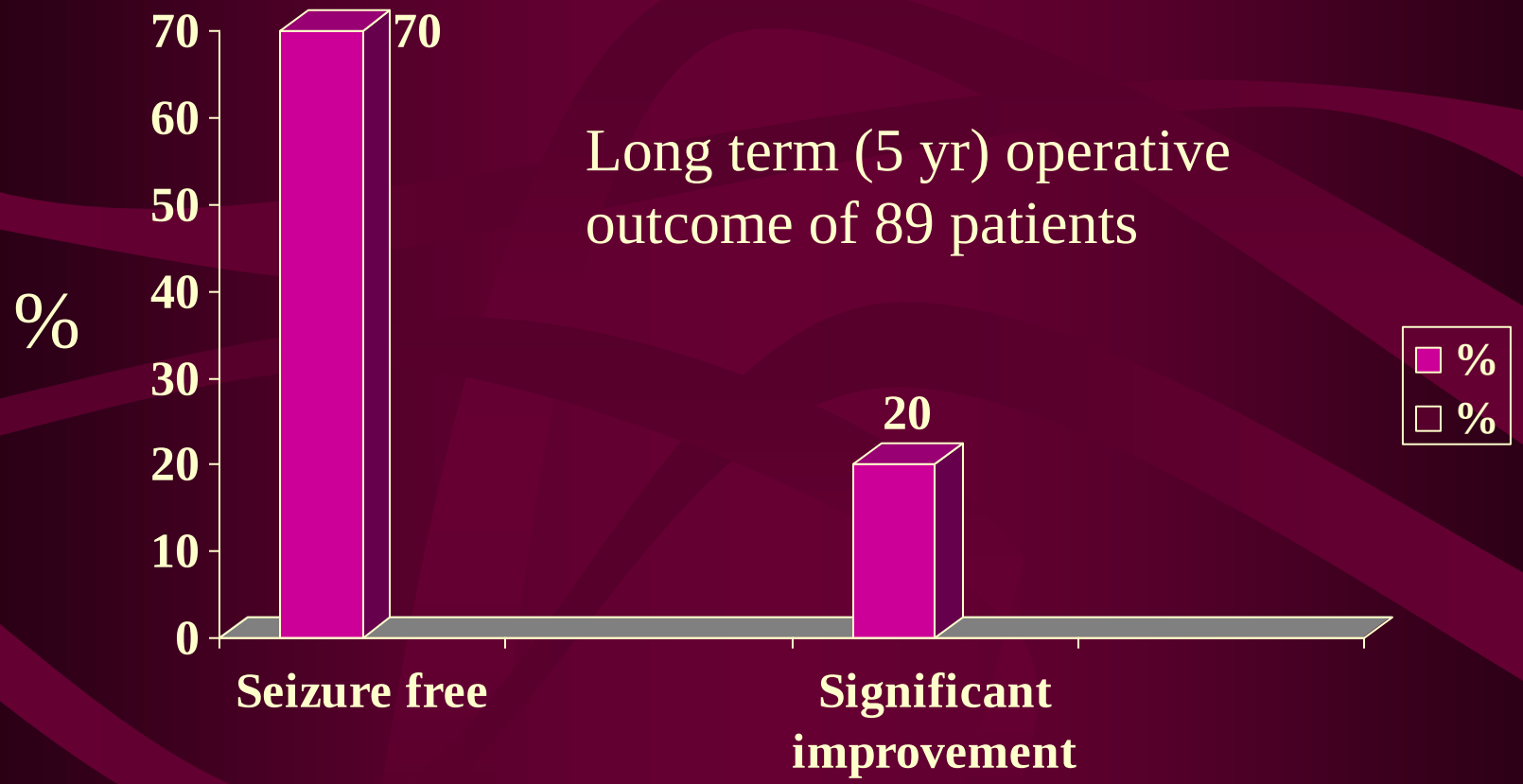
Temporal lobectomy



S/P right temporal lobectomy

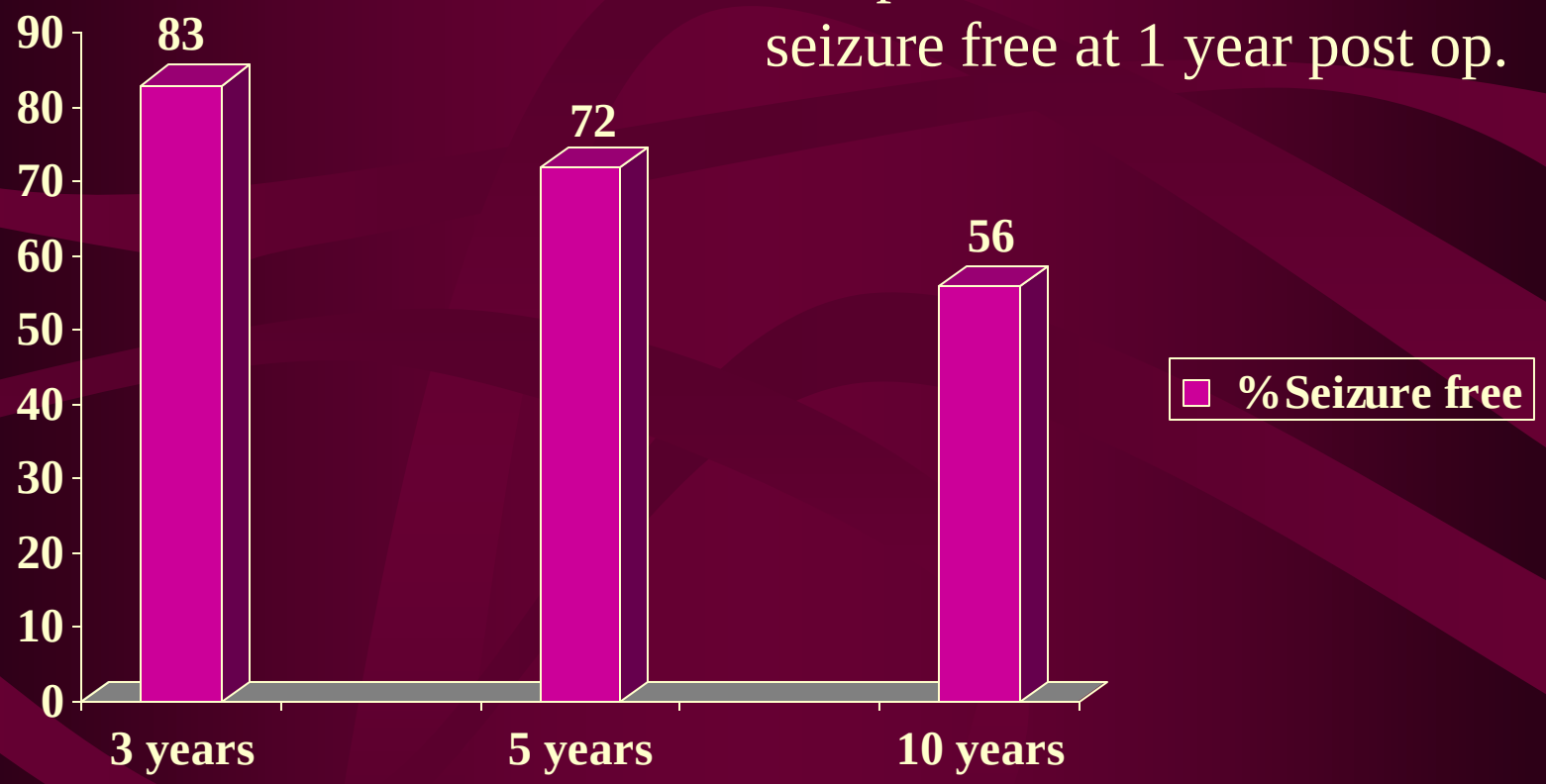


Temporal lobectomy efficacy
Sperling et al, JAMA 1996: 276:470-75

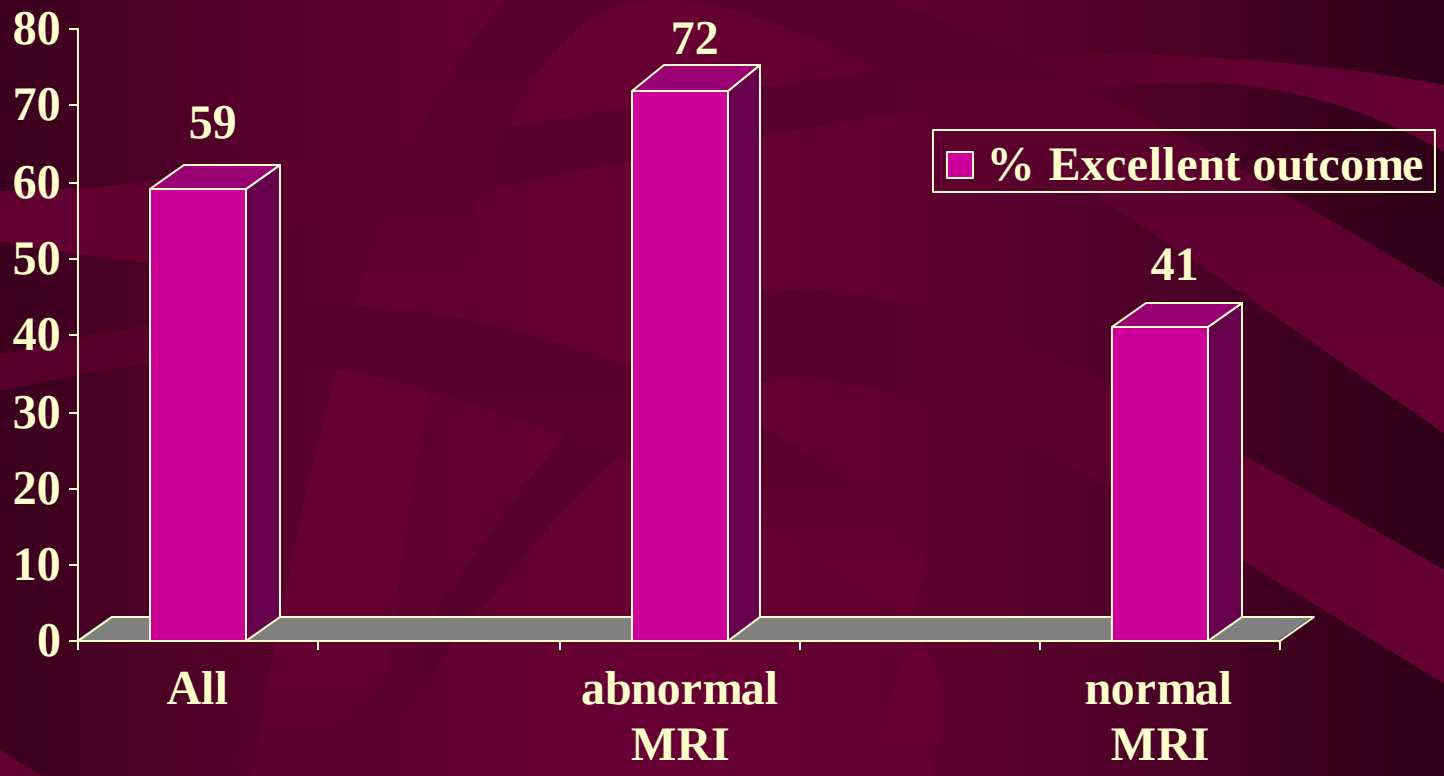


Temporal lobectomy: long term outcome. Yoon et al Neurology 2003;61: 445-450

175 patients with TLE who were seizure free at 1 year post op.



Frontal lobectomy: operative outcome (68 patients) . Mosewich et al Epilepsia 2000;41:843-849



Vagus nerve stimulation

Status Epilepticus

- Continuous or recurrent seizures without recovery of consciousness for 30 minutes or more (tendency now to use shorter time definition like 5 minutes and more.

AED in Status Epilepticus

Drug	Loading dose	Maintenance dose	Adverse effect
Diazepam	10-20 mg	None	Respiratory depression Hypotension Sialorrhea
Lorazepam	4 mg	None	As above
Phenytoin	20mg/kg	5mg/kg/day	Cardiac depression Hypotension
Phosphenytoin	30mg/kg	None	Hypotension Parasthesia

AED in Status Epilepticus

Drug	Loading dose	Maintenance dose	Adverse effect
Phenobarbital	20mg/kg	1-4 mg/kg/hr	Respiratory suppression
Pentobarbital	2-8mg/kg	0.5-5 mg/kg/hr	Respiratory suppression Hypotension
Midazolam	0.2 mg/kg	0.75-10 micgm/kg//min	Hypotension Respiratory suppression
Propafol	2 mg/ kg	5-10 mg/kg/hr initial then 1-3 mg/kg/hr	Respiratory depression Hypotension Lipemia Acidosis
Valproic acid	25-40mg/kg @ 3-5 mg/kg/min	None or oral 500-2000 mg / day	? Hepatic encephalopathy ? Coagulopathy Safe in unstable patients

CONCLUSIONS:

- Epilepsy is still a challenge
- New AED improved our treatment
- Need for more understanding of basic mechanism of epilepsy and its genesis
- Need to develop specific and target specific treatment
- Surgery is quite effective in properly selected patients but quite underused
- Intravenous benzodiazepines, phenytoin, phenbarb and valproic acid are available, effective and safe Rx for status epilepticus

THANK YOU