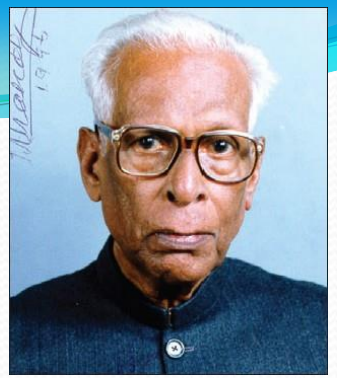
History of Neurosurgery
Neurosurgical Giants
and
Indian Neurosurgery

Dr.A.K.Srivastava
Professor
Dept. of Neurosurgery
G.B.Pant Institute of Medical Education and Research
Maulana Azad Medical College
University of Delhi
New Delhi

Harvey Williams Cushing

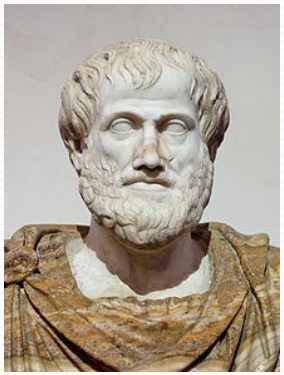
Background



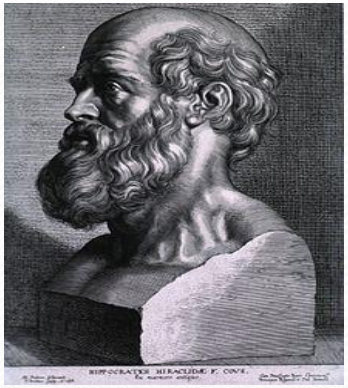
Dr.(Prof.) Jacob Chandy

"Only the man who knows exactly the art and science of the past and present is competent to aid in its progress in the future"

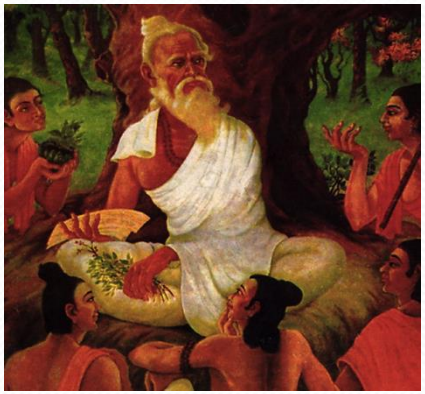
(Christian Albert Theodor Billroth)



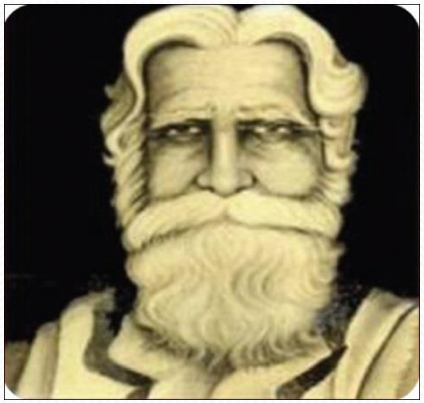
Aristotle



Hippocrates

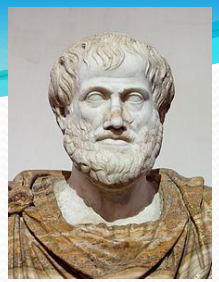


Jivaka



Sushruta

Brain(Introduction)



- The brain was not always held in high regard.
- The **Greek philosopher, Aristotle**, thought the heart, not the brain, was the location of intelligence and thought.
- The ancient Egyptians also did not think much of the brain.
- In fact, when creating a mummy, the Egyptians scooped out the brain through the nostrils and threw it away.
- However, the heart and other internal organs were removed carefully and preserved.
- These organs were then placed back into the body or into jars that were set next to the body.

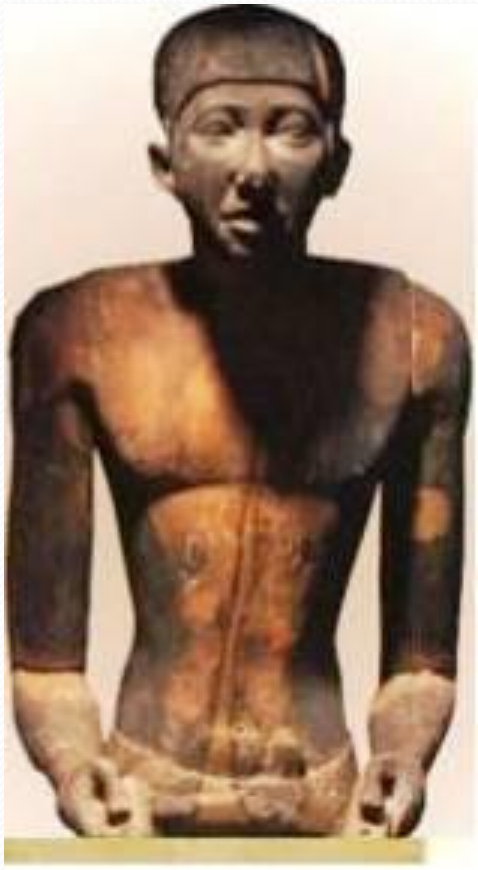
Brain

- Nevertheless, the ancient Egyptians are responsible for the oldest written record using the word "brain" and have provided the first written accounts of the anatomy of the brain, the “Meninges” (coverings of the brain) and cerebrospinal fluid.
- The word "brain" appears on an ancient paper-like document (a "papyrus") called the Edwin Smith Surgical Papyrus.
- This document was written around the year 1700 BC, but is based on texts that go back to about 3000 BC.
- This document is considered to be the first medical document in the history of mankind.
- It is possible that the papyrus was written by the great Egyptian physician named Imhotep.

Bronze statue of Imhotep

The start was here
In Egypt

- The Egyptian Imhotep (2667-2648) is the first physician in history.
- To him, Edwin Smith Papyrus, the oldest paper was attributed.
- It is the 1ST Surgical textbook that differentiate between medicine and magic.
- He is considered the father of medicine.
- Besides, He was an architect and a priest.



THE UNIVERSITY OF CHICAGO
ORIENTAL INSTITUTE PUBLICATIONS
VOLUME IV

THE EDWIN SMITH SURGICAL PAPYRUS

PUBLISHED IN FACSIMILE AND HIEROGLYPHIC TRANSLITERATION WITH TRANSLATION AND COMMENTARY IN TWO VOLUMES

BY

JAMES HENRY BREASTED

VOLUME TWO
FACSIMILE PLATES AND
LINE FOR LINE HIEROGLYPHIC
TRANSLITERATION

THE UNIVERSITY OF CHICAGO PRESS
CHICAGO, ILLINOIS

Case 4. A head wound with damage to the plates of the skull (2,2 - 11)

Title

Practices for a gaping wound in his head, which has penetrated to the bone and split his skull.

Examination and Prognosis

If you treat a man for a gaping wound in his head, which has penetrated to the bone and split his skull, you have to probe his wound. Should you find something there uneven under your fingers, should he be very much in pain at it, and should the swelling that is on it be high, while he bleeds from his nostrils and his ears, suffers stiffness in his neck, and is unable to look at his arms and his chest, then you say about him: "One who has a gaping wound in his head, which has penetrated to the bone and split his skull, while he bleeds from his nostrils and his ears and suffers stiffness in his neck: an ailment I will fight with."

Treatment

Since you find that man with his skull split, you should not bandage him. He is to be put down on his bed until the time of his injury passes. Sitting is his treatment, with two supports of brick made for him, until you learn that he arrives at a turning point. You have to put oil on his head and soften his neck and shoulders with it. You should do likewise for any man you find with his skull split.

Explanations

As for "which has split his skull," it is the pushing away of one plate of his skull from another, while the pieces stay in the flesh of his head and do not fall down.

As for "the swelling on it is high," it means that the bloating that is on that split is great and lifted upward.

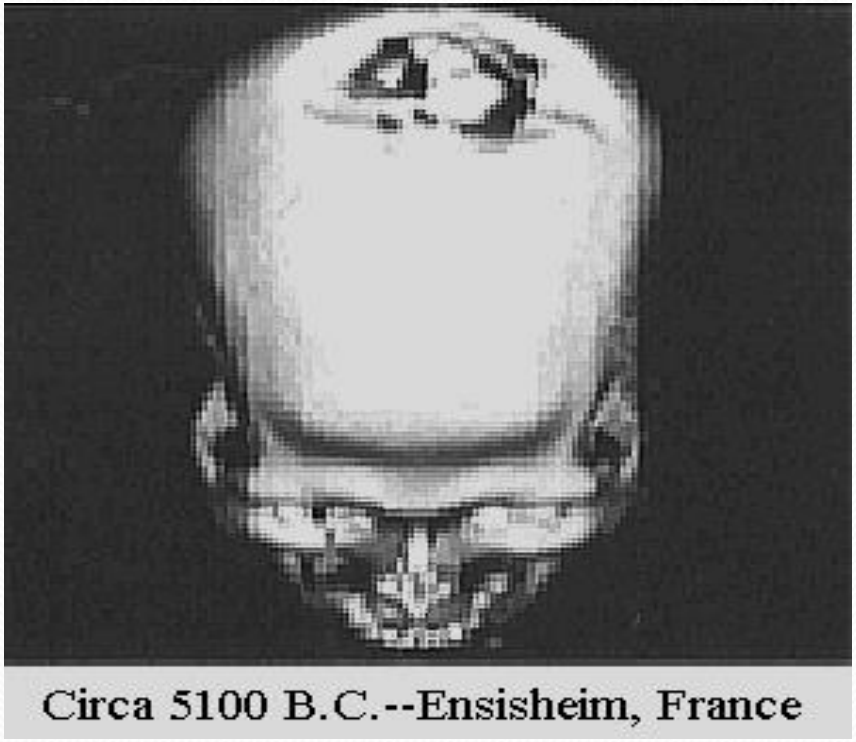
As for "you learn that he arrives at a turning point," it is to say you learn that he will die or until he has revived, since it is "an ailment I will fight with."

Neurosurgery

1700 B.C.- Edwin Smith (surgical Papyrus)

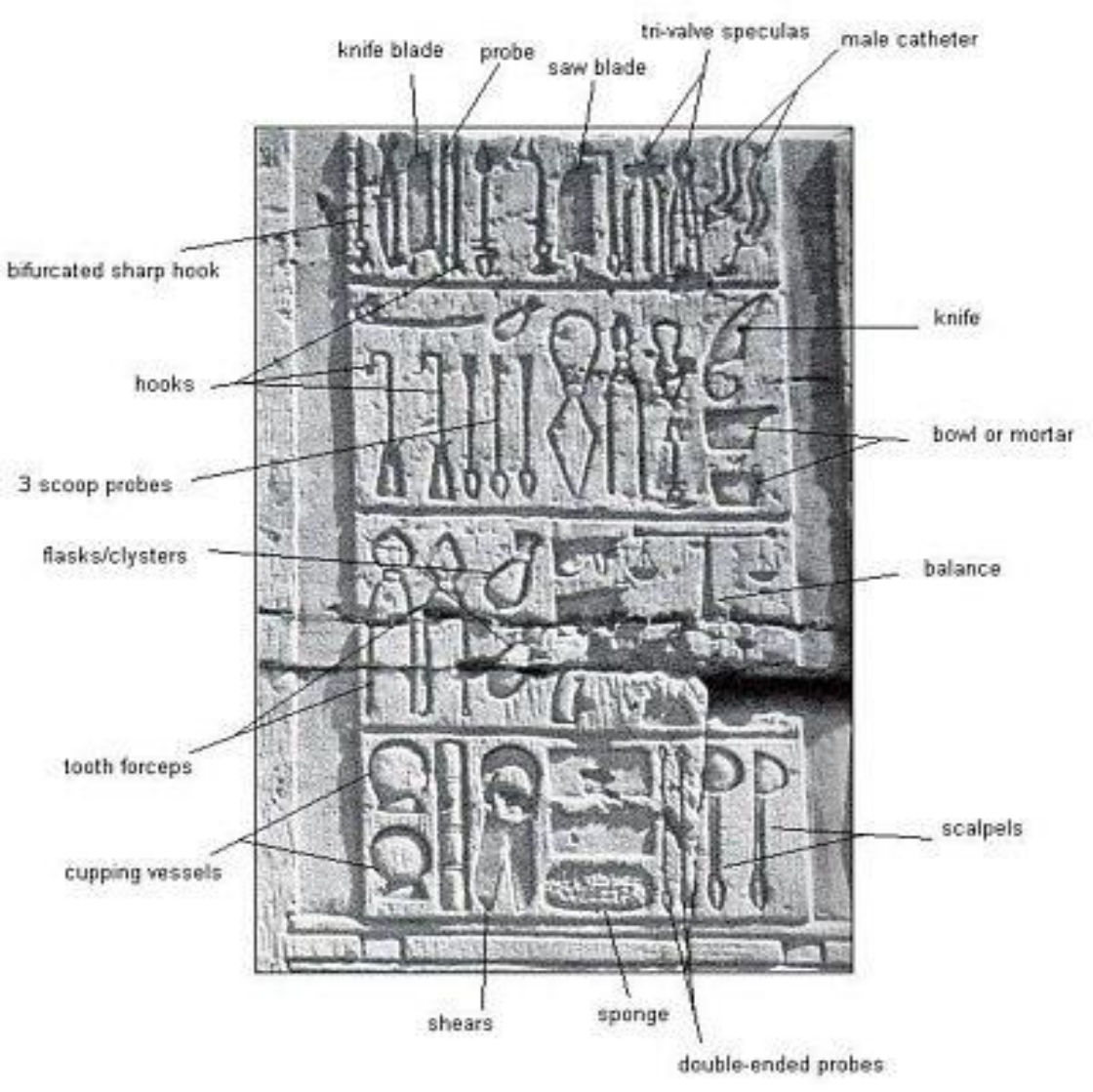
The first use of "neuro" words in recorded history

"Father of Medicine"

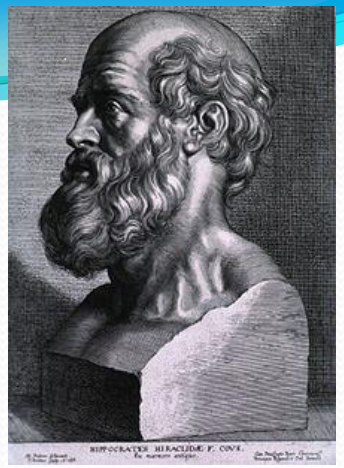


Circa 5100 B.C.--Ensisheim, France

Ancient instruments



Hippocrates



- Hippocrates of Kos (460 –370 BC), was a Greek Physician of the Age of Pericle, and is considered one of the most outstanding figures in the history of medicine.
- He is referred to as the father of western medicine.
- Hippocrates is commonly portrayed as the paragon of the ancient physician, credited with coining the Hippocratic Oath, still relevant and in use today.
- He is also credited with greatly advancing the systematic study of clinical medicine, summing up the medical knowledge of previous schools, and prescribing practices for physicians through the Hippocratic Corpus and other works.

History of Neurosurgery

- Dr Greenblatt proposes two basic premises which lead to the subdivision of the history of neurosurgery into three epochs.
- The first premise is that the development of neurosurgery depended upon three technological advances: cerebral localization theory, antiseptic/aseptic techniques, and anaesthesia, both general and local.
- The second premise is that neurosurgery fulfills the definition of a distinct profession.
- The three technological advances have continued to evolve, but neurosurgical practice has also changed enormously and more rapidly in relatively recent times as a result of the operating microscope and the phenomenal advances in imaging.

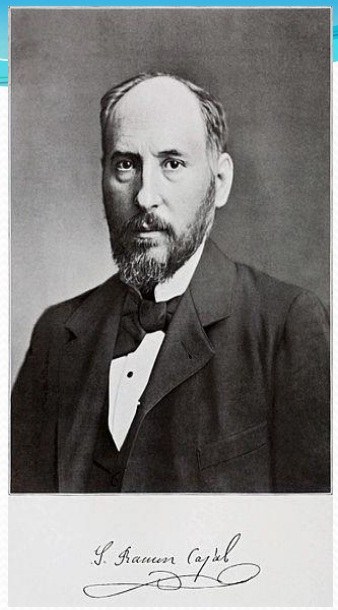
History of Neurosurgery

The three epochs are:

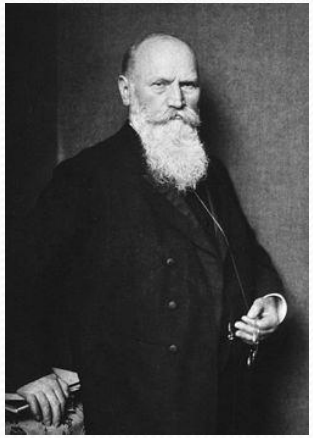
- Premodern (1879)
  - Premodern is before Macewen, 1879, i.e. before the tenets of the first premise were combined into practice. (*when all 3 tenets used in practice.)*
- Gestational(1879–1919)
  - Gestational refers to the period of transition into a distinct profession.(*transition into distinct profession.)*
- Modern
  - Modern is after Cushing, 1919, with the realization of the second premise. (*develops into distinct profession.)*
- It might be argued that there is a fourth epoch: Contemporary Neurosurgery (present day, operative microscope, imaging advances, GKS).

Neurosurgery

- Camillo Golgi: *Nerve network doctrine(1883)*
- Cajal: *Neuron theory*
- Waldeyer: *Coined 'Neuron' for independent nerve unit*
- Berger : *introduced EEG*(1929)
- Foerster & Altenburger: *1st described EEG*(1935)



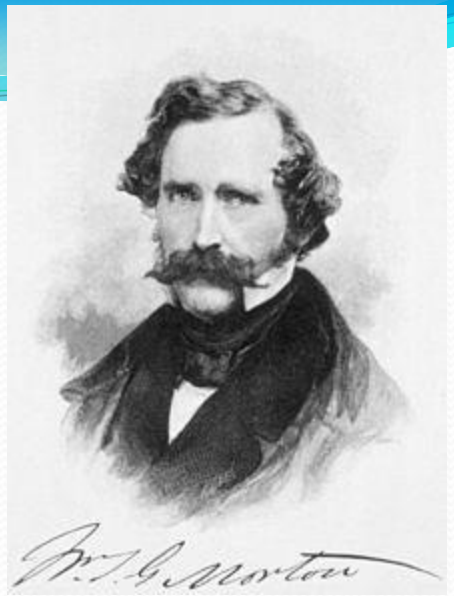
- Cajal: Neuron theory



Waldeyer

William T. G. Morton

- Born: 9,August 1819
  Charlton, Massachusetts
- Died: July 1868 (aged 48)
  New York City
- Nationality: United States
- Fields: Dentistry
- Known for: Ether for surgical operation
- Influences: Charles T. Jackson
  Horace Wells



William T. G. Morton

Replica of the inhaler used by
William T. G. Morton in 1846
in the first public demonstration of
surgery using ether

Ernst von Bergmann (Dec 16, 1836-March 25, 1907)

- German surgeon and author of a classic work on cranial surgery, *Die Chirurgische Behandlung der Hirnkrankheiten* (1888; "The Surgical Treatment of Brain Disorders").
- Bergmann was educated at Dorpat, where he was professor of surgery from 1871 to 1878.
- In addition to his contributions to cranial surgery, Bergmann is noted for introducing steam sterilization of instruments and dressings (1886), and in 1891 he introduced aseptic methods to the practice of surgery.

Ernst von Bergmann

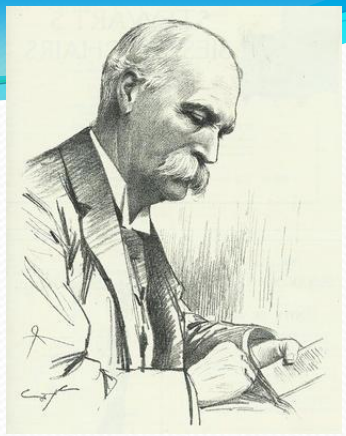
Pierre Paul Broca

- Paul Pierre Broca, brilliant French surgeon and anthropologist, was born in Sainte-Foy-la-Grande, in 1824.
- Broca studied Medicine in Paris.
- He became very early a professor of surgical pathology at the University of Paris and a noted medical researcher in many areas.
- As a superb brain anatomist, he made important contributions to the understanding of the limbic system, rhinencephalon.
- He arrived at this discovery by studying the brains of aphasic patients.

Pierre Paul Broca

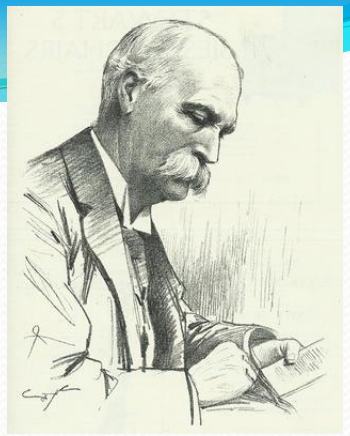
- But the field of study where Broca became famous and a towering figure in the history of medicine and the neurosciences, was his discovery of the speech center (now known as the Broca's area or the third circumvolution of the frontal lobe).
- Broca was also a pioneer in the study of physical anthropology.
- He described for the first time trephined skulls from the Neolithic.
- He was very interested in the relation between anatomical features of the brain and mental capabilities, such as intelligence.

Sir William Macewen



- William Macewen (1848-1924) was a Scottish surgeon who was a pioneer in modern brain surgery.
- He also contributed to the first development of bone graft surgery, the surgical treatment of hernia and of pneumonectomy.
- Macewen was born in Rothesay (Isle of Bute, Scotland) in June 22, 1848, and got his medical degree in 1872 at the University of Glasgow.
- He was greatly influenced by his former teacher of surgery, the great Lord Joseph Lister (1827-1912), who revolutionized surgery by developing antisepsis, by the use of phenol, thus decreasing drastically the enormous mortality of surgical patients due to infections.

Sir William Macewen

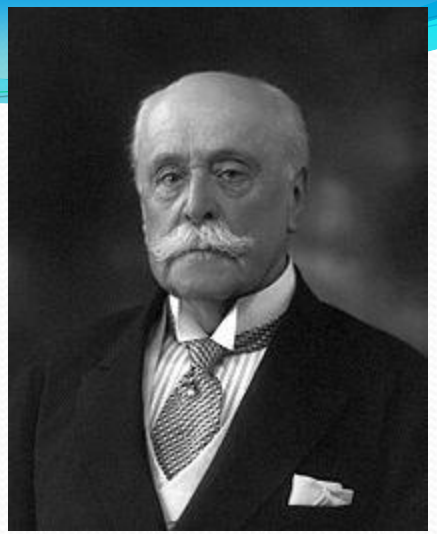


- Macewen demonstrated in 1876 that it was possible to use a precise clinical examination to determine the possible site of a tumor or lesion in the brain, by observing its effects on the side and extension of alterations in motor and sensory functions.
- Thus, in 1876 he diagnosed an abscess in the frontal lobe of a boy, but the family refused permission to operate. When the patient died his diagnosis and localization were found to be correct.
- Another important contribution by Macewen to modern surgery was the technique of endotracheal anaesthesia with the help of orotracheal intubation, which he described in 1880, and still in use today

Neurosurgical Giants
Francesco Durante (1844-1934)

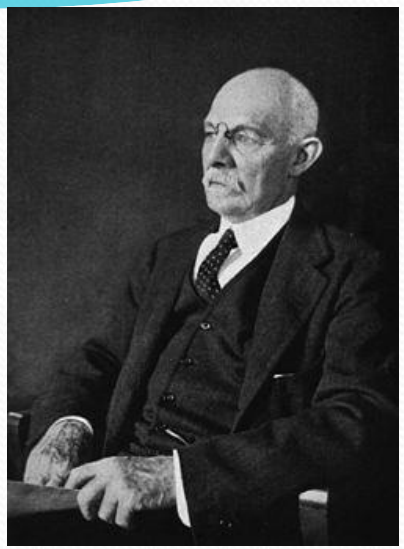
- Durante- Conheim theory:
  - *genesis of tumors from enclosed embryonic rests*
- General sugery:
  - *Cure of surgical TB with iodo-iodurate*
  - *Cuneiform resection of knee articulation*
  - *Partial/ total astragalectomy*
  - *First arterial suture*
- Osteoplastic flap.
- Hypophysectomy by pharyngeal approach
- He was one of the first surgeons in Italy and in the world to successfully remove brain tumors (Olfactory groove meningioma) in 1884.

William H. Bennett



- Sir William Henry Bennett (1852 – 24 December 1931) was a British surgeon.
- His most important contribution to medical science was a paper in which he introduced the *surgical procedure of posterior rhizotomy for the relief of spasmodic pain in a lower extremity.*
- He was knighted as a Knight Commander of the Royal Victorian Order (KCVO) in July 1901.

Neurosurgical Giants
William Halsted



- 'Asepsis' practice.
- Rubber glove.
- Surgical technique:
  - Gentle dissection.
  - Fine silk ligature to secure vessels "only".
  - Sealing wound with silver foil.
  - Avoidance of drainage and frequent dressing.
- Cocaine as local anaesthetic agent- 'truncal block'

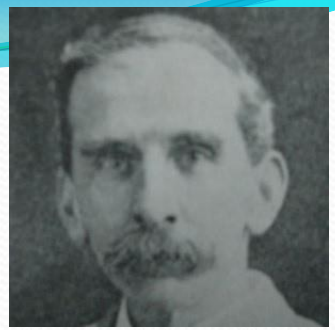
Neurosurgical Giants
Sir Victor Horsley (1857-1916)

Immortalized in surgical history for the introduction of "antiseptic wax“. Sir Victor Horsley played a pivotal role in shaping the face of standard neurosurgical practice. His contributions include

1. Experimental research:

- Electrical stimulation of motor area in rhesus monkey for localization (1888).
- Horsley’s cortical map Surface markings for the underlying cortex Epilepsy.
- Motor function of internal capsule.
- Cerebral edema.
- Artificial respiration.

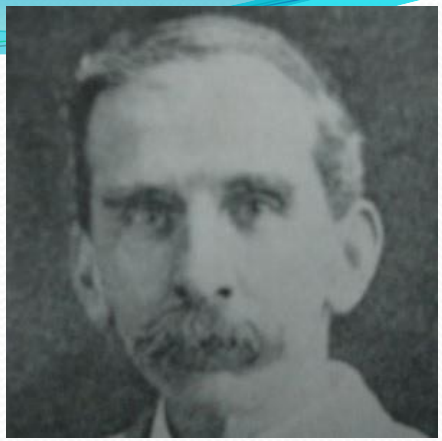
Sir Victor Horsley (1857-1916)



2. Contributions in Forms of treatment

- Acceptable operative mortality .
- Antiseptic technique.
- Smooth anaesthesia- preferred chloroform over ether.
- Excision of gasserian ganglion in *trigeminal neuralgia*.
- Significance of *papilledema in raised ICP*.
- Decompression to save eyesight in *raised ICP* (1887).
- Removed spinal neoplasm.
- Decompressive laminectomy for *potts spine*.
- Decompressive craniectomy for *microcephaly*.
- Secondary debridement - infected craniocerebral wound.
- Lumbar Drain to decrease ICP.

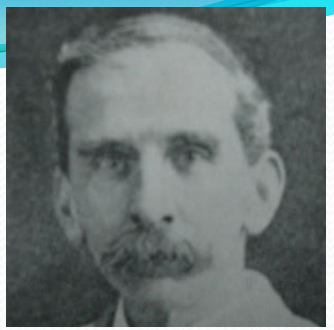
Sir Victor Horsley (1857-1916)



Surgical craft

- Dexterity - speed of operating.
- Small vessel hemorrhage- hot saline douches.
- Bone bleed- *'bone wax'.*
- Use of muscle to control bleed.
- Curved skin incision.
- 1st surgery for focal epilepsy (1886).
- Retrogasserian neurotomy - *tic douloureux* (1890).

Sir Victor Horsley (1857-1916)



- A tireless scientist, he was a significant player in discovering the cure for myxedema and the eradication of rabies from England
- He invented the Horsley-Clarke stereotactic frame.
- As a pathologist, Horsley performed research on bacteria and edema and founded the Journal of Pathology.
- He is the founder of modern Neurological Surgery.
- He was awarded as 'First specialized surgical neurologist'.

Neurosurgical Giants

Harvey Williams Cushing

(April 8, 1869- October 7, 1939)

- He is the first American neurosurgeon.
- He is known as Father of modern Neurosurgery.
- W S Halsted & William Osler were his teachers.
- Ernest Amory Codman: 1st anaesthetic , “Ether Chart”.
- First to map human cerebral cortex with faradic stimulation in conscious patients.
- first operation for acromegaly (March 1909).
- small silver clip (Cushing’s clip) (1910).

Neurosurgical Giants

Harvey Williams Cushing

(April 8, 1869- October 7, 1939)

- Introduced suction to deal with blood in deep recesses of brain.
- Described Cushing's law & Cushing's triad.
- With Dr William Bovie: electric coagulation (1926).
- Defined acoustic neuroma & syndrome of CPA.
- Syndromes & Clinical entities:

  -Cushing's Syndrome

  -Rokitansky Cushing Ulcer

  -Neurath-Cushing syndrome

  -Cushing's symphalangism

Neurosurgical Giants

Harvey Williams Cushing

(April 8, 1869- October 7, 1939)

- Standardisation of Surgical techniques.
- Compressing scalp for hemostasis.
- Waxing the bone edges.
- Hemostatic clips.
- Electrocautery, motor driven suction.
- Classified brain tumors with Percival Bailey.
- Exp with cocain nerve blocks.
- Coined ‘ regional anaesthesia’.
- Medical Historian: Biographer of Sir William Osler (Pulitzer, 1926).

Neurosurgical Giants
Walter Edwards Dandy

- April 6, 1886-April 19, 1946.
- With Kenneth Blackfan, established modern concept of circulation of CSF and hydrocephalus.
- Developed choroid plexectomy, third ventriculostomy and catherisation of aqueduct of sylvius.
- First to discover pneumoperitoneum.
- Ventriculography in 1918.
- Exposed & resected pineal tumor.

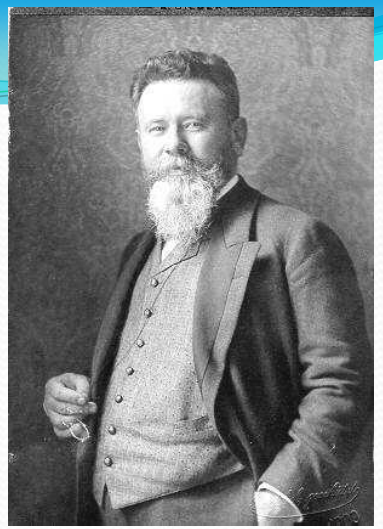
Neurosurgical Giants
Walter Edwards Dandy

- 1917, Removed 1st acoustic neuroma completely.
- Pioneer in Surgery of AVM and intracranial aneurysm.
- Clipped aneurysmal neck.
- Treatment of Meniere's disease by sectioning of VIII CN.
- First to section IX CN (Glossopharyngeal) intracranially for neuralgia.
- Sectioned sensory root of CN V for tic douloureux.

Neurosurgical Giants
Antonio Egas moniz

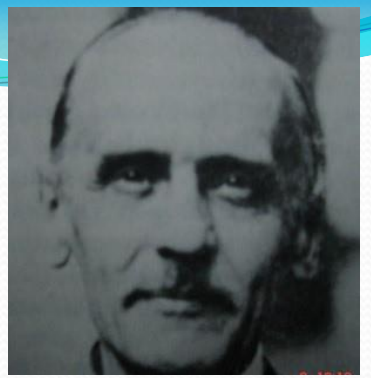
- Portugese neurologist, Lisbon: 1874-1955.
- 1927-Cerebral angiography & encephalography.
  (Nominated for nobel prize, 1928).
- Founder of neuroradiology.
- 1935- Prefrontal leucotomy for schizophrenia (Nobel prize, 1949).
- Coined term – psychosurgery.

Neurosurgical Giants
Fedor Krause (1856- 1937)



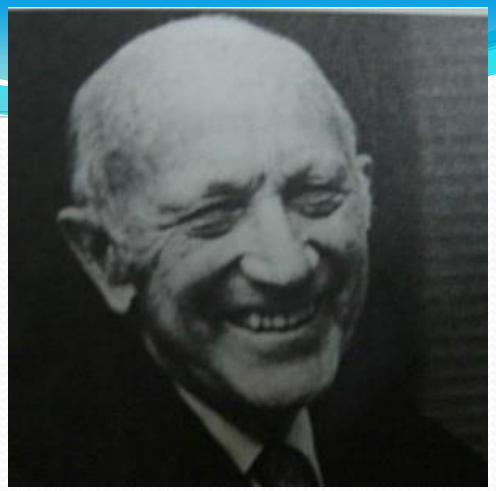
- Father of German surgical neurology.
- Extensively used radiography for diagnosis.
- 'Modified' Preganglionic resection of CN V- trigeminal neuralgia.
- Transfrontal craniotomy for pituitary tumors.
- Acoustic neuromas-sitting position.
- Posterior fossa craniectomy.
- Suprasellar subtentorial approach to pineal gland & posterior third ventricle.

Neurosurgical Giants
Otfrid Foerster (1873- 1941)



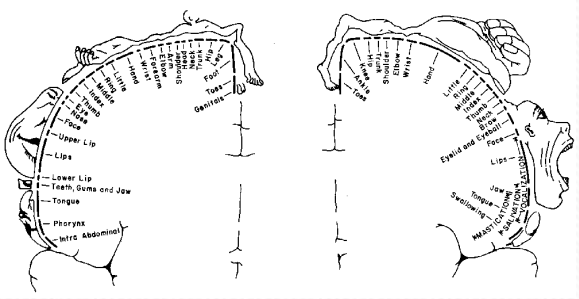
- Foerster's operation: Posterior rhizotomy for the treatment of spasticity.
- Defined dermatomal borders.
- Anterolateral cordotomy for pains.
- Successful removal of intramedullary tumor.
- Surgery for post traumatic epilepsy.
- With Altenburger: 1st EEG of brain tumor.
- Hyperventilation to evoke seizure.
- Coined psychomotor epilepsy.

Neurosurgical Giants
Wilder Graves Penfield



1891- 1976

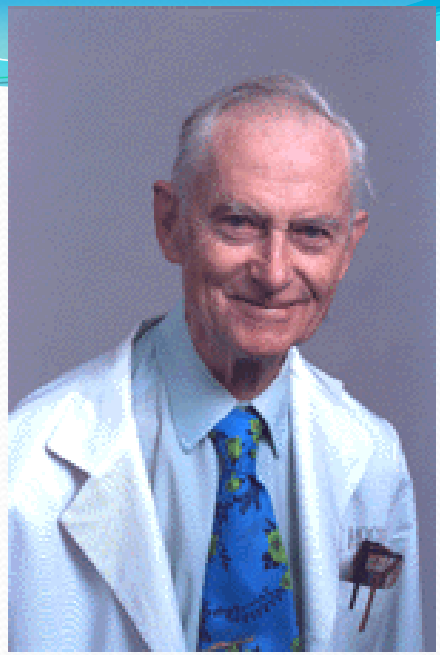
- “Greatest living canadian”.
- Centrencephalic theory of generalised epilepsy.
- t/t of seizures by destroying originating nerve cells.
- ‘Penfield dissector’.
- “Montreal neurological institute”.
- Explained Deja vu in temporal lobe epilepsy.
- Penfield’s homunculus.



Neurosurgical Giants
Arthur Earl Walker

- 1907- 1995.
- An American neurosurgeon.
- Topical application of penicillin.
- Stereotactic and functional neurosurgery.
- Post traumatic epilepsy.
- Anatomic studies on thalamic systems.
- Dandy-Walker syndrome.

Neurosurgical Giants
William H Sweet

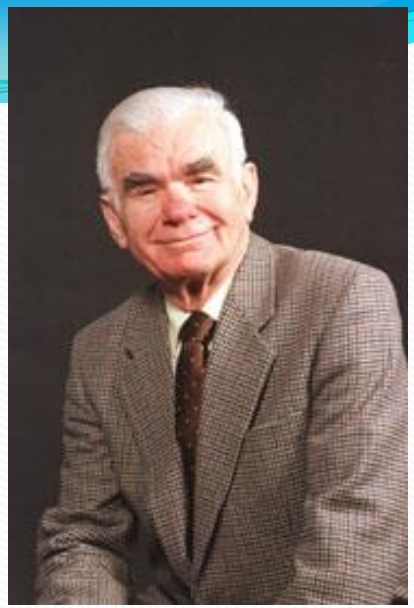


- With Gordon Brownell- PET.
- Boron Neutron Capture therapy for brain tumors.
- Pituitary stalk section –diabetic retinopathy
- Percutaneous thermal rhizotomy.
- Radiofrequency lesioning of ganglion Trigeminal neuralgia.
- Hypothermia during neurosurgical operations.
- First carotid bifurcation reconstruction.
- Editor of “Operative Neurosurgical Techniques: Indications, Methods and Results”.

Neurosurgical Giants
Irwing S Cooper

- Pioneer in functional neurosurgery.
- Parkinson Disease.
- Ligated anterior choroidal artery to control tremor and rigidity.
- Chemopallidectomy and Cryothalamectomy.
- Electrical stimulatation of Cerebellum/ Thalamus to treat spasticity.

Neurosurgical Giants
Mahmud Gazi Yasargil



- Turkish.
- Greatest 20th century neurosurgeon.
- Founder of micro neurosurgery.
- 1967: first cerebral vascular bypass under microscope.
- Invented:
  - floating microscope.
  - self retaining adjustable retractor.
  - microsurgical instruments.
  - Ergonomic aneurysm clips and appliers.
  - Leyla retractor (1977)

Neurosurgical Giants
Albert Rhoton Jr

- University of florida.
- Fatherly figure for microscopic neurosurgery.
- Brain anatomy - microsurgical perspective.
- Microneurosurgical techniques.

Neurosurgical Giants

- Herbert Olivercrona- *AVM, parasagittal meningioma.*
- Norman McOmish Dott- *aneurysm, facial pain.*
- Sir Geoffrey Jefferson- *atlas #.*
- Charles Harrison Frazier
  - *subtemporal approach (tic douloureux), cordotomy.*
- Charles Albert Elsberg- *spinal cord surgery.*
- James Clark White- *ANS, chronic pain, neuroprotection.*
- William Jason Mixter-*herniated PIVD ,spinal injuries.*
- William William Keen Jr.-Suture duramater to*decrease CSF leak.*

Neurosurgical Giants

- Max Minor Peet- *pineal gland, senory root (gasserian ganglion) division, 50% dextrose in raised ICP, arterial HTN (B/L splanchnic section), favored local anaesthesia*
- Kenneth G Mckenzie- *TCS, clips, skull tongs*
- Gerard Guiot- *hypothermia in NS, pituitary tumors (TNTS), thalamus, stereotaxic frame, parasaggital approach*
- Paul C Bucy- *premotor cortex, oliogdendroglioma*
- Alfred W Adson- *nerve regeneration, sympathectomy (PVD),ANS , upright position, vertical incision*
- 1910, Oscar Hirsch- *Trans-septal approach to pituitary*
- 1932, W Gayle Crutchfield- *skeletal traction for cervical spine fractures*
- 1952, Irving Cooper-*Chemo-pallidectomy for parkinsonism*

Neurosurgical Giants

Howard Christian Naffziger-

SDH, CSF spaces, pineal shift, occipital flap, fascial fringe closure, depressed skull fracture, orbital decompression in exophthalmos, scalenus anterior syndrome (Naffziger syndrome),

B/L jugular compression test (Naffziger's test).

Murray Falconer- *amygdalohippocampectomy, skin incisions.*

Lars Leksell- *stereotaxy, radiosurgery, Leksell rongeurs, recanalisation of cerebral aqueduct in atresia*

Frank Henderson Mayfield

Jules Hardy- *microscopic transeptal approach*

Madjid Samii- *microscopic nerve repair,cp angle tumors.*

Neuroendoscopy

- 1879, Max Nitze- *1st Endoscope.*
- 1910, L' Espinasse- *1st Neurosurgical Endoscope.*
- 1922, Walter Dandy- *Fulguration of choroid plexus.*
  Endoscopic choroid plexectomy.
- 1923, Mixter- *1st ETV using urethroscope.*

Neuroradiology

- 1895, Wilhelm Conrad Rontgen : *X rays*.
- 1901, Oppenheim : *Cranial Roentogenology*.
- Walter Dandy: *Ventriculography*.
- Arthur Schuller: *Father of modern Neuro-radiology*.
- 1947, George Moore: *Radionuclide imaging*.
- 1960s, Lars Leksell: Stereotactic Frame and *GKS*.

Microneurosurgery

1892; 'microsurgery'- neurologic pathway, amphibia.

1950s: William Lougheed in lab

1957: Theodore Kurze & William House-*acoustic neuroma.*

1960: Julius Jacobson- *1st microvascular neurosurgery MCA embolectomy.*

1962: Jules Hardy, *Microscopic TNTS.*

1964: Robert Rand, *Microscopic Aneurysm Surgery.*

1967: M. Gazi Yasargil, *1st EC-IC bypass.*

1967: Peter Jannetta & Rand, *CN. V decompression.*

Neurosurgical Society
Society of Neurological surgeons

- Started in 1920
- Founders:

-Harvey Cushing (President)

-Ernest Sachs (Secretary Treasurer)

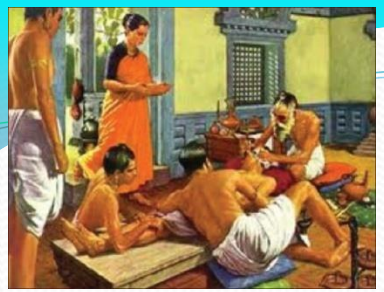
-Charles H Frazier

-Edward Archibald

Neurosurgical Society

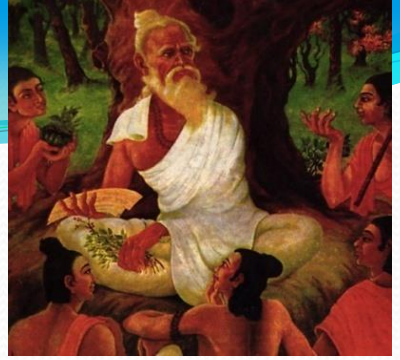
World Federation of Neurological Society

- World Federation of Neurological Society was founded in 1955.
- Brain child of Dr. William B Scoville, Connecticut.
- Sir Geoffrey Jefferson, England (President).
- First congress in 1957



Indian Neurosurgery

Legend and History



1. Hindu mythology-
   Ganesha: First recipient of head transplant.

2. Sushrutha- *'Sushrutha Samhita'*

3. 'Jivaka'- *Personal physician of Lord Buddha who Removed intracranial tumors through trephine hole.*

- 2 drugs- *'sammohini' and 'sanjivini'.*
- Neurology flourished before birth of Christ.
- *Yoga*- means to realize one's true self.

History of Indian Neurology

- The first account of a neurosurgical procedure in India is of a *transsphenoidal hypophysectomy* in 1935, which was performed by Lt. Col. Frederick Jasper Anderson.
- The first Neurological training facility was established in 1948 when the Director of Christian Medical College, Vellore extended an invitation to *Dr. Jacob Chandy* to start the Department of Neurosurgery at the college.
- In 1950, *Dr. B Ramamurthi* initiated the second neurosurgery at Government General Hospital in Madras.
- In 1951, the third neurosurgery department was initiated at Seth GS Medical College, Mumbai.

Indian Neurosurgery

- The history of neurology in India is divided into two periods:

  -Ancient and

  -Modern.

- The ancient period dates back to the mid-second millennium Before Christ (B.C.) during the creation of the Ayurvedic Indian system of Medicine, which detailed descriptions of neurological disorders called Vata Vyadhi.
- The early 20th century witnessed the birth of modern Indian medicine with the onset of formal physician training at the nation's first allopathic medical colleges located in Madras (1835), Calcutta (1835) and Mumbai (1848).
- In 1951, physicians across the field of neurology and neurosurgery united to create the Neurological Society of India (NSI).

Indian Neurosurgery

Legend and History

(Pre- Independence)

- 1935, Col Anderson- *Trans-sphenoidal Hypophysectomy*
- Bombay:
  Ardeshir P Bacha, GV Deshmukh,
  RN Cooper, AV Baliga
- Madras:
  NS Narasimhan, CP Vishwanatha Menon,
  U Mohan Rao
- Amritsar: Col R Mirajkar, Baldev Singh
- Bangalore: Bala krishna Rao

Indian Neurosurgery

Legend and History

(Post Independence)

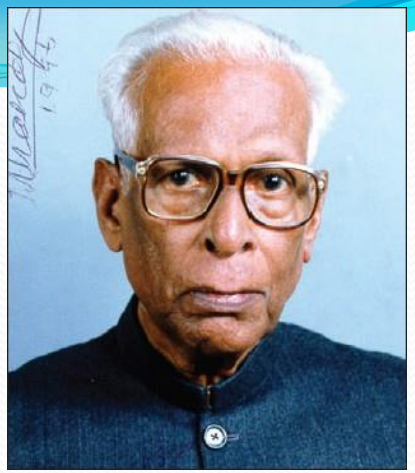
- Dr. Jacob Chandy: *(1949, 1st Neurosciences Dept. at Christian Medical College,Vellore).*
- Dr. Ram Ginde : *(1953, Neurosurgery Dept.at Seth GS Medical College & KEM Hospital, Bombay)*
- Dr. Narasimhan :(*1948,Private NSx and EEG clinic (Madras)*
- Dr. B.Ramamurthi: *(1950, Neurosurgery Dept.at Madras Medical College Later became Institute of Neurology)*
- Dr. Baldev Singh: *Founder of Modern Neurology in India.*

Indian Neurosurgery

Other Leaders

- Col. Ray: 1st Indian Army Neurosurgeon
- R N Chatterjee, Calcutta (1955)
- Victor Rao, Delhi (1956)
- Balaparameswara Rao, Vishakapatnam (1956)
- Dayanand Rao, Hyderabad (1957)
- Homi Dastur, Bombay (1958)
- R M Varma, Bangalore (1958)
- P N Tandon, Lucknow (1961); AIIMS
- Desraj Gulati, Chandigarh (1962)

Dr.Jacob Chandy
Pioneer neurosurgeon of India.

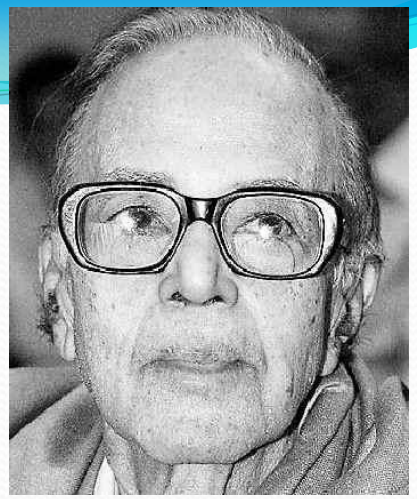


- Dr. Jacob Chandy, who passed away in 2007 at the age of 97, was born into a deeply religious Christian family in Kerala, South India.
- After obtaining his medical education at the Madras Medical College, Madras, he came to work with Dr Paul Harrison, a renowned medical missionary, in the Gulf state of Bahrain.
- He received his neurosurgical training at the Montreal Neurological Institute with Wilder Penfield and in Chicago with Theodore Rasmussen.
- At Harrison's urging, Dr. Chandy decided to return to India after completing his training to work at the Christian Medical College in Vellore.

Dr.Jacob Chandy
Pioneer neurosurgeon of India.

- He initiated the first neurosurgical training program in India at the Christian Medical College, with a distinct North American neurosurgical tradition in 1949.
- As the Principal (Dean) of the Christian Medical College, Chandy displayed his skills as a medical educator and administrator.
- In this role, he was instrumental in starting specialty training programs in several other medical and surgical disciplines.

Prof. Balasubramaniam Ramamurthi (1922–2003)



- October 24, 1950 started the neurosurgical service at the Government General Hospital, Chennai.
- December 8, 1951 - Neurological Society of India- (founder Secretary).
- First editor of Neurology India.
- 1970, Institute of Neurology.
- Established 1st comprehensive neurosciences center, South Asia.

Neurological Society of India

(Premier society of

Neurosurgeons, Neurologists and allied neuroscientists)

- In the year 1951 four young men, conceptualised, created and constituted India's first ever neurological society. Dr. Jacob Chandy, Dr. B. Ramamurthi, Dr. S.T. Narasimhan and Dr. Baldev Singh brought all the disciplines associated with the science of neurology under one roof and into the forefront with the Neurological Society of India.

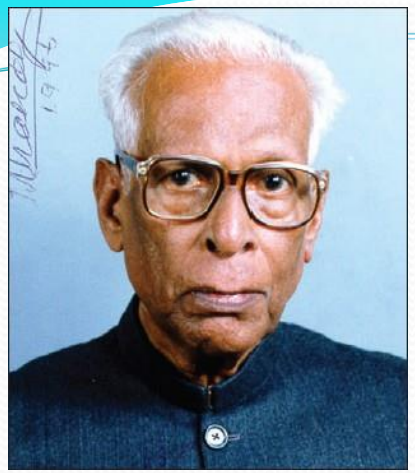
Indian Neurosurgery

Neurological Society of India

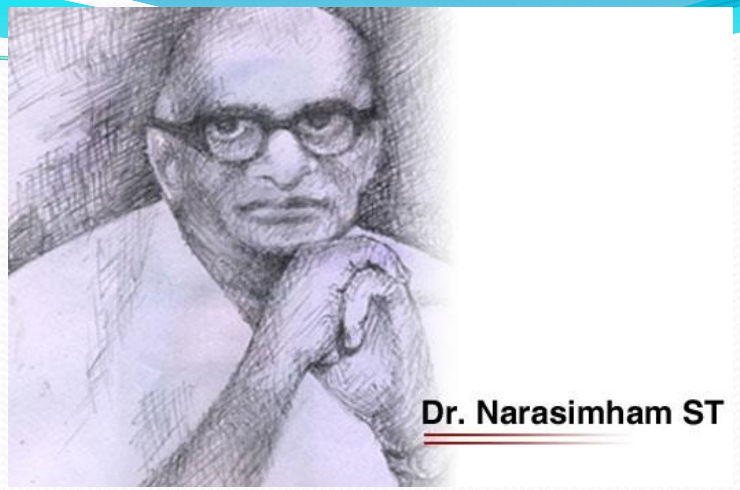
(8th December, 1951)

- Founder President: Dr .Jacob Chandy
- Founder Treasurer: Dr. Baldev Singh, Dr.S T Narasimhan
- Founder Secretary: Dr.B. Ramamurthy

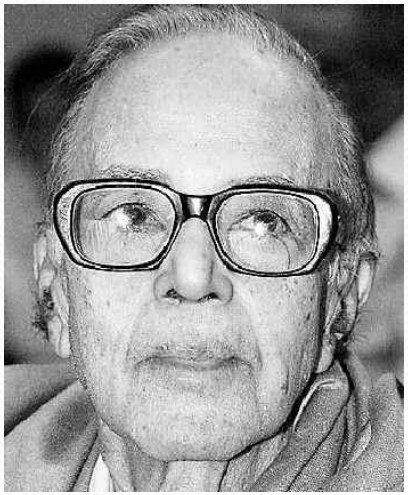
- 1st Meeting: Hyderabad, 1952; 32 members
- 1953: Journal of *Neurological Society of India(*NSI) (Neurology India).
- 1974: Started CME.
- 1985: Progress in Clinical Neurosciences.
- NSx subsection: member of WFNS.



Dr.(Prof.) Jacob Chandy



Dr. S.T. Narasimhan



Dr.Balasubramaniam Ramamurthi

Dr. Baldev Singh

Other Indian Societies

- *Neurological Society Of India*
- *Neurotrauma Socirty Of India*
- *Cerebrovascular Society Of India*
- *Skull Base Society Of India*
- *Indian Society Of Pediatric Neurosurgery*
- *Indian Academy Of Neurology*

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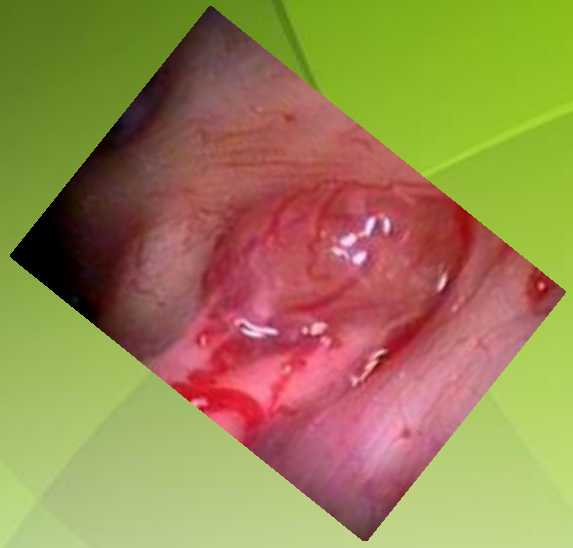

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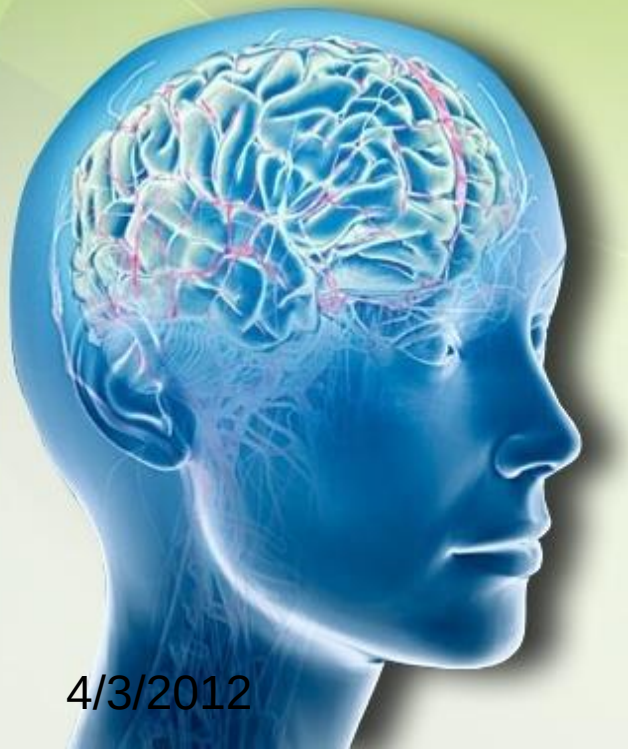
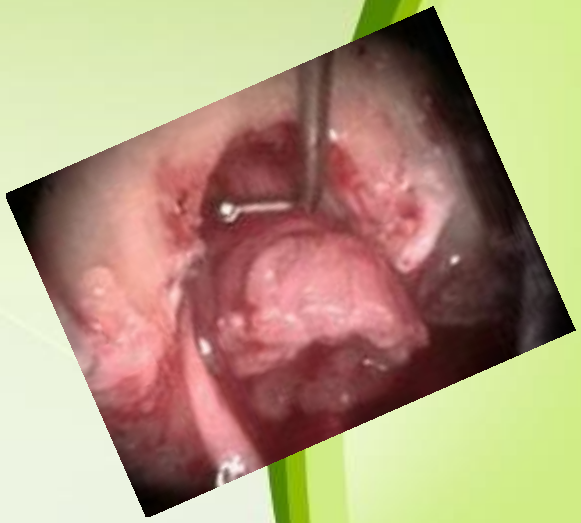




Thank you

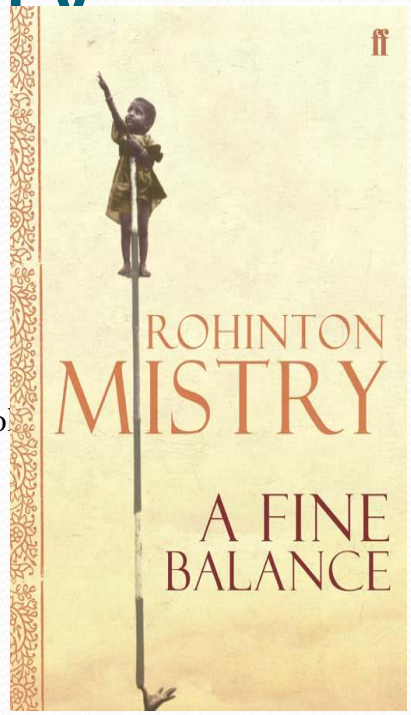
Water and Electrolyte disturbances in Neurosurgery

Dr.Shibu Pillai

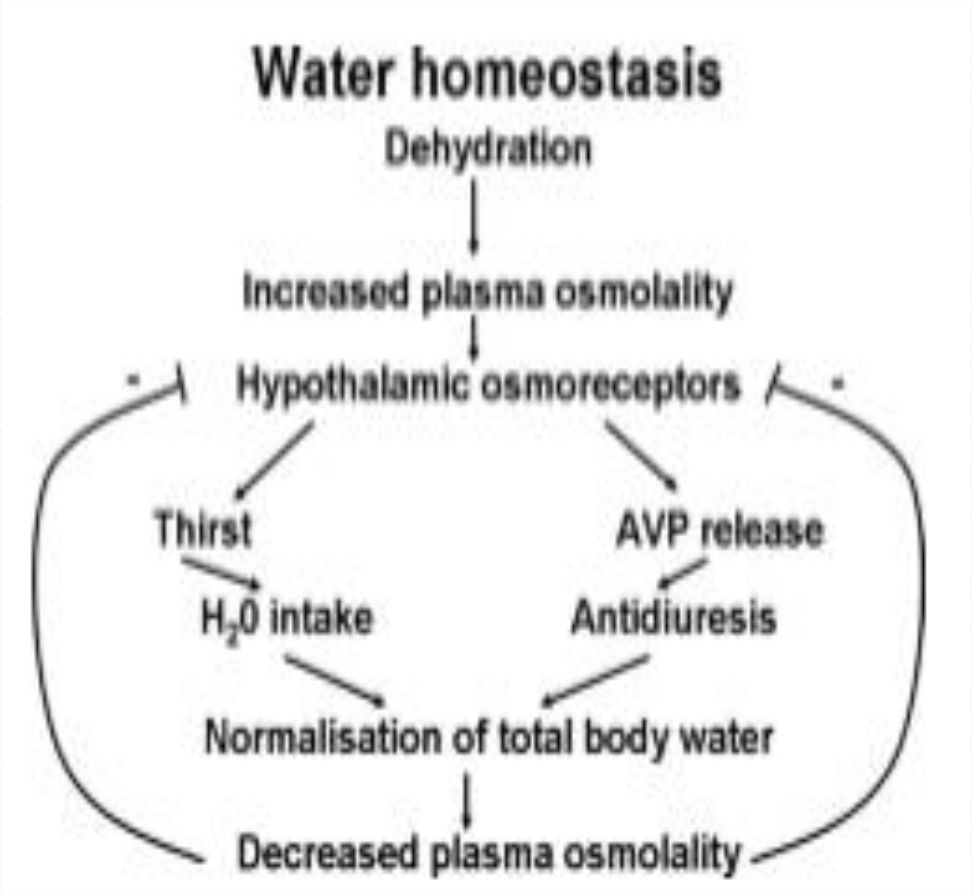
Sr.Consultant Neurosurgeon,

Acknowledgements: Dr. Subramanian Kannan and Dr.Satish, Consultant Endocrinol

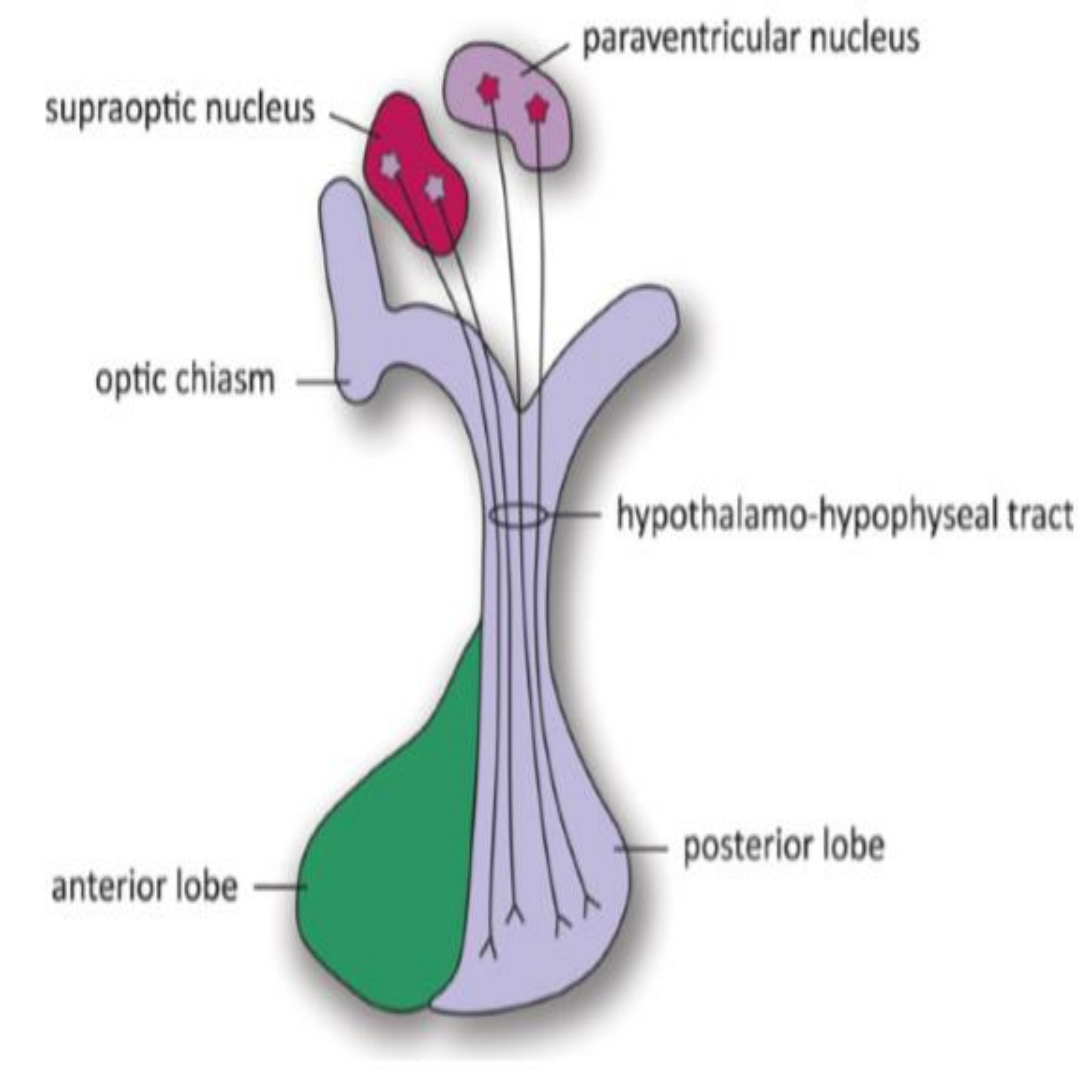
Narayana Health City, Bangalore, India



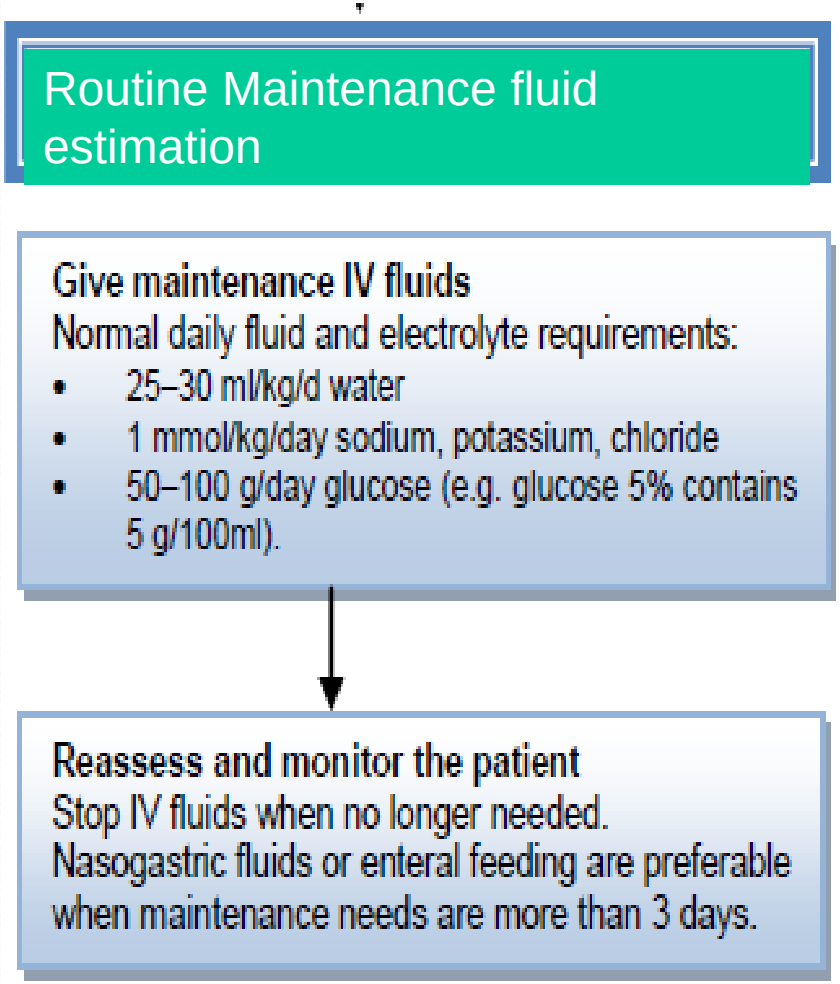
Regulation of this homeostatic process is so precise that plasma osmolality rarely varies by more than 2% (280–295 mOsm/kg).



...ior hypothalamus. When plasma
osmolality rises, these neurons depolarize and via the nucleus medianus



Fluid requirement in Adults



Fluid requirement in Babies

Use saline free Solution on Day1 And Day 2 of life

Formula Method

(100 ml for each of the first 10kg) + (50ml for each kg 11-20) + (20 ml for each additional kg) / 24hour

Example:

Calculate the hourly maintenance fluid rate for a child who weighs 25kg

(100mL x 10kg) + (50mL x 10kg) + (20mL x 5kg) / 24hrs

(1000mL) + (500mL) + (100mL) = 1600mL / 24hrs = 66.7ml/hr

Using this formula the hourly fluid maintenance for this child is 67mL/hr

4 / 2 / 1 Method

(4ml/kg for the first 10kg) + (2ml/kg for kg 11-20) + (1ml/kg for every kg above 20) = hourly rate

Example:

Calculate the hourly maintenance fluid rate for a child who weighs 25kg

(4ml x 10kg) + (2ml x 10kg) + (1ml x 5kg) = hourly rate

40ml + 20ml + 5ml = 65ml/hr

Using the 4/2/1 method, this child's hourly maintenance fluid rate is 65mL/hr

A question of balance

More or less ADH

More or less water intake

More or less excretion of Na or water

Hypernatremia and Diabetes Insipidus in NS

Settings:

- Pituitary surgery
- Craniopharyngioma
- SAH
- Traumatic Brain Injury (TBI)
- ??Radiation

Hypotonic polyuria onset 1-3 days after the surgery/trauma

Clinical diagnosis of DI: Hypotonic Polyuria

Hypotonic urine:

Urine osmolality <300 mOsm/kg or Urine Specific gravity <1.005

Polyuria

>300 ml/h for 2 consecutive hours or 2-3 ml/kg/hr

>3 liters/d

Plasma sodium greater than 145 mmol/liter

Serum Osmolality >300 mOsm/kg

All polyuria is not DI !

Excessive IV fluids

Mannitol therapy

Diuretics

Hyperglycemia (steroid worsened)

urine osmolality is typically similar to the plasma osmolality

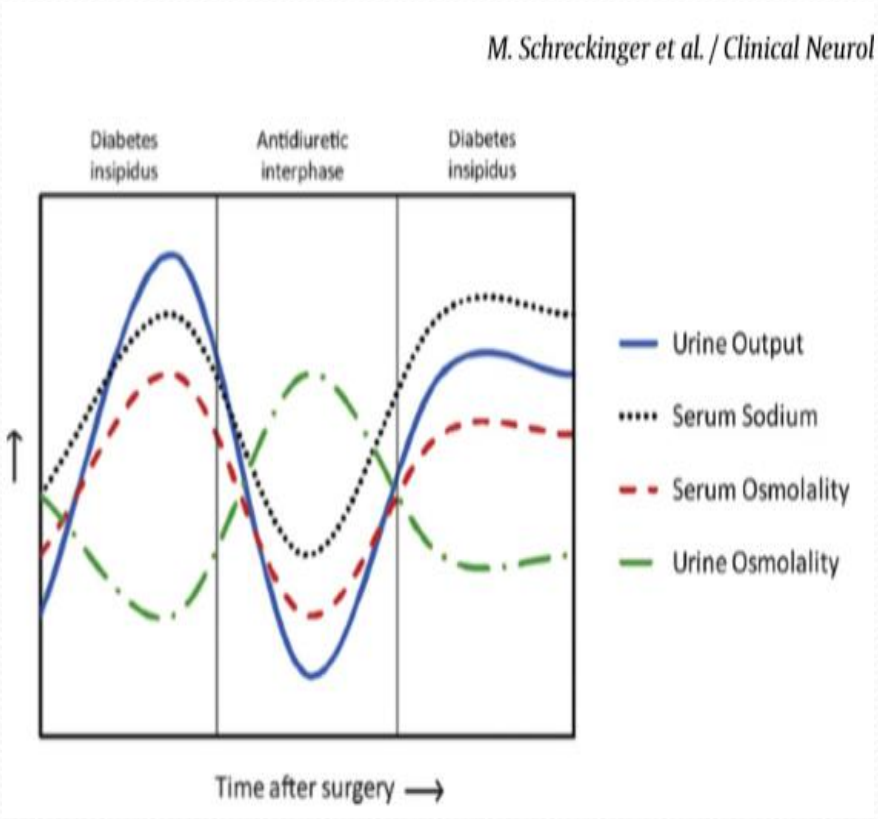
and polyuria is driven by the solute load

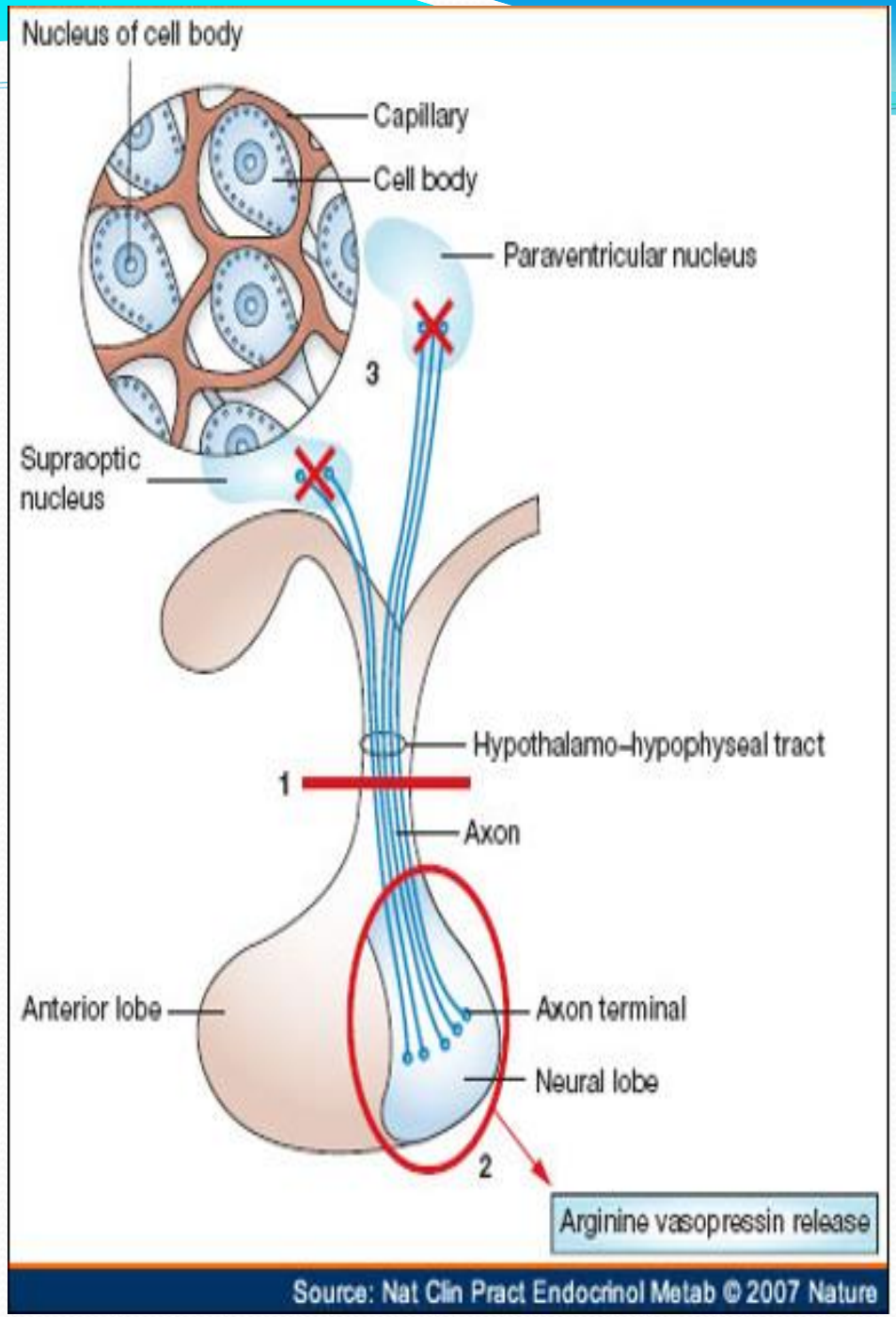
Variations in Clinical Course: Triphasic and other responses

Commonest is Transient polyuria- starts at 1-3 days and lasts 1-7 days

Partial DI- starts within 2-3 days Post-Op and then polyuria partially decreases

Permanent DI- starts within 2-3 days Post-Op




Nucleus of cell body
Capillary
Cell body
Paraventricular nucleus
3
Supraoptic nucleus
Hypothalamo–hypophyseal tract
1
Axon
Anterior lobe
Axon terminal
Neural lobe
2
Arginine vasopressin release
Source: Nat Clin Pract Endocrinol Metab © 2007 Nature

More likelihood of developing permanent DI

Craniopharyngioma

Rathke cleft cyst

CSF leak intra-operatively

Steps to prevent DI

? Decreasing dose of hydrocortisone

Free water excretion is impaired in the presence of cortisol deficiency

Management of DI: Monitoring is the key

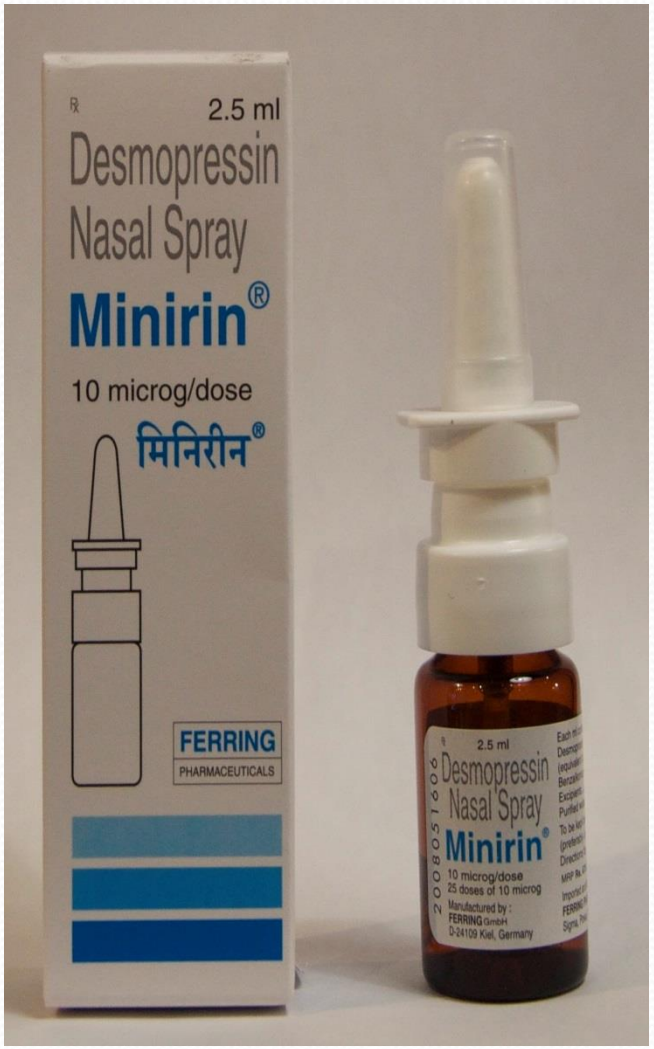
Low salt and low protein diet

Free water adlib

Dextrose solutions ONLY. NEVER SALINE solutions

Calculation of water deficit: 0.6 X body weight (kg) X [(S.Na/140)-1]. Rate = give half the deficit in 12 hours PLUS normal requirement.

Desmopressin



Safe during pregnancy for both the mother and the fetus

Desmopressin injection

A usual antidiuretic dose is 1 mcg administered subcutaneously every 12 hours.

Some patients do not respond well to subcutaneous desmopressin due to inadequate absorption.

The duration of action, as judged by increased urine osmolality, will be 12 hours or more

Desmopressin nasal spray dosing

The usual daily maintenance dose is 10 to 20 mcg intranasally once or twice a day.

Using a urine osmolality of 400 mosmol/kg or greater to judge effect

Mean duration of action after 10 and 20 mcg intranasal doses was seven to nine hours, respectively

Desmopressin oral tablet dosing

The absorption of desmopressin in normal persons is decreased by 40 to 50 percent when taken with meals

The oral form has about one-tenth to one-twentieth the potency of the nasal form because only about five percent is absorbed from the gut.

Thus, a 0.1 mg tablet is the equivalent of 2.5 to 5 mcg of the nasal spray

The initial dose of the tablet form is 0.05 mg (one-half a 0.1 mg tablet) at bedtime

Desmopressin

Desmopressin dosing is an empiric process

Hyponatremia can usually be avoided by giving the minimum desmopressin dose that is required to control the polyuria.

The initial aim of therapy is to reduce nocturia, thereby permitting adequate sleep.

The size of and necessity for a daytime dose is determined by the effectiveness of the evening dose

Other drugs for DI

Chlorpropamide

Carbamazepine

Thiazide diuretics

Paracetamol

Adipsic Diabetes Insipidus

Craniopharyngiomas

ACOM clipping

TBI

Extensive surgery of pituitary adenomas

Neurosarcoidosis

Adipsic DI

Other Hypothalamic dysfunction

Polyphagia, obesity, and sleep apnea

Seizures, disturbances of temperature regulation

Thromboembolic complications consequent to the increased hematocrit

Adipsic DI

Free water prescription

DDAVP

LMWH

Hyponatremia

Incidence of significant hyponatremia (plasma sodium 130 mmol/liter) in patients admitted to the neurosurgical unit in Beaumont Hospital between January 2002 and September 2003

Diagnosis	**No. of patients with plasma sodium <130 mmol/liter**	**Total (n)**	**%**
All patients	187	1698	11
SAH	62	316	19.6
Intracranial tumor	56	355	15.8
TBI	44	457	9.6
Pituitary surgery	5	81	6.2
Spinal disorders	4	489	0.81

Adapted from M. Sherlock *et al.*: Incidence and pathophysiology of severe hyponatraemia in neurosurgical patients. *Postgrad Med J* 85: 171–175, 2009 (1), © The Fellowship of Postgraduate Medicine

Differential diagnosis of Hyponatremia in Neurosurgical patients

Key to diagnosis: Accurate assessment of Volume status of the patient and Urine Sodium

Fluid status	Clinical features	Urine sodium <20 mmol/liter	Urine sodium >40 mmol/liter
Hypovolemic	Tachycardia, hypotension, low CVP, raised urea	Dehydration	Cerebral salt wasting, diuretics, Addison's disease, salt-wasting nephropathy
Euvolemic	Normal pulse, normal blood pressure	SIADH with fluid restriction	SIADH, carbamazepine, postoperative pneumonia, ACTH insufficiency, hypothyroidism
Hypervolemic	Edema, ascites, basal crackles on auscultation	Inappropriate iv fluids, cirrhosis, cardiac failure	Renal failure

CONFUSION IN ICU: SIADH vs CSW

Hypotension ?sepsis ? Glucorticoid deficiency

Tachycardia ?fever ?inotropes

Raised ICP

IV Fluids

CVP available: great!

Track and correlate hourly intake to urine output, blood pressure changes, changes in sodium, changes in urea

Diagnostic criteria for SIADH

Plasma osmolality <275 mOsm/kg

Urine osmolality >100 mOsm/kg

Urine sodium > 40 mmol/L in presence of normal dietary sodium

Euvolemia(heart rate, body weight, CVP 6-10cmH_2O, urea, haematocrit, albumin,serum bicarbonate, serum uric acid)

Exclusion of glucocorticoid (clue in HI: hypotension/hypoglycemia) and thyroid deficiency

Normal renal function

Treatment

CSW: I.V. Sodium Chloride in large volumes for few days because self limiting

Stop Drugs causing Euvolemic hyponatremia: carbamazepine, oxcarbamazepine, ACE inhibitors, omeprazole, SRI

SIADH: fluid restriction –down to 500-1000ml (acute) to 1500ml/day (chronic)

What about SAH patients with potential or ongoing vasospasm?

??1500-2000 ml/day of normal saline

??add pressors early

Close observation of parameters

Severe, Symptomatic hyponatremia

Calculation of sodium deficit=(140-S.Na) X 0.6 X Body weight(kg)

Central pontine myelinolysis

Deficit correction rate=/< 0.5 meq/L/hour and 25 meq/L in 48 hours

Rate of infusion of 3% NaCl solution is approximately =0.6 X Body weight (kg)

Furosemide 20-40mg/day helps to clear free water

Thank you

AED selection & Evidence based guidelines to clinical practice:

Dr. Dwarakanath Srinivas
Additional Professor
Neurosurgery, NIMHANS

Antiepileptic Drug

- A drug which decreases the frequency and/or severity of seizures in people with epilepsy
- Treats the symptom of seizures, not the underlying epileptic condition
- Goal—maximize quality of life by minimizing seizures and adverse drug effects
- Currently no “anti-epileptogenic” drugs available.

Therapy Has Improved Significantly

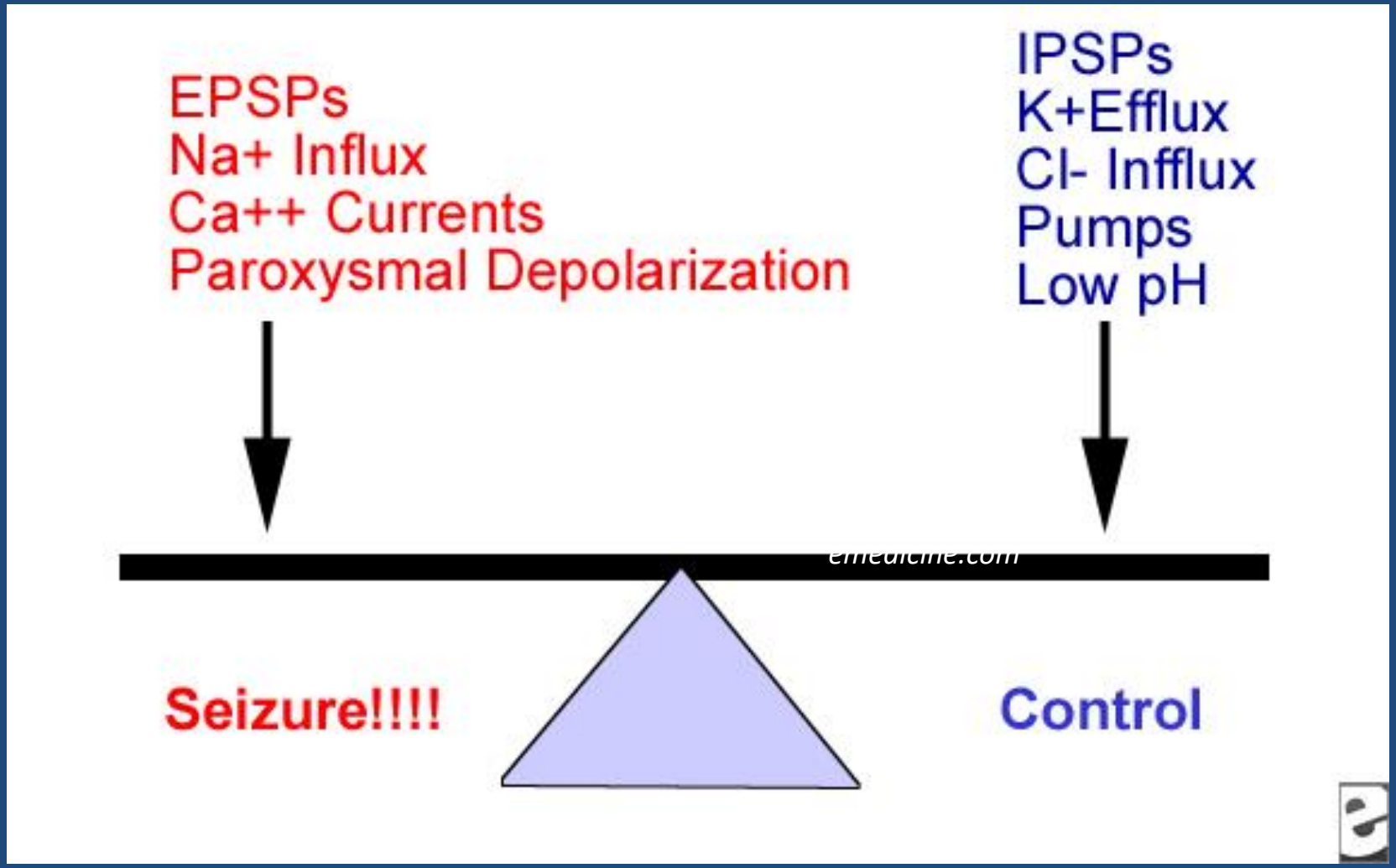
"Give the sick person some blood from a pregnant donkey to drink; or steep linen in it, dry it, pour alcohol onto it and administer this".

– Formey, Versuch einer medizinischen Topographie von Berlin 1796, p. 193

Current Pharmacotherapy

- Approx. 60% of all people with epilepsy can become seizure free with **single drug therapy**
- In another 20% the seizures can be drastically reduced, with **more than one drug.**
- ~ 20% epileptic patients, seizures are refractory to currently available AEDs.

Cellular Mechanisms of Seizure Generation

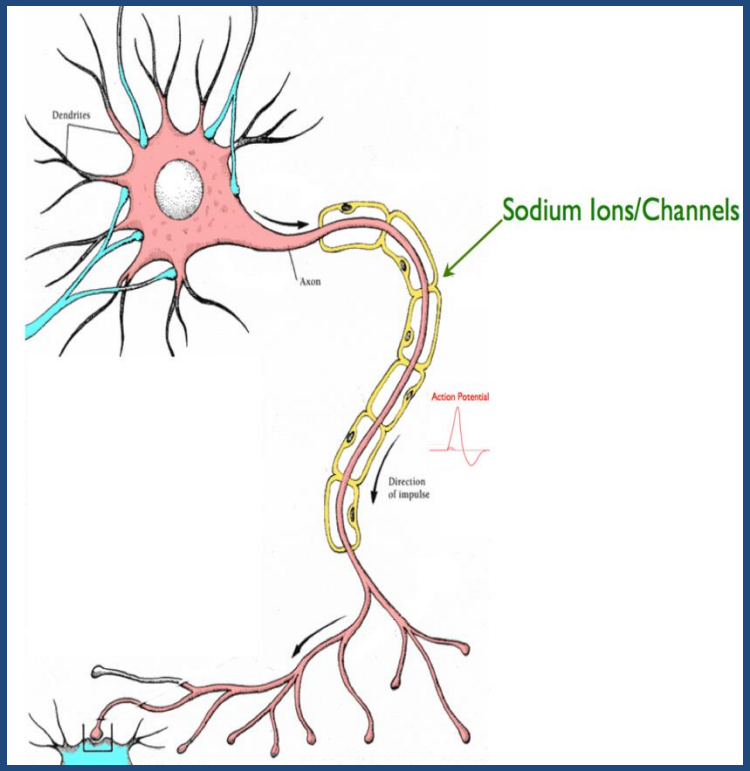


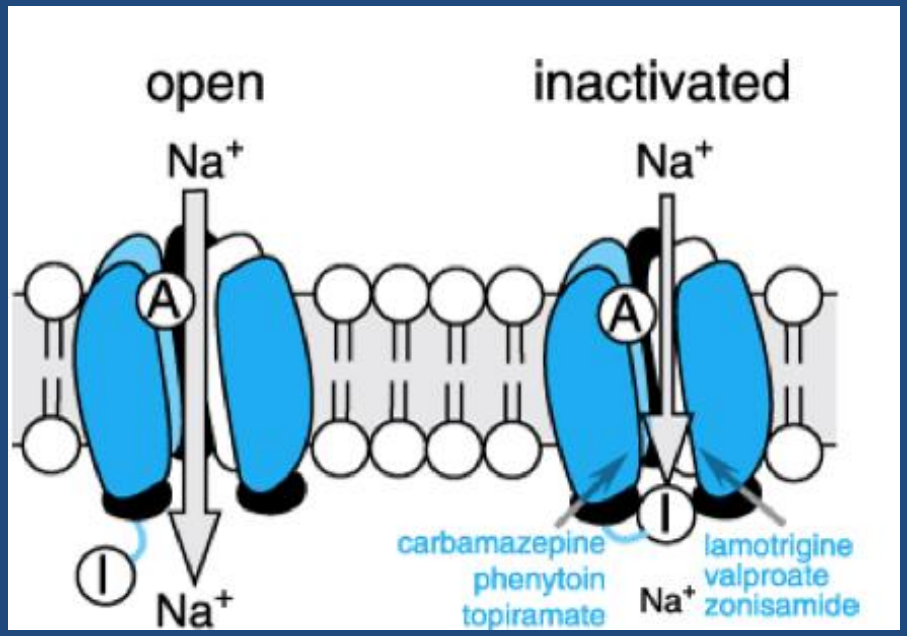
Mechanism of action

3 main categories of therapeutics:

1. Inhibition of voltage-gated Na+ channels to slow neuron firing.
2. Enhancement of the inhibitory effects of the neurotransmitter GABA.
3. Inhibition of calcium channels.

Na+ Channel Inhibitors





blocks voltage-gated sodium channels by selectively binding to the channel in the inactive state and slowing its rate of recovery

Na channel inhibitors

- ✓ Phenytoin (Dilantin, Eptoin)
  - ✓ Fosphenytoin
- ✓ Carbamzepine (Tegretol)
  - ✓ Oxcarbazepine (Trileptal)
- ✓ Valproic Acid (Valproate, Depakote)
- ✓ Lamotrigine (Lamictal)
- ✓ Topiramate (Topamax)
- ✓ Zonisamide (Zonegran)

Phenytoin

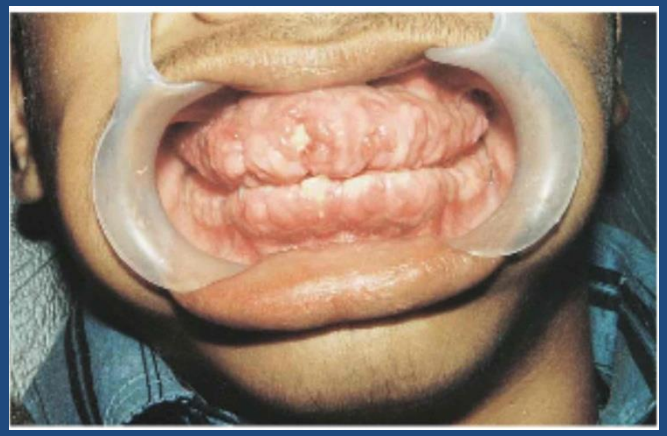
- Oldest non-sedative antiepileptic drug.
  - Indications:
    - First choice for partial and generalized tonic-clonic seizures .
    - Some efficacy in clonic, myoclonic and atonic seizures.
    - status epilepticus
    - No effect on infantile spasms or absence seizures

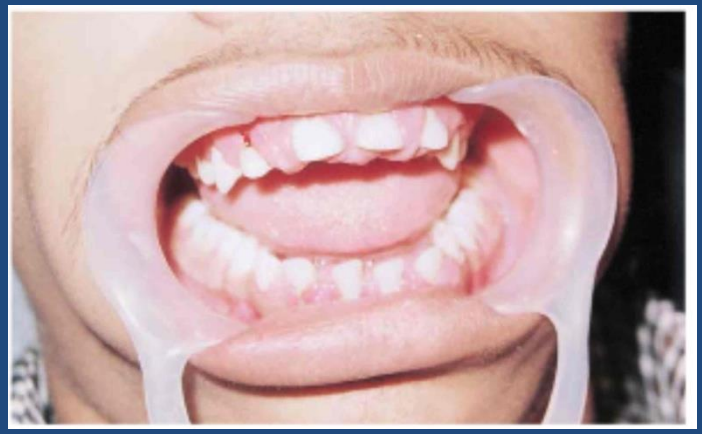
Pharmokinetics

- Potent enzyme inducing properties;
- lowers the level of
  - CBZ, VA, FBT, LTG, TRM, ZNS, and TGB.
  - warfarin, oral contraceptives, and cyclosporine.
- **PHT and Valproate**:
  - PHT is highly protein bound and is displaced from serum proteins by valproate resulting in increase of the free fraction of PHT.
- Elimination is saturable at therapeutic concentrations resulting in a nonlinear relationship between maintenance doses and steady-state concentrations.
- in the upper therapeutic range, small increases in dosage can cause relatively large increases in levels.
- Steady-state levels are achieved in 2 to 3 weeks of a stable maintenance dose.

Side effects:

- Bradyarrhythmia, Hypotension, as well as skin necrosis on i.v.
- Dose related CNS side effects-Nystagmus, ataxia, and lethargy.
- Hypersensitivity reactions
- Gingival hyperplasia, hirsutism, peripheral neuropathy, and bone demineralization





Fosphenytoin

- Prodrug
- rapidly converted to phenytoin in the blood,
- providing high levels of phenytoin within minutes.
- Can also be administered intramuscularly.
- Phenytoin sodium should never be given IM because it can cause tissue damage and necrosis.

Carbamazepine

- ***Was a, not is a*** exclusive drug of first choice for partial and secondarily generalized seizures.
- The elimination kinetics of CBZ is linear.
- ***Autoinduction of its metabolism,***
  - which results in an increase in CBZ clearance during the first weeks of treatment
  - the elimination half-life of CBZ decreases from about 36 hours to 10 to 20 hours.
- ***No parenteral preparation for CBZ***.

SIDE EFFECTS

- ***Dose-related CNS toxicity***
  - is the most common side effect
  - subsides with time,
  - careful titration,
  - closely related to CBZ serum levels.
- Neutropenia, Severe blood dyscrasias, hyponatremia, movement disorders, allergic rashes, and hypersensitivity syndrome are rare ADRs.
- Contraindications:
    - May exacerbate absence or myoclonic seizures.
    - Blood disorders
    - Liver disorders

Oxcarbazepine

- **Prodrug** and is rapidly metabolized to the active compound monohydroxycarbamazepine.
- No parenteral preparation.
- Half-life of 10 to 15 hours.
- level can be reduced by 30% to 40% by PHT, CBZ, or PB.
- OXC is an enzyme inducer, but less so than phenytoin, phenobarbital, or carbamazepine.
- same narrow spectrum of efficacy as carbamazepine, with efficacy limited to partial onset and secondarily generalized seizures.

- **Fewer adverse effects than CBZ, phenytoin.**
- **Hyponatremia is more common with OXC** than with carbamazepine and is more frequent in adults, especially in the elderly.
- The **side effects of OXC are similar** to those of CBZ, although they may be **somewhat milder**.
  - somnolence, dizziness, ataxia, diplopia, and blurred vision.
  - An allergic rash can occur, and cross-reactivity with carbamazepine is at least 25%.

Valproate

- Broad spectrum of activity.
- Other Mechanisms of Action:
    - 1) Some inhibition of T-type Ca2+ channels.
    - 2) Inhibition of GABA transaminase.
- Drug of first choice in patients with primary (idiopathic) generalized epilepsies
- It is also highly effective against absence seizures, generalized tonic-clonic seizures, and myoclonic seizures, infantile spasms and Lennox-Gastaut syndrome

Two types of pharmacokinetic interactions

1. Its **metabolism is accelerated by inducing drugs** such as phenytoin, carbamazepine, phenobarbital, and primidone.
2. VPA **itself can prolong the elimination (and raise the levels) of other drugs**, such as phenobarbital, ethosuximide, lamotrigine, and felbamate.
   - Highly bound to serum proteins and tends to displace other drugs, such as phenytoin.
   - In adults, the half-life is 13 to 16 hours in the absence of inducing drugs; and 9 hours in induced patients.

Adverse Effects

- Weight gain (30-50%)
- Dose-related tremor
- Transient hair loss
- Polycystic ovary syndrome and menstrual disturbances
- Bone loss
- Ankle swelling
- **Fatal hepatotoxicity** and **pancreatitis** are the most serious
- Thrombocytopenia, in conjunction with impaired platelet function, fibrinogen depletion, and coagulation factor deficiencies may cause ***excessive bleeding***.
- The common practice of withdrawing VPA before elective surgery is recommended, although reports have found ***no objective evidence of excessive operative bleeding in neurosurgical patients*** maintained on VPA.
- In women of childbearing age, increased risk for ***neural tube defects*** in the fetus.

Lamotrigine

- Relatively long half-life; Twice a day.
- Other Mechanism of Action:
  - May *inhibit synaptic release of glutamate*.
- Indications:
  - Adjunct therapy (ages 2 & up):
    - Simple & complex partial seizures
    - Generalized seizures of Lennox-Gastaut Syndrome
  - Monotherapy (adults):
    - Simple & complex partial seizures and Absence seizures
- Contraindications:
  - May make myoclonic seizures worse

Topiramate

- Broad-spectrum AED. Other Mechanism of Action:
  - Enhances post-synaptic GABA receptor currents.
- Indications:
  - Adjunct therapy for partial and primary generalized
  - seizures in adults and children over 2.
  - Decreases tonic and atonic seizures in children with Lennox-Gastaut syndrome.

Common side effects

Somnolence, impaired concentration, abnormal thinking, and impaired verbal memory, anorexia, weight loss, and **nephrolithiasis**, as well as metabolic acidosis and decreased sweating in children.

Zonisamide

- Sulfonamide derivative that has a broad spectrum of action
- Other Mechanism of Action:
    - Inhibits T-type Ca2+ currents.
    - Binds to GABA receptors.
    - Facilitates dopaminergic and serotonergic neurotransmission.
- Long half-life of 60 hours once or twice daily.
- Serum levels are lowered by PHT, CBZ , PB, PRM, and VA.
- No known effect on the kinetics of other drugs.

- Indications:
  - Approved for adjunct treatment of partial seizures in adults.
  - Appears to have a broad spectrum:
    - Myoclonic seizures
    - Infantile spasms
    - Generalized & atypical absence seizures
    - Lennox-Gastaut Syndrome
- Side effects

  Psychomotor slowing, behavioral or psychiatric side effects, allergic rash. Metabolic acidosis ,hypohidrosis, **nephrolithiasis (1% to 2%),** paresthesias.

Enhancement of GABA Inhibition

1. Barbiturates

   Phenobarbital and Primidone.

2. Benzodiazepine drugs:
   - Diazepam (Valium).
   - Lorazepam (Ativan).
   - Clonazepam.
   - Clorazepate
3. Tiagabine.

– Mechanism of Action for first two is Increase in the frequency of GABA-A-activated Cl- channel opening.

– While for Tiagabine it is Inhibition of GABA transporter (GAT-1) – reduces reuptake of GABA by neurons and glial cells.

Phenobarbital and Primidone

- The use of PB and PRM for the treatment of seizures has declined steadily
  - ***more sedative and behavioral side effects***
- relatively little systemic toxicity.
- **PB** has excellent pharmacokinetic properties,
  - **can be administered intravenously and intramuscularly**,
- effective in patients with status epilepticus,
- inexpensive.

Other Side effects

- allergic reactions.
- Dupuytren's contracture
- frozen shoulder.

Primidone

- PRM has independent pharmacologic activity
  - probably **is not just a prodrug**.
  - much shorter half-life than PB.
  - Daily dosage requirements of PRM are about five times higher
- Other enzyme-inducing drugs, in particular **phenytoin, accelerate the conversion of PRM to PB**, thereby increasing the PB-to-PRM serum level ratio.
- **Partial and secondarily generalized seizures** as carbamazepine and phenytoin but were found to be associated **with more treatment failures because of mostly early CNS side effects**.

Uses

- Status epilepticus and neonatal seizures,
- Prophylaxis of febrile seizures.
- PB is C/I in absence seizure and PRM is C/I in Porphyria.

Benzodiazepine drugs

- Diazepam and lorazepam are used in treatment of status epileticus.
  - Diazepam is painful to inject
  - lorazepam is more commonly used in acute treatment.
- Only clonazepam & clorazepate approved for long-term treatment.
  - Clorazepate
    - In combination for partial seizures
  - Clonazepam
    - Lennox-Gastaut Syndrome, myoclonic, atonic, and absence seizures
    - Tolerance develops after about 6 months
- Contraindications:
  - Diazepam in children under 9
  - Narrow angle glaucoma

- Adverse Effects:
  - Hypotonia, Dysarthria (Difficulty in articulating words, caused by impairment of the muscles used in speech)
  - Muscle in-coordination (clonazepam)
  - Behavioral disturbances (especially in children)
    - Aggression, Hyperactivity, Irritability and Difficulty concentrating

Tiagabine

- Approved in 1998 as an adjunct therapy for partial seizures in patients at least 12 years old.
- Narrow spectrum of activity and CNS side effects, not found widespread use.
- Contraindications:
    - Absence seizures
- No other pharmacokinetic interactions.
- No severe or potentially life-threatening side effects.
- Difficulty with concentration, nervousness, and emotional lability may be seen.

Calcium Channel Blockers

- Ethosuximide
- Pregabalin.
- Gabapentin.

Ethosuximide

- Mechanism of Action:
  - Reduces low -threshold Ca2+ currents (T currents) in the thalamic neurons.
  - Half-life is ~60 hr in adults; ~30hr in children.
- Indications:
  - First line for absence seizures
- Contraindications:
  - May exacerbate partial & tonic-clonic seizures
- Adverse Effects:
  - Psychotic behavior, Blood dyscrasias, Persistent headaches
  - Anorexia, Hiccups , Lupus-like syndromes
  - Parkinson-like symptoms
  - photophobia

Gabapentin

- Originally designed to be a centrally acting GABA agonist. Selective inhibition of v-g Ca2+ channels containing the α2δ1 subunit.
- Focal onset seizures and Rolandic epilepsy with centrotemporal spikes on EEG.
- Eliminated entirely by the kidneys, has no pharmacokinetic interactions.
- Serious side effects are exceedingly rare. Can exacerbate myoclonic & absence seizures.
- excessive weight gain and behavioral problems in children are common.

Pregabalin

- Very similar to gabapentin in most aspects, except **that PGB has better bioavailability than gabapentin**.
- Half-life of PGB is about 6 hours, twice or three times daily dose.
- Not bound to serum proteins.
- Eliminated mostly unchanged in urine, and has no pharmacokinetic interactions.
    - Approved in 2005 for Adjunct therapy for partial & secondarily generalized seizures
- Other uses:
    - Prescribed for neuropathic pain, fibromyalgia

- Most common side effects
  - Dizziness, somnolence, dry mouth.
  - Peripheral edema, blurred vision, weight gain.
  - difficulty with concentration.
- Because of a slight potential for recreational abuse and dependence, it is a controlled substance .

Miscellaneous AEDs :

Felbamate.

Levetiracetam.

Felbamate

- Potential serious side effects and multiple pharmacokinetic interactions---**used only in special circumstances**. (**drug of third choice** for **Lennox-Gastaut syndrome, focal onset** seizures)
- Raises levels of phenytoin and valproate.
- Common side effects –
  - nausea and vomiting,
  - anorexia and weight loss,
  - somnolence, and insomnia.
  - relatively high incidence of potentially **fatal aplastic anemia** and **hepatic necrosis**
- Multiple proposed mechanisms including :
  - Voltage-dependent sodium channels blockade.
  - competing with the glycine-coagonist binding site on the N-methyl-D-aspartate (NMDA) glutamate receptor
  - Potentiation of GABA actions.

Levetiracetam

- Short half-life of 6 to 8 hours, still used in twice daily dose.
- Linear pharmacokinetics
  - low Protein binding
  - No pharmacokinetic interactions.
- Broad-spectrum antiepileptic drug.
- Indications-
  - Partial and secondarily generalized seizures
  - GTCS in idiopathic general epilepsies, and
  - Myoclonic seizures in JME.
  - Absence seizures,
  - Rolandic epilepsy and
  - Posthypoxic and postencephalitic myoclonus.

- Virtually no serious or life-threatening side effects.
- Side effects-
  - Somnolence, asthenia, dizziness,
  - Emotional lability, depression, and psychosis.
  - Behavioral problems (children).
- Rare-
  - Allergic reactions, liver failure; and
  - Bone marrow suppression.

Selecting an AED

- **Patient factors**
  - Seizure type and syndrome
  - Age
  - Gender
  - Pregnancy potential
  - Comorbidities
  - Comedications
  - Individual lifestyle (once-daily dosing, etc)

AED factor

- Spectrum of efficacy
- Mechanism of action
- Indications (e.g. monotherapy, children, etc)
- Tolerability / safety
- Neuropsychological implications
- Dosing frequency, titration complexity, simplicity of use
- Drug–drug interaction profile
- Teratogenic potential (pregnancy registries)
- Availability, cost, reimbursement

Table 4. Summary of studies and level of evidence for each seizure type and epilepsy syndrome

Seizure type or epilepsy syndrome	Class I studies	Class II studies	Class III studies	Level of efficacy and effectiveness evidence (in alphabetical order)
Adults with partial-onset seizures	4	1	34	Level A: CBZ, LEV, PHT, ZNS Level B: VPA Level C: GBP, LTG, OXC, PB, TPM, VGB Level D: CZP, PRM
Children with partial-onset seizures	1	0	19	Level A: OXC Level B: None Level C: CBZ, PB, PHT, TPM, VPA, VGB Level D: CLB, CZP, LTG, ZNS
Elderly adults with partial-onset seizures	1	1	3	Level A: GBP, LTG Level B: None Level C: CBZ Level D: TPM, VPA
Adults with generalized onset tonic–clonic seizures	0	0	27	Level A: None Level B: None Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA Level D: GBP, LEV, VGB
Children with generalized-onset tonic–clonic seizures	0	0	14	Level A: None Level B: None Level C: CBZ, PB, PHT, TPM, VPA Level D: OXC
Children with absence seizures	1	0	7	Level A: ESM, VPA Level B: None Level C: LTG Level D: None
Benign epilepsy with centrotemporal spikes (BECTS)	0	0	3	Level A: None Level B: None Level C: CBZ, VPA Level D: GBP, LEV, OXC, STM
Juvenile myoclonic epilepsy (JME)	0	0	1	Level A: None Level B: None Level C: None Level D: TPM, VPA

THANK YOU

What about K+ channels?

- K+ channels have important inhibitory control over neuronal firing in CNS—repolarizes membrane to end action potentials
- K+ channel agonists would decrease hyperexcitability in brain
- So far, the only AED with known actions on K+ channels is valproate
- Retiagabine is a novel AED in clinical trials that acts on a specific type of voltage-dependent K+ channel (M-channel)

Epilepsia, 54(3):551–563, 2013
doi: 10.1111/epi.12074

SPECIAL REPORT

Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes

*Tracy Glauser, †Elinor Ben-Menachem, ‡Blaise Bourgeois, §Avital Cnaan, ¶Carlos Guerreiro, #Reetta Kälviäinen, **Richard Mattson, ††Jacqueline A. French, ‡‡Emilio Perucca, §§Torbjorn Tomson for the ILAE Subcommission on AED Guidelines

*Comprehensive Epilepsy Center, Division of Neurology, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio, U.S.A.; †Institution for Clinical Neuroscience, Sahlgrenska Academy, University of Göteborg, Göteborg, Sweden; ‡Department of Neurology, The Children's Hospital and Harvard Medical School, Boston, Massachusetts, U.S.A.; §Division of Biostatistics and Study Methodology, Center for Translational Science, Children's National Medical Center, Washington, District of Columbia, U.S.A.; ¶Department of Neurology, University of Campinas (UNICAMP), Hospital das Clínicas, Campinas, Sao Paulo, Brazil; #Department of Neurology, Kuopio Epilepsy Center, Kuopio University Hospital, Kuopio, Finland; **Department of Neurology, Yale University School of Medicine, Yale New Haven Hospital, New Haven, Connecticut, U.S.A.; ††Comprehensive Epilepsy Center, New York University Langone Medical Center, New York, New York, U.S.A.; ‡‡Clinical Pharmacology Unit, Institute of Neurology, IRCCS C. Mondino Foundation, University of Pavia, Pavia, Italy; and §§Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden

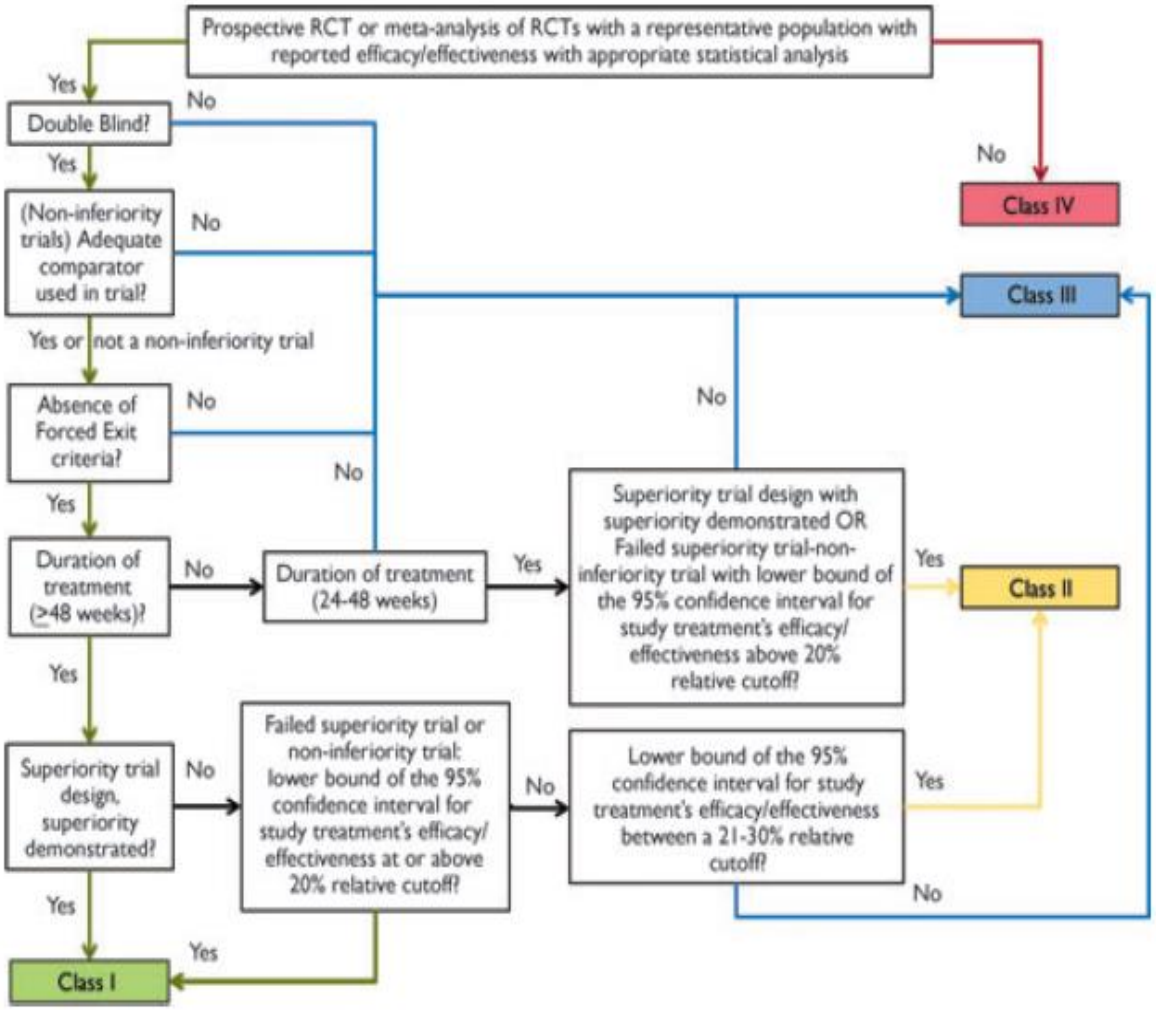


Figure 1.
Application of evidence rating criteria for efficacy/effectiveness studies.
Epilepsia © ILAE

Table 3. Relationship between clinical trial ratings, level of evidence, and conclusions

Combination(s) of clinical trial ratings	Level of evidence	Conclusions
≥ 1 Class I studies or meta-analysis meeting class I criteria sources OR ≥ 2 Class II studies	A	AED established as efficacious or effective as initial monotherapy
1 Class II study or meta-analysis meeting class II criteria	B	AED probably efficacious or effective as initial monotherapy
≥ 2 Class III double-blind or open-label studies	C	AED possibly efficacious or effective as initial monotherapy
1 Class III double-blind or open-label study OR ≥ 1 Class IV clinical studies OR Data from expert committee reports, opinions from experienced clinicians	D	AED potentially efficacious or effective as initial monotherapy
Absence of directly applicable clinical evidence upon which to base a recommendation	E	No data available to assess if AED is effective as initial monotherapy
Positive evidence of lack of efficacy or effectiveness based on class I to IV studies OR Significant risk of seizure aggravation based on class I to IV studies	F	AED established as ineffective or significant risk of seizure aggravation

Principles of AEDs administration

- what seizure type the patient probably has?
- Correctly diagnose the seizure type and syndrome in order to select the most appropriate AED.
- Discuss the possible choices (depending on seizure type) with the patient and make the choice together- efficacy and potential side effects.
- If at all possible, start with slow titration.
- Monitor side effects and communicate with the patient.

- Select the most appropriate initial treatment with not only focusing on seizure freedom, but also considering factors such as: tolerability profile, titration regimen, simplicity of use (once daily) and impact on overall patient outcomes.
- Selection of an appropriate monotherapy should consider the current level of evidence available in conjunction with patient factors and AED characteristics.

- Once the decision is made to use combination therapy, the perceived best combination is one that produces best efficacy with fewest adverse effects.
- •Different AEDs appropriate to the epilepsy syndrome should be added as necessary in sequence, increasing the dose of each slowly to obtain the best response.
- The law of diminishing returns may require patient and doctor to accept the persistence of some seizures once a range of treatment options has failed and no surgically remediable epilepsy detected.

- AEDs generally have good oral absorption and bioavailability.
- Most metabolized in liver but some excreted unchanged in kidneys e.g. Gabapentin.
- Classic and older AEDs generally have more severe CNS sedation than newer drugs (except ethosuximide)

The established, or older, drugs are no longer the drugs of first choice for the majority of seizure types.

Many newer AEDs offer the main advantages of relative safety, favorable pharmacokinetics and interaction profiles, or the absence of need for blood level or other routine laboratory monitoring.

Conclusion about Guidelines

- When selecting a patient`s AED, all relevant variables and not just efficacy and effectivenes should be considered.
- Guidelines or evidence reviews can be seen as additional tool, not the only tool in the clinician armamentarium.
- Absence of evidence does not mean evidence of absence.

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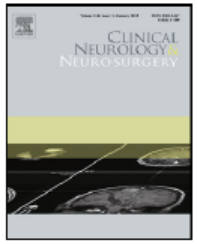

Considerations in prophylaxis for tumor-associated epilepsy: Prevention of status epilepticus and tolerability of newer generation AEDs

Thomas Wychowski[a], Hongyue Wang[b], Liana Buniak[a], J. Craig Henry[a], Nimish Mohile[a,*]

[a] Department of Neurology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA
[b] Department of Biostatistics and Computational Biology, University of Rochester, New York, USA

Conclusion:

More than half of GBM patients ultimately developed TAE and 35% of seizure-free patients at diagnosis went on to have at least one seizure. Prophylactic AED therapy did not reduce Post-op TAE but may have prevented SE. Patients with brain tumors were associated with high relative risk of mortality in critically ill patients with refractory status epilepticus; as well as SE can be associated with significant morbidity and higher cost, thus; results would strongly support the use of AED prophylaxis.

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Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

Levetiracetam compared to phenytoin for the prevention of postoperative seizures after craniotomy for intracranial tumours in patients without epilepsy

K. Kern [a], K.M. Schebesch [a], J. Schlaier [a], E. Hansen [b], G.C. Feigl [a], A.T. Brawanski [a], M. Lange [a,*]

[a] Department of Neurosurgery, University Medical Center Regensburg, Franz-Josef-Strauss-Allee 11, Regensburg 93053, Germany
[b] Department of Anesthesiology, University Medical Center Regensburg, Regensburg, Germany

A total of 235 patients were treated with an antiepileptic drug: 81 patients received LEV, and 154 patients, PHT. Two patients receiving LEV (2.5%) and seven receiving PHT (4.5%) had a seizure despite this treatment but the difference was not significant (p = 0.66). LEV may be a valid option for perioperative anticonvulsant medication in patients with contraindications for PHT who have undergone a craniotomy.

Epilepsy in patients with brain tumours

Lancet Neurol 2007; 6: 421–30

- ✓ A consensus statement has advised discouragement of antiepileptic drugs or their discontinuation after the fi rst operative week in patients with brain tumours who have never had seizures.
- ✓ Enzyme-inducing antiepileptic drugs (CBZ) is discouraged; because of concomitant Chemotherapeutic agents.
- ✓ Existing brain damage from previous surgery or radiotherapy increases the risk of developing side-effects from antiepileptic drugs.
- ✓ Lamotrigine, valproic acid, and topiramate are first-line or second-line antiepileptic agents, although levetiracetam or gabapentin can be used as add-on treatment to a firstline antiepileptic drug.
- ✓ Prefer to start with valproic acid, and to add levetiracetam if needed.

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

The efficacy of antiepileptic drug prophylaxis in the prevention of early and late seizures following repair of intracranial aneurysms

Daniel M.S. Raper[a,*], Nima Kokabi[b], Martin McGee-Collett[c]

[a] Royal North Shore Hospital, Reserve Road, St. Leonards, New South Wales 2065, Australia
[b] Wollongong Hospital, Wollongong, New South Wales, Australia
[c] Department of Neurosurgery, Royal Prince Alfred Hospital, Sydney, Australia

The timing of AED prophylaxis had no effect on the incidence of early or late seizures in either group. AED use was associated with an increased rate of early seizures. Postoperative seizures remain important adverse outcomes following aneurysm repair, but despite their traditional role, the routine use of AED should be reconsidered carefully. AED should be used for prophylaxis only when the potential benefit of their use outweighs the likely harm.

Interaction of AEDs with OCPs

AEDs that *decrease the effectiveness* of oral contraceptive steroids

Carbamazepine Oxcarbazepine
Felbamate
Phenobarbital Primidone Phenytoin
Topiramate (doses >200 mg/day)

AEDs that do not decrease the effectiveness of oral contraceptive steroids

Benzodiazepines Gabapentin Tiagabine Zonisamide
Lamotrigine Levetiracetam Valproic acid Vigabatrin

CEREBRAL DECONGESTANTS

Dr. Dwarakanath Srinivas
Additional Professor
Neurosurgery, NIMHANS

Cerebral Oedema

- **Increase in brain water content above normal (80%) in response to primary brain insult.**

- **Intracranial hemorrhage**
  - **Traumatic brain injury**
  - **Ruptured aneurysm**
  - **Arteriovenous malformation**
  - **Other vascular anomalies**
- Neoplasms
- Inflammation (Meningitis, Abscess)
- Metabolic (Hyponatremia, Hepatic Encephalopathy)
- Vasculitis
- Ischemic infarcts
- Hydrocephalus
- Pseudotumor cerebri

CLASSIFICATION

Cytotoxic

- Cell swelling
- Substrate and energy failure
- Gray and White matter
- Resistant
- TBI, Hypoxia, Ischaemia

Interstitial

- Impaired absorption
- Acute hydrocephalus
- Resistant

Vasogenic

- BBB breakdown
- Neoplasm, inflammatory
- White matter
- Response to Steroids

EFFECTS

- Focal or Global oedema
- Raised/Normal ICP
- Decreased Cerebral perfusion (CPP)
- Compromised Regional or Global CBF
- Compression (Herniation)

INDICATIONS FOR DECONGESTION

- RAISED ICP DUE TO ANY CAUSE

Treatment of raised ICP

General Principles –

- First address the cause of the raised ICP.
- Monroe-Kellie doctrine
- Try for reduction of any one space in the intracranial compartment – CSF, blood or brain volume.
- Ideal to have a ICP monitoring system.
- Use the method which rapidly and effectively brings down the ICP in as little time as possible.

Management

- General Measures
  - Head and Neck positioning, oxygenation
  - Maintenance of Perfusion
  - Normothermia, Glycemic control
  - Seizure control
  - Nutrition
- Specific Measures
  - Controlled Hyperventilation
  - Osmotherapy
  - Diuretics
  - Corticosteroids
  - Pharmacological Coma
  - Hypothermia

Therapeutic Modalities for reduction of ICP

- **CEREBROSPINAL FLUID VOLUME**
  - Acetazolamide
  - Furosemide
  - Corticosteroid
  - External drainage(ventriculostomy)
  - Internal Drainage
  - Ventriculoperitoneal shunt

Therapeutic Modalities for reduction of ICP

- **CEREBRAL BLOOD VOLUME**
  - Hyperventilation
  - Head elevation
  - Barbiturates

Therapeutic Modalities for reduction of ICP

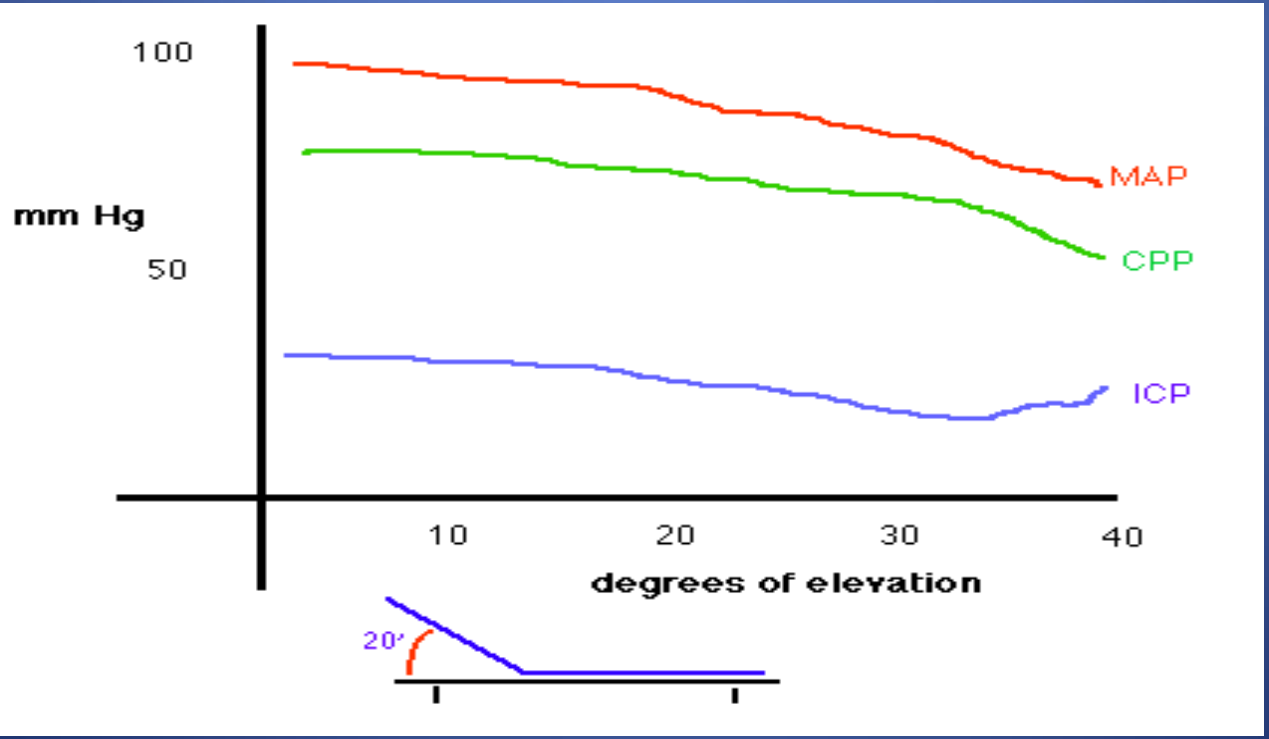
- BRAIN VOLUME
  - CPP management
  - Lund protocol
  - Antihypertensive
  - Fluid restriction
  - Corticosteroids
  - Barbiturates
  - Osmotic agents (Mannitol, glycerol, urea)
  - Diuretics
  - Hypothermia

Strategies

- Physiological
- Pharmacological-
  - Anti-edema medications
  - anesthetic agents
- Surgical

Physiological

- Head end elevation 30 degrees facilitates venous drainage and possibly CSF drainage.
- 30^0: reduction in ICP without compromising CPP
- Head position should be neutral to reduce any possible compression of jugular veins.

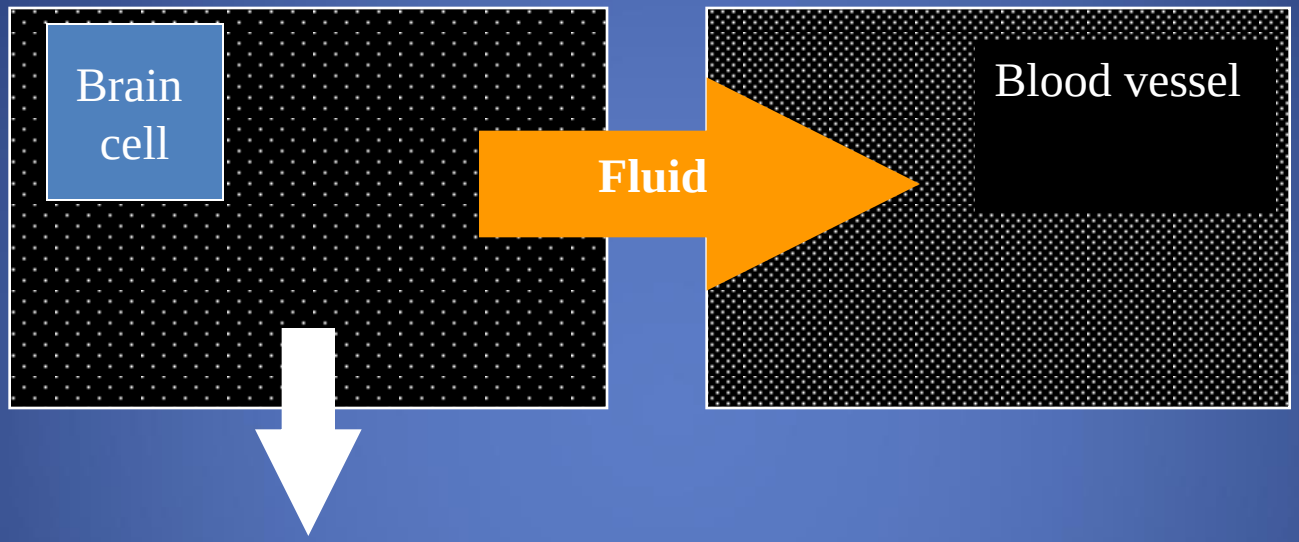


Osmotic therapy

Mechanism of action:

- The solute used must be relatively restricted in its entry across the BBB.
- Osmotic gradient is necessary.
- Once solute reaches equilibrium in both plasma and brain cell intracranial volume returns to original state
- Min of 10mosm/l gradient in serum osmolality needed

Hyperosmolar Therapy: Increase Blood Osmolarity



Osmosis: Fluid will move from area of lower osmolarity to an area of higher osmolarity

Osmotic therapy

- Mechanism of Rebound: Limiting factor in the use of osmotherapy.
  - Damaged BBB allows the solutes into brain leading to influx of water and increase in the brain edema.
  - Solute reaches equilibrium in the CSF and rate of clearance of the solute from the CSF decreases, leading to more water in CSF, hence increasing ICP.

Osmotic therapy

MANNITOL

- Metabolically inert
- Remains in the extracellular compartment
- Excellent diuretic, with a MW of 182 Daltons.
- Dose 1gm/kg over 10minutes
- Time to action 20min, peak at 90min; ICP returns to baseline by 4hours

- Influences intracranial compliance: hence improvement in neurological status can occur despite little measurable effect on ICP.
- Biphasic effect; rapid infusion $\Rightarrow$ osmotic gradient across BBB $\Rightarrow$ drawing water in intravascular compartment $\Rightarrow \Downarrow$ brain volume $\Downarrow$ ICP
- Osmotic diuretic $\Rightarrow$ cleared by kidneys $\Rightarrow$
- $\Uparrow$ free water clearance $\Uparrow$ serum osmolality $\Rightarrow$ prolonged intracellular dehydrating effect

Rheological effects of mannitol

- IV mannitol
  - leads to transient acute expansion of the intravascular cerebral blood volume:
  - hypoviscosity which leads to cerebral vessel constriction and reduction in ICP. (intact autoregulation)
  - causes shrinkage of RBCs
  - improves deformation of cell wall
  - improves flexibility and thus tissue oxygenation.
  - Decreases CSF production
  - Antioxidant

Disadvantages of Mannitol

- Rebound Phenomenon.
- Congestive cardiac failure
- Controversy: Causes a compartmentalised ICP difference , thus increasing the chances of unilateral brain shifts and herniation syndromes.
- Hypokalemia and hypernatremia
- Hyperosmolar state
- Renal failure due to hypoperfusion

Glycerol

- Trivalent alcohol.
- Used systemically and orally to decrease the ICP.
- Not metabolically inert. Partially metabolised to CO2 and water.
- Oral Glycerol decreases the ICP in 30-60min.
- DOSAGE: 1.2gm/kg, maintenance 0.5-1gm/kg every 3-4 hrs
- IV Preparation: 10% glycerol in 0.4 N saline
- Complications: Hemolysis, hemoglobinuria, renal failure and hyperosmolar coma.

Hypertonic saline

Mechanism of action:

- Membrane stabilising effect helps in preserving BBB.
- Direct vasodilatation of pial vessels
- Reduction of blood viscosity due to enhancement of the intravascular volume
- Rapid absorption of cerebrospinal fluid
- Restoration of the normal membrane potentials
- Local dehydration of brain tissue

Hypertonic saline

Complications

- Coma, seizures and rebound phenomenon.
- Systemic effects: CCF , Hypokalemic acidosis.
- Deranged platelet aggregation
- Phlebitis and renal failure

Dosage:

- ICP reduction best with 23.4 % saline
- 10%, 7.2% and 3% have also been used
- Dosage of 3% saline 1-2ml/kg Q12h. over 5 min.

Mannitol Vs Hypertonic saline

Mannitol

- High dose for TBI
- 4 – 6 hr duration
- σ = 0.9
- Chances of Renal insufficiency, hypotension, Hyperkalemia, pulmonary oedema

Hypertonic Saline

- More effective in Refractory cases
- > 8hr duration
- σ = 1.0
- Better outcome in Ischemic stroke and SAH – vasospasm
- Risk of Myelinosis, hypomagnesimia, hypocalcemia, arrhythmias

Loop diuretics

- **Used in conjunction with mannitol to treat raised ICP.**
- **Furosemide works synergistically with mannitol**
  - **Removes free water**
  - **Appropriate in patients with fluid overload**
  - **Decreases CSF production**
  - **Decreases edema in pathological areas (disrupted BBB)**

Steroids

- Dexamethasone is the most widely used
- Steroids are effective in reducing ICP in tumors.
- Chemotoxic edema
- Mechanism of action:
  -reduction in CSF production
  -membrane stabilisation & restoration of BBB
  -reduction in ICP secondary to anti edema action
  -improves CSF bulk outflow at arachnoid villi
- Dosage:
  Dexamethasone: 10mg loading dose f/b 4mg Q6H

Anaesthetic agents

Pharmacological Coma

- ↓sed cerebral metabolism → ↓ed CBF → ↓ed CBV

Barbiturates (Pentobarbital), Propofol

- Barbiturates - to treat refractory intracranial hypertension
  Loading dose- 10–20 mg/kg, repeated in 5 mg/kg boluses.
  Maintenance- 1-4 mg/kg/hr
- Barbiturates produce cardiac suppression & hypotension
- Invasive cardiopulmonary monitoring may be needed

Sedation, Analgesia and relaxation

- **Lidocaine** may be used intravenously, or as a local anesthetic, to prevent ICP surges
- **Etomidate** is generally favored as a sedative because of its rapid onset of action and minimal side effects, particularly in the multitrauma patient with hemodynamic instability
- **Thiopental** is classically recommended for patients with elevated ICP who are haemodynamically stable
- **Midazolam** provides some cerebral protective effects, but it can also cause hypotension in the dose required for RSI. In addition, its onset of action is slower and less reliable than thiopental.
- **Ketamine** is contraindicated because it can increase MAP and ICP.
- **Rocuronium** is preferred for paralysis

Hyperventilation:

- Goal for ICP control ⇒ to lower pCO_2 to 30 mmHg / 25–30 mmHg in extreme cases. Respiratory alkalosis ⇓ ICP by cerebral vasoconstriction and reduced CBV.

- Peak effect ⇒ within 30 min.

- Over next 1–3 hours effect gradually ⇓, as compensatory acid-base buffering mechanisms correct alkalosis within CNS.
-
- Patients ⇑ ICP [hyperemia & ⇑ CBV] ⇒ effect is prolonged, and hyperventilation may be the treatment of choice.

- Tapered slowly over 4–6 hours ⇒ abrupt cessation ⇒ vasodilation and rebound ⇑ ICP.

Hypothermia

- Causes a decrease in ICP by reducing the $CMRO_2$ and depression of metabolic requirements.

- Body temperature has to be reduced to 32.8deg.
- (Fall in ICP was average of 45% to a maximum of 80%.)

- At 27deg C: cardiac arrhythmias

- Problems during rewarming: seizures, drowsiness, coma

SURGICAL DECOMPRESSION

- Allows for the expansion of edematous tissue outside the cranial vault
- Issues:
  - Patient Selection
  - Timing of surgery

THANK YOU

BREAKING BAD NEWS

Dr. Seema Mehrotra

Additional Professor of Clinical Psychology

NIMHANS, Bangalore

WHAT IS BAD NEWS?

Bad News

Any news that drastically & negatively alters the patient's view of his/her future.

Buckman (1984)

Breaking Bad News

- Why is it difficult?

Sources of Difficulty……

- Discomfort with negative emotions
- Messenger of bad news… causing hurt, taking away hope ?
- Perceived lack of skills in handling awkward questions
- Feeling not- equipped to manage the emotional impact on self and others

Breaking Bad News

- Best Strategy ?

Breaking Bad new

Changing trends……

- Non disclosure
- Full disclosure
- Individualistic disclosure

GOALS?

Goals : Breaking Bad news

- To determine the patient's knowledge and expectations and readiness to hear the bad news
- **To provide important information** in accordance with needs and patient's preferences
- To provide support & assistance to reduce the emotional impact of the news
- To jointly develop a strategy in the form of an action-plan

Breaking Bad News :

- STEPS?

Breaking Bad News: Steps

- Getting the ***Setting*** right / preparation **S**
- Find out what the patient knows (***Perceives***) **P**
- Find out what the patient wants to know **I**
  (Obtain **Invitation)**
- Giving information ***(Knowledge)*** ***K***
- Responding to ***Emotions*** **E**
- ***Summary*** & ***Strategy*** : Closing **S**
  - (support, planning, follow up)

(Not necessarily a single point event)

SPIKES Protocol (Baile et.al,2000)

Points to remember…….

- Bad news : Has objective & subjective dimensions
- Do not assume what is known
- Full information vs. right information
- Explore preferences- ?presence of a significant other/family member

Points to remember…….

- Identify concerns
- Explore resources
- Small bits-pause-check (Ask-tell-ask)
- Pace/language-individualize
  (Clarity and appropriateness)

Encourage to ask rather then only tell

- Encourage : There are no stupid questions
- Empathize with distress regarding uncertainty (e.g. wish statement)
- Preferences for quantitative information varied
- Respect need to maintain some ambiguity about future & need to hope

Do not just acknowledge a fact Address the associated emotions…

Acknowledging emotions

Purposes served: - Signals given:

- You are allowed to feel this
- I can somewhat understand
- We can discuss

Points to remember…….

- Convey respect

  (where, how, who)

- Honesty…. I don't know

- False reassurance X

- Sensitivity to family-centered decision making

Points to remember…….

Dealing with family's resistance :

- Explore reasons for keeping secret…
- Emotional and other costs of withholding information
- Negotiate access to patient to check understanding of situation by the patient
- Address concerns: optimum information and support following disclosure

Points to remember…..

- Explain options
- Check understanding
- Offer to make recommendations & assistance
- Discuss dilemmas and concerns
- Discuss time-frame for decisions
- Repeat information- critical for decision making, check
- Arrange support & review

Points to remember…

- Monitor one's own feelings and behaviors

- Discussion with others in the team:

  support, feedback & preparation

Learning through practice and through observations

Collaborate.. collaborate.. collaborate..

Points to remember….

What is most valued

by the clients in the process:

Clarity

Competence

Caring attitude

(Knowledge, skills, attitude)

THINGS GO WRONG WHEN

WE TRY TO ESCAPE BY…….

- Inappropriate Delegation
- No Effort to Validate Distress
- Focus on facts alone- Intellectualization
- Minimization & empty reassurance

THINGS GO WRONG WHEN:

WE REACT IN ANGER TO

- To Denial
- To Idolization
- To Rehearsal of the Story
- To ‘Unreasonable’ Demands
- To Anger & Blame

Breaking Bad news

Point to Ponder….

- *What NEEDS to be discussed*
- *What MIGHT be discussed*
- *What SHOULD be discussed*
- *What OUGHT to be kept silent*

……are Issues that require negotiation

- (Kutner,1991)

No time…..?

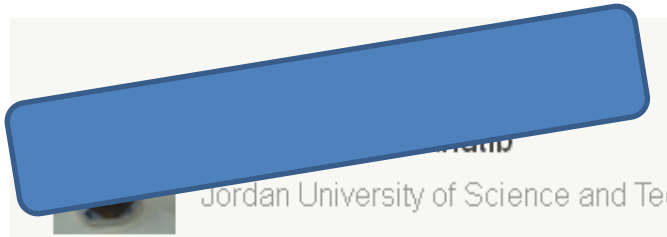
- Being aware of the ideal- helps to move closer towards it
- Like any other skill-efficiency improves with practice
- Collaboration
- Integration with an overall approach to communication (not a single-point event)

Thank you!

Research Methodology and how to choose thesis topics: frequently unanswered questions

Dr N Girish

Additional Professor of Epidemiology,
CENTRE FOR PUBLIC HEALTH, NIMHANS,
Bengaluru – 560029
girishnrao@yahoo.com



Jordan University of Science and Technology

Can someone suggest a research topic in neurosurgery?

Considering conducting research in neurosurgery

TOPICS

Neurobiology and Brain Physiology | Pediatric Neurosurgery | Functional Neurosurgery | Neurosurgery

Sep 12, 2013

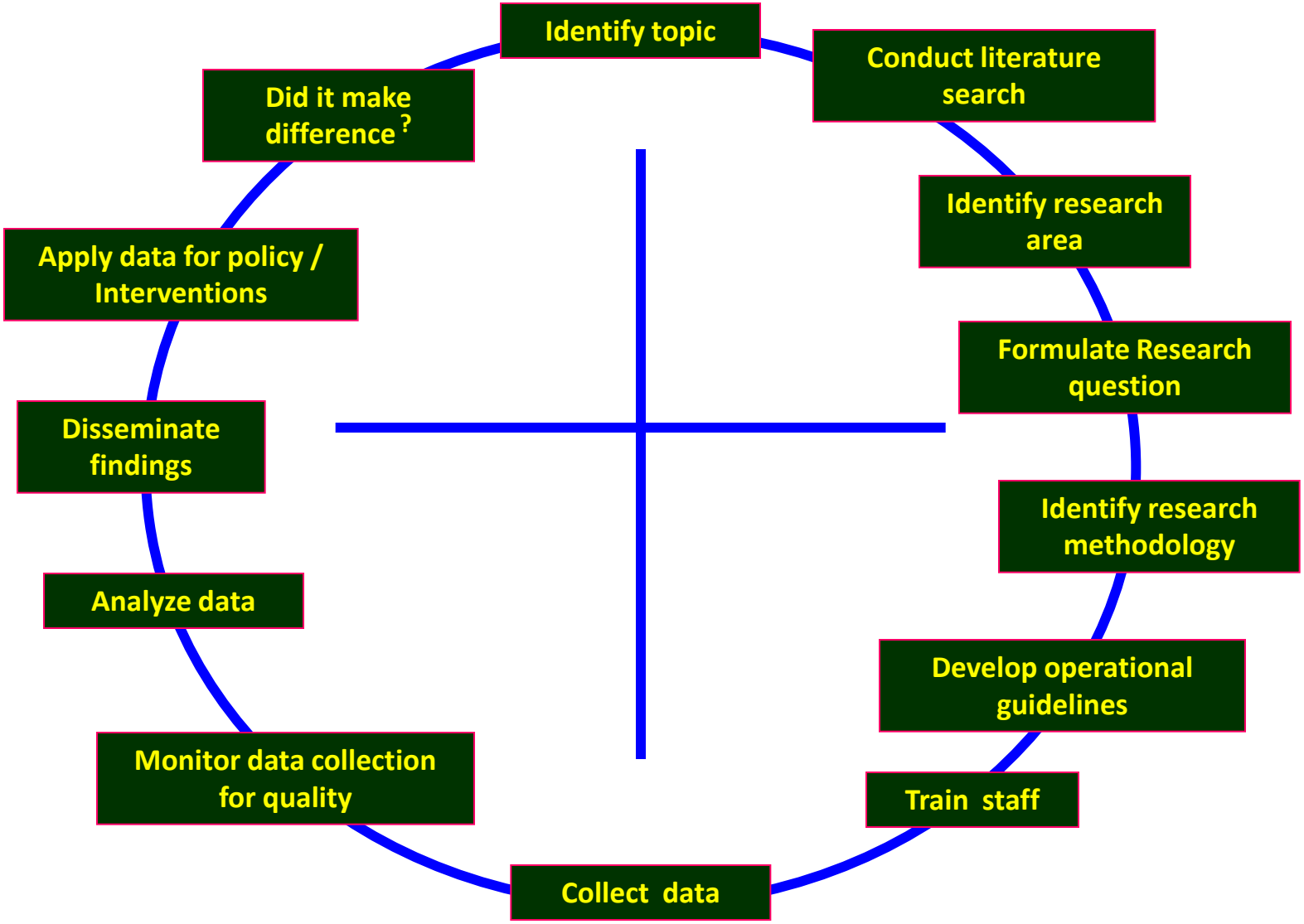
Why undertake research

Academic requirements
Participating in a scientific meet
Career prospects
Peer pressure

Planning, Implementing and Evaluating health care services
Generating evidence for better / effective management strategies

- Doing research is imperative
- Doing good research is a choice
- Doing beneficial research with sound methods is a possibility
- Generating evidence for improving clinical and public health outcomes is to be the goal

Research is a Continuous Process



What is evidence-based medicine?

The practice of EBM is the integration of

- **individual clinical expertise**

  with the

- **best available external clinical evidence from systematic researchand**
- **patient's values and expectations**

Outcome of research

1. Risk measurements
2. Prognosis
3. Treatment
4. Cause
5. Diagnosis – methods and tests
6. Predictions
7. Classification

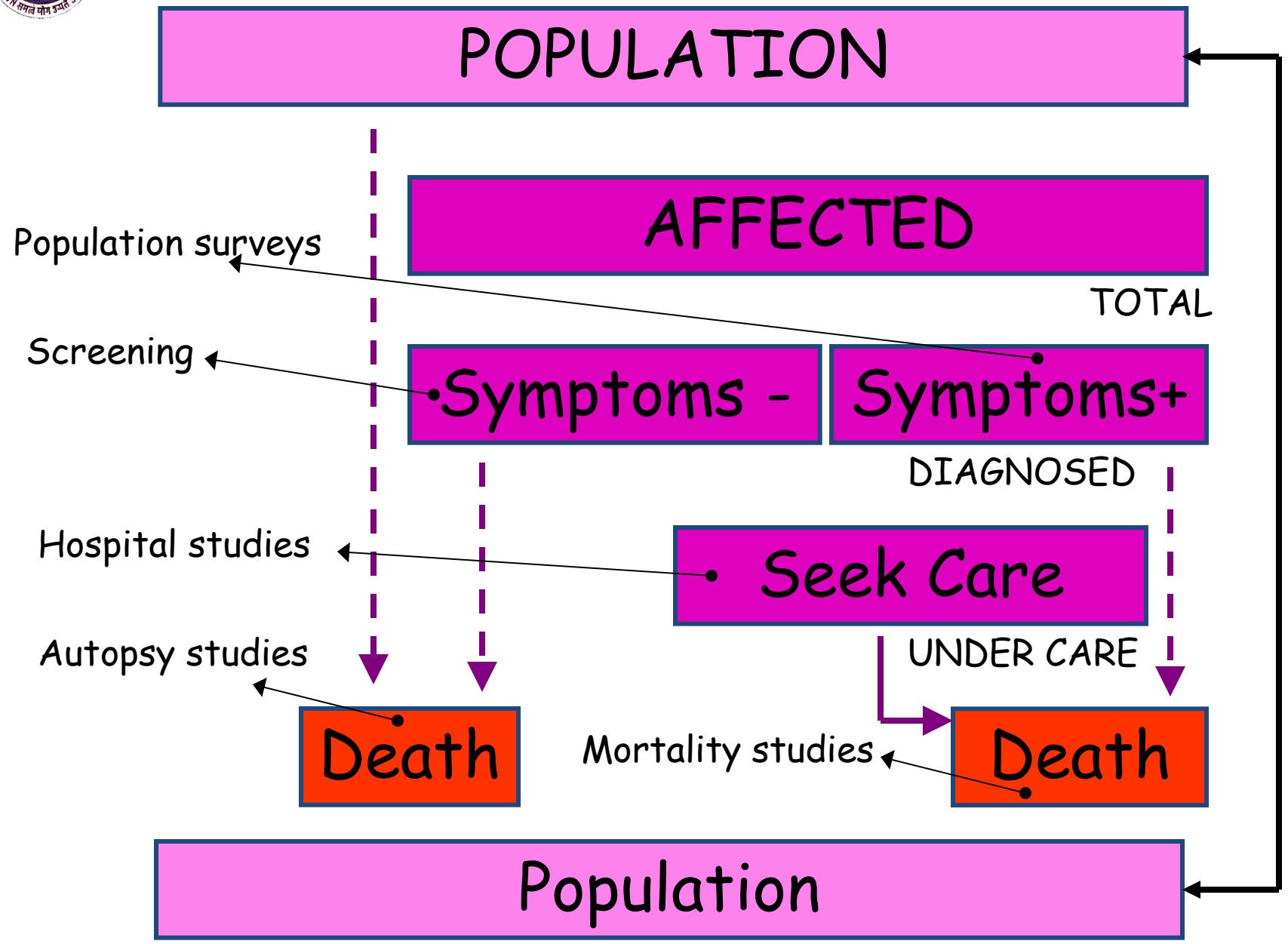
Research methods

QUANTITATIVE

- Survey
- Records review
- Registries
- Focused studies
- Before & After
- Experimental V/s Control

QUALITATIVE

- Key informants
- FGD
- Case studies
- Staff reviews
- KABP
- Guided interviews
- Mapping events
- ‘Tree meetings’


POPULATION
AFFECTED
Population surveys
TOTAL
Screening
Symptoms -
Symptoms+
DIAGNOSED
Hospital studies
Seek Care
Autopsy studies
UNDER CARE
Death
Mortality studies
Death
Population

Basic tenet

- Diseases do not occur in random
- Diseases have causal & initiating factors
- Diseases can be adequately managed and prevented

DETERMINANTS OF A STUDY

- Literature search
- Research Hypotheses / Objectives of the study

- Burden of the problem (Prevalence / Incidence / Proportions / Rates)

- Resources available
- Follow up action planned / possible

PLANNING THE STUDY

- Identifying a problem, defining the problem and refining the problem
- Formulating the research question
- Writing Objective (s) and Sub-objective (s)

  Objective is a verb statement with SMART attributes (Specific, Measurable, Attainable, Reliable and Time bound)

- Identify method(s) to achieve the objective (s)

- LITERATURE REVIEW
  - available / accessible
  - light-house on a stormy ocean - chart the course of study.
    - Identify the variables
    - **To decide study designs options**
    - Compare and contrast the process and results.
- Enriching with collective wisdom.

FORMULATING THE RESEARCH QUESTION

- Need
- Clear
- Focused / specific
- Relevant
- Possible
- Previous answers

CRITERIA FOR CHOOSING A QUESTION

- Relevance
- Feasibility
- Prior knowledge
- Cultural appropriateness
- Logistics

A good question is about a relevant issue, feasible to pursue, the answer to which will have a measurable impact, leading us to more of knowledge or understanding, or to a course of action which attempts to make this world a little better.

SOURCE: Problem Solving for Better Health

- **Are deaths and injuries more among poor communities?**
- **Are deaths and injuries more among poor communities living in rural areas?**
- **Are deaths and injuries more among poor communities using public / private transportation and living in rural areas?**
- **Are deaths and injuries more among poor communities and alcoholics using public / private transportation and living in rural areas?**

Formulate a focused question

Patient / **P**roblem / **P**opulation

Intervention

Comparison

Outcome

Focused question

P: Pregnant smokers

I: nicotine replacement

C: N/A

O: cessation

Is nicotine replacement therapy an effective and safe smoking cessation treatment in pregnant women?

OPERATIONAL ISSUES

- Sampling
  - Random sample
  - Minimum sample needed
- Study instrument
  - ? Suited to Indian Context
  - ? Time taken to complete (Consent + Examn + Others)
- Conducting interviews
  - ? Respondent fatigue / Interviewer fatigue
  - Incomplete / inadequate responses
- Data recording sheet
  - Format (tick / encircle / write)
  - Not applicable / Not available / No Info
- Data entry
  - Who, when, where, how
  - Coding the responses

PILOT STUDY

Study Protocol

To be developed before the start of the study, modified after the pilot study experience and to remain unchanged till completion of the study

- Background
- Objectives
  - primary and secondary questions
- How the study would be carried out

Desirable Protocol Format

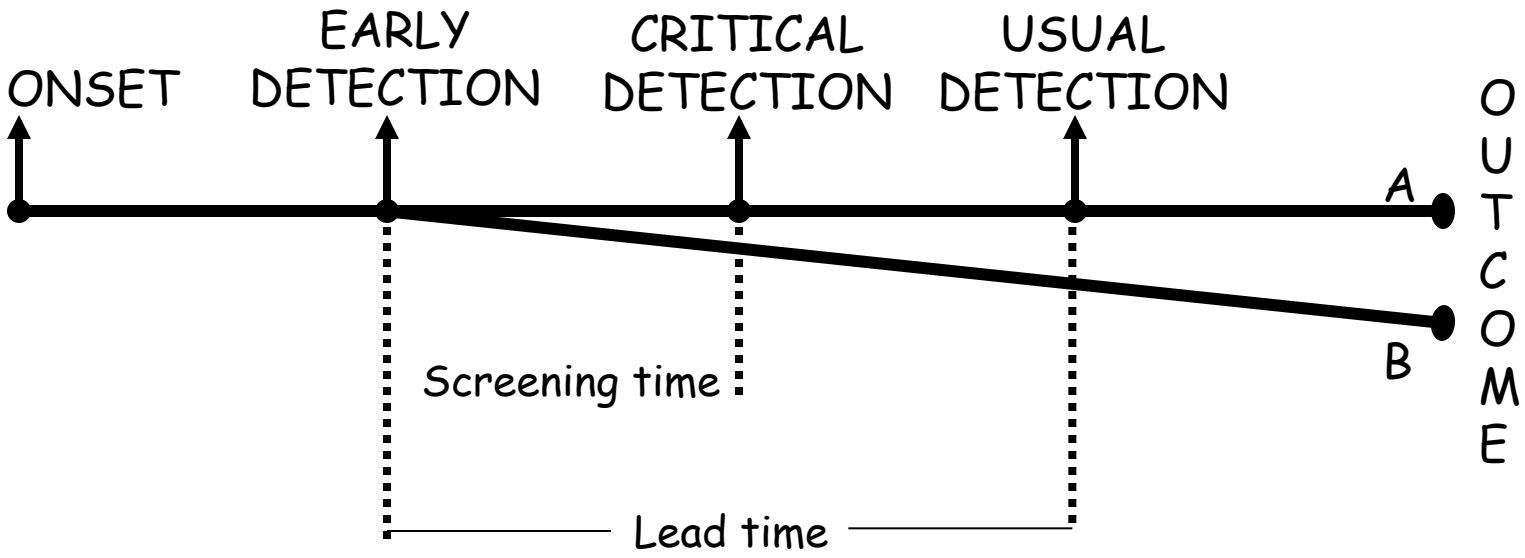
- Introduction including need for the study
- Brief review of literature
- Study Objectives (primary and secondary)
- Study Methodology
  - Study area:
  - Study period:
  - Study population:
    - Inclusion criteria
    - Exclusion criteria
  - Study variables (derived from Study Objectives)
    - Primary
    - Secondary
  - Study instruments
  - Study design
- References

Possible study designs

- Case series
- Medical Records analysis
- Screening
- Case – control studies
- Mortality / Autopsy study
- Clinical trials

SCREENING

- *"Search for unrecognised diseases or defects are identified by means of rapidly applied tests, examinations or other procedures in apparently healthy individuals"*
- **Screening procedure is not "Periodic Health Examination" or a "Diagnostic test"**
- TYPES
  - Mass Screening
  - High Risk Screening
  - Multiple Screening
  - Opportunistic Screening



- USES
  - Case detection (prescriptive screening)
  - Control of disease (prospective screening)
  - Research purposes
  - Educational opportunities

Research Methods

- Non-Experimental (Observational)
  - Descriptive
    - Cross sectional
    - Longitudinal (Prospective , Retrospective)
  - Analytical
    - Group (Ecological / trend)
    - Individual
      - Cross sectional
      - Longitudinal (Prospective , Retrospective)
- Experiments / Quasi experiments

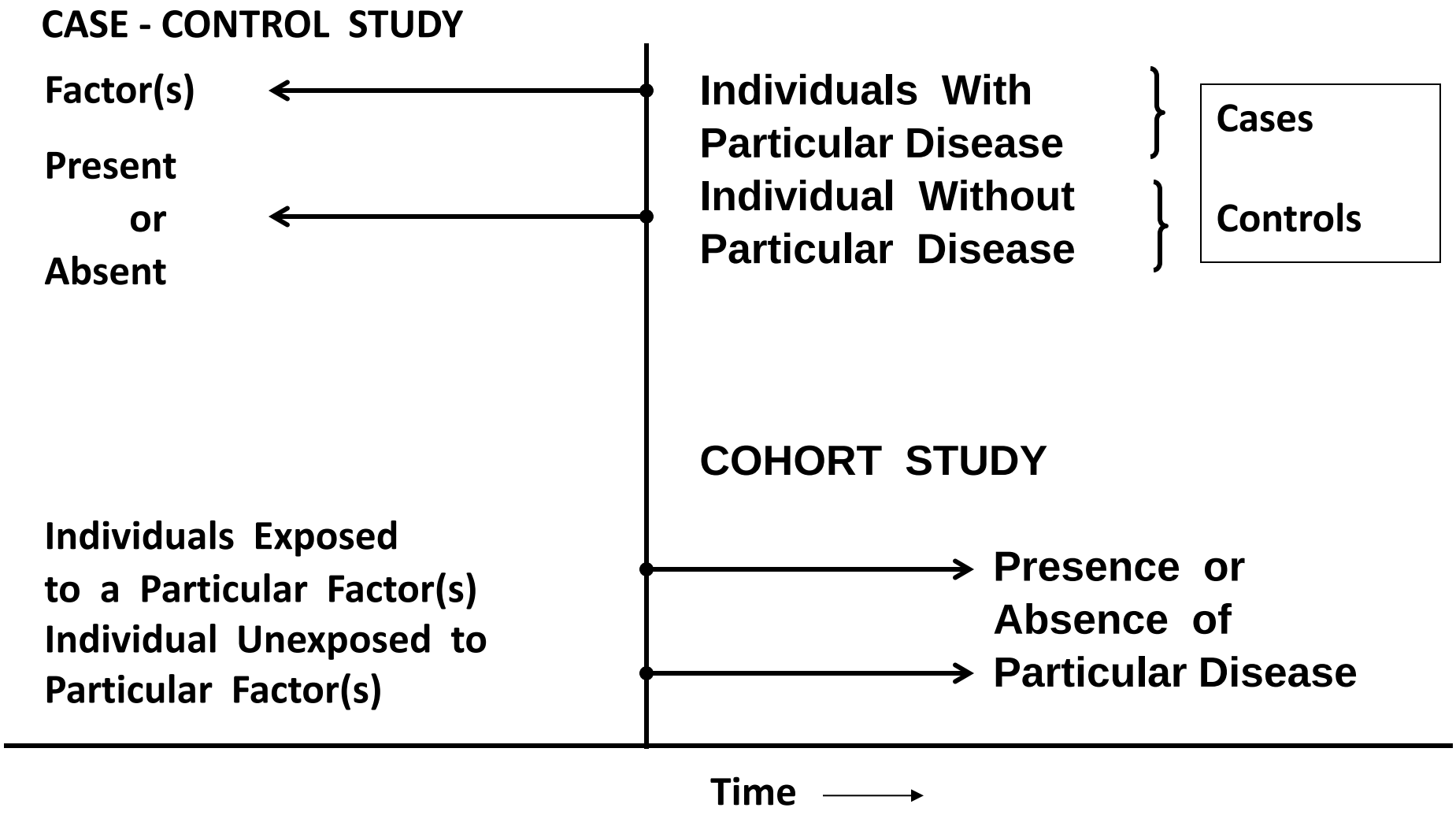
- DESCRIPTIVE STUDY sets out to describe Eg: Distribution of the disease in relation to age, sex, and other characteristics
- ANALYTIC STUDY tries to explain i.e., study the determinative process

  Eg: Why the occurrence; what could be the reason that could be attributed

  ACHIEVED BY FORMULATING AND TESTING HYPOTHESIS

- EXPERIMENTS
  - Studies of deliberate intervention
- NATURAL EXPERIMENTS
  - Experiment of opportunity

ANALYTIC EPIDEMIOLOGY



Case Control and Cohort Studies

DIFFERENCES

Case Control Study

- "Effect to Cause".
- Starts with disease.
- Cause occurs more frequently in those with disease.

Cohort Study

- "Cause to Effect".
- Starts with people.
- Disease occurs more frequently in those exposed.

Case Control and Cohort Studies

DIFFERENCES *(continued)*

Case Control Study

- First approach to testing of a hypothesis
- Fewer number of subjects
- Quick results
- Rare diseases

Cohort Study

- Testing of precisely formulated hypothesis.
- Large number of subjects.
- Long follow - up period.
- Exposure under investigation is rare.

Some issues in undertaking research

1. Ethics
2. Compliance
3. Resources
4. Consent
5. Duration of study
6. Termination
7. Statistical techniques
8. Measurements
9. Placebo effect
10. Generalizability

Matching

To ensure comparability

Similar except for the event in question

- Overmatching / Under matching
- 1: 1 or >1: 1 or 1: >1

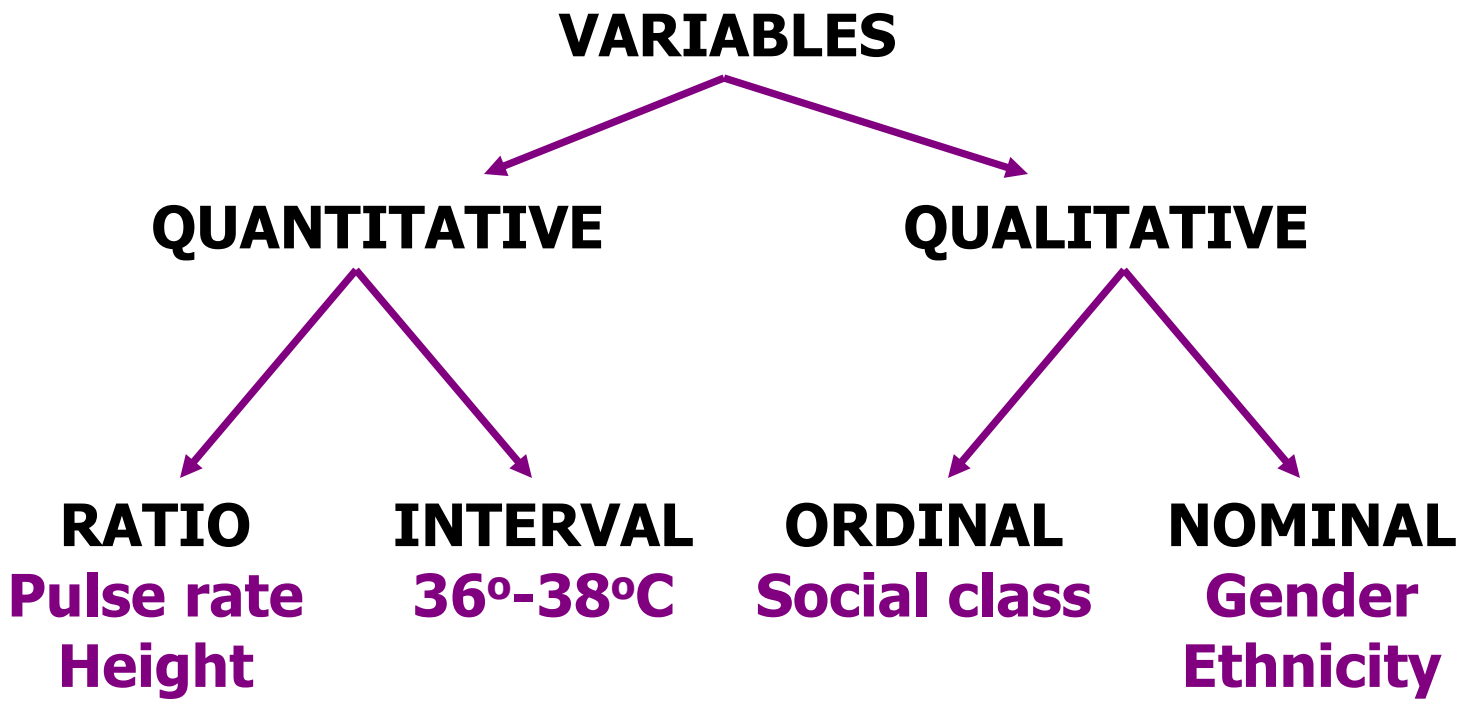
TYPES

- Group
- Pairs

BIAS

- Any factor or process that tends to deviate the results or conclusions of a trial systematically away from the truth.
- Deviation from the truth can result in underestimation or exaggeration of the outcome.
- Types
  - Selection: Self selection Bias or Berksonian bias in Hospital based studies
  - Ascertainment
  - During the course of a the study
  - During dissemination
  - During uptake

TYPES OF DATA



Calculating sample size

- ***Patients I need*** approach: based on calculations of sample size for a given power, significance, and clinically meaningful difference
- ***Patients I can get*** approach: based on calculations of power for a given sample size & level of significance

Calculating sample size

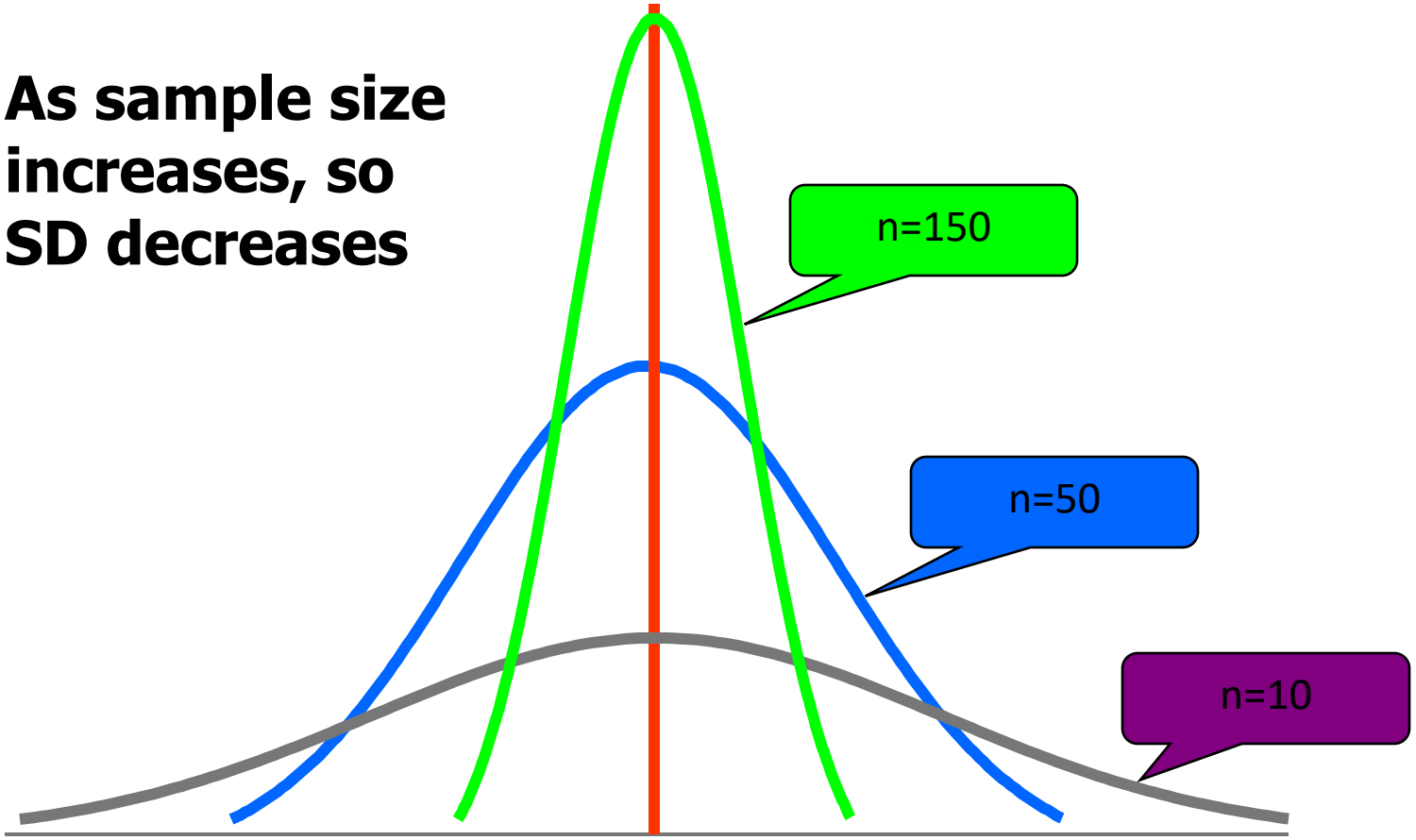
1. Blind guess
2. Available budget
3. Rules of thumb
   - Main group $n > 100$
   - Subgroups $20 < n < 100$
   - 5 to 10 for each variable
4. Standards for comparable studies
5. Statistical precision
   1. Mean and SD, Rate or Difference in expected outcomes
   2. Acceptable variation in results
   3. Significance level

Questions before asking for sample size?

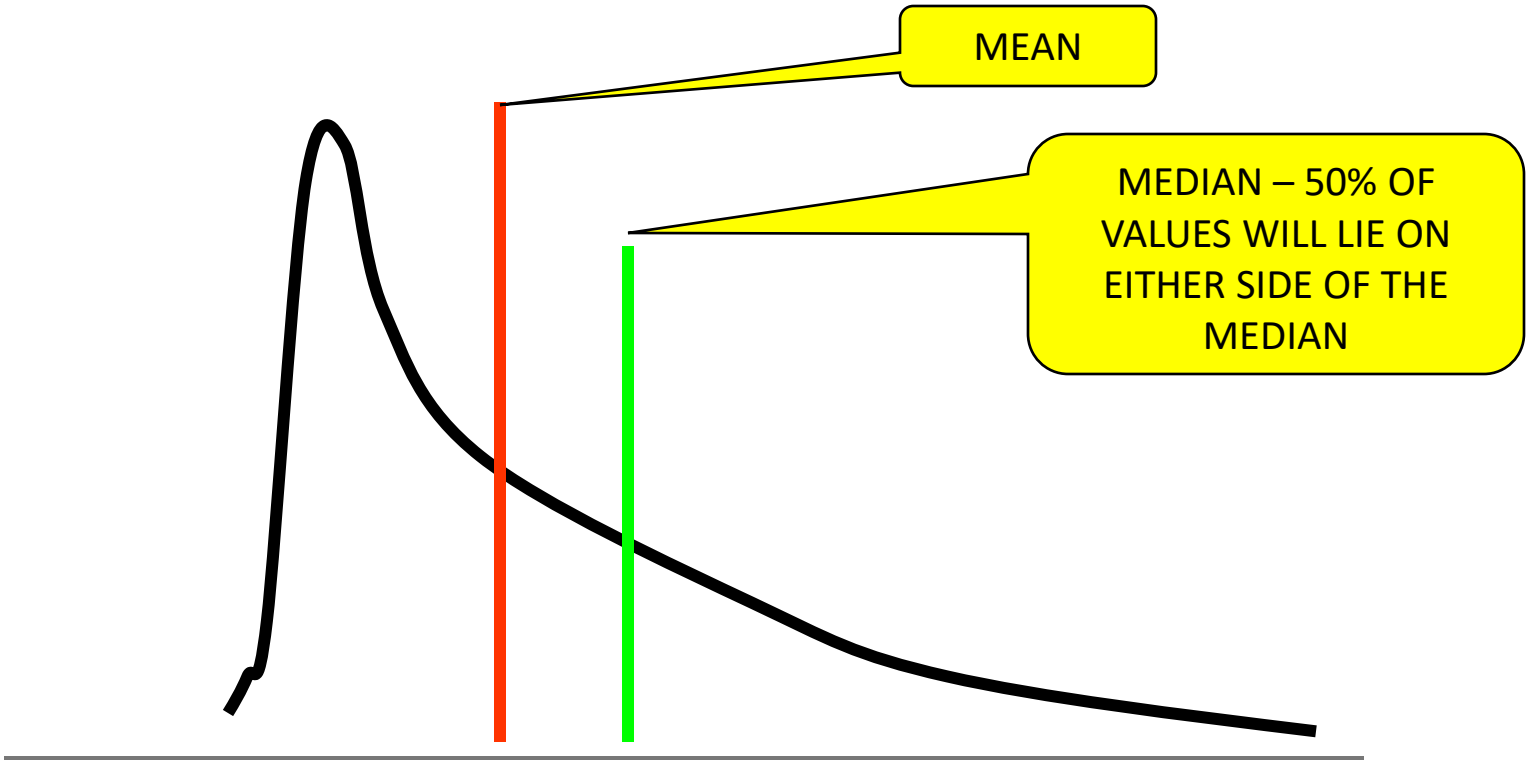
- What is the main purpose of the study?
- What is the primary outcome measure? Is it a continuous or dichotomous outcome?
- How will the data be analyzed to detect a group difference?
- How small a difference is clinically important to detect?
- How much variability is in our population?
- What is the desired α and β?
- What is the sample size allocation ratio?
- What is the anticipated drop out rate?

STANDARD DEVIATION AND SAMPLE SIZE

As sample size increases, so SD decreases



SKEWED DISTRIBUTION

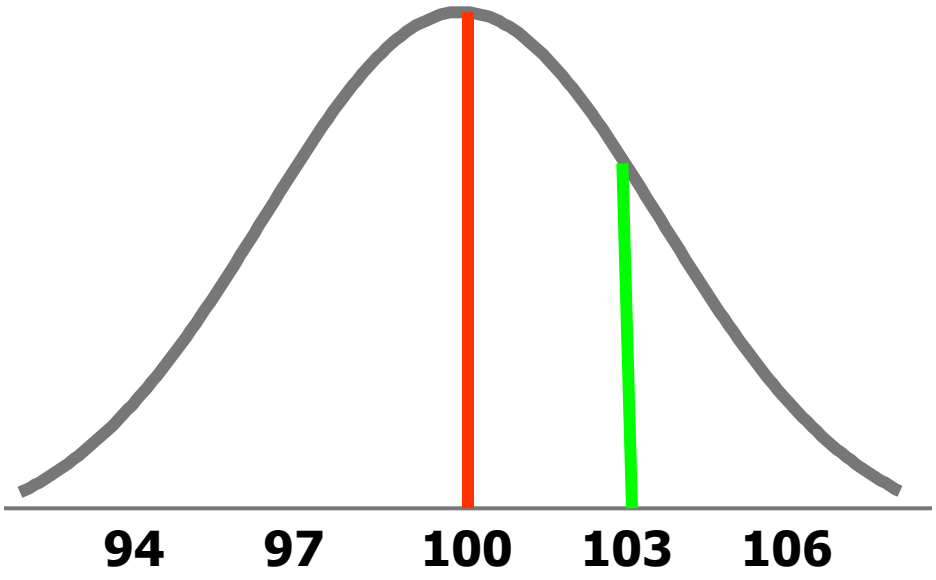


DOES A VARIABLE FOLLOW A NORMAL DISTRIBUTION?

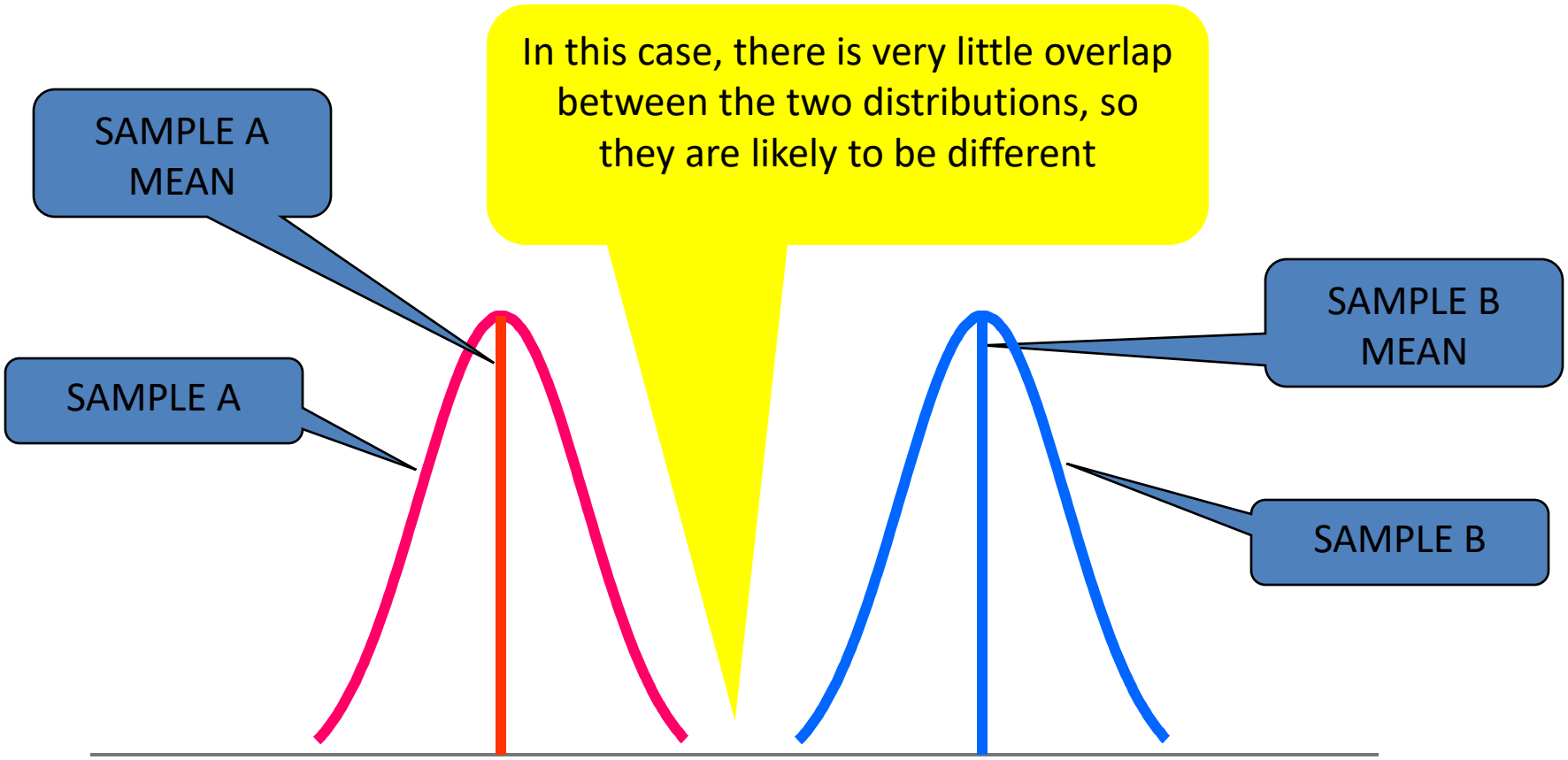
- Important because parametric statistics assume normal distributions
- Statistics packages can test normality
- Distribution unlikely to be normal if:
  - Mean is very different from the median
  - Two SDs below the mean give an impossible answer (eg height <0 cm)

NORMAL DISTRIBUTION	SKEWED DISTRIBUTION
• Height • Weight • Haemoglobin	• Income • Number of marriages

IQ = 103 What does this mean

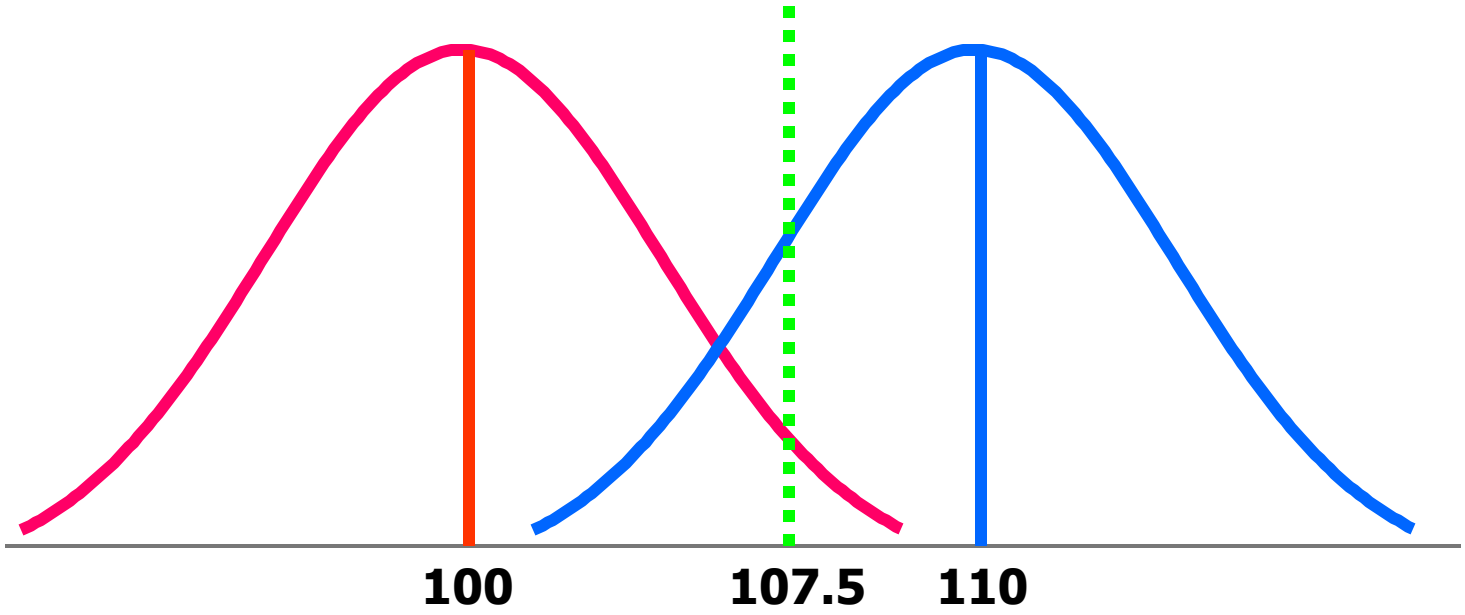


COMPARING TWO SAMPLES



COMPARING TWO SAMPLES

Returning to the IQ example, let's say that we know that the sample we tested (IQ=107.5) actually came from a population with a mean IQ of 110



STATISTICAL SIGNIFICANCE IS NOT NECESSARILY CLINICAL SIGNIFICANCE

Sample Size	Population Mean	Sample Mean	p
4	100.0	110.0	0.05
25	100.0	104.0	0.05
64	100.0	102.5	0.05
400	100.0	101.0	0.05
2,500	100.0	100.4	0.05
10,000	100.0	100.2	0.05

CLINICALLY SIGNIFICANT IMPROVEMENT

Large proportion of patients improving

A change which is large in magnitude

An improvement in patients' everyday functioning

Reduction in symptoms by 50% or more

Elimination of the presenting problem

SUMMARY OF BASIC STATISTICAL TESTS

	2 groups	>2 groups
Continuous variables	**Independent t-test**	**ANOVA**
Continuous variables+same sample	**Matched pairs t-test**	**Repeated measures ANOVA**
Categorical variables	**Chi square test**	**(Chi square test)**
Ordinal variables (not normally distributed)	**Mann-Whitney U test**	**Kruskal-Wallis ANOVA**

ABSOLUTE AND RELATIVE RISKS

	CBT	Usual Care (TAU)
Deterioration	3 (13%)	11 (52%)
No Deterioration	20 (83%)	10 (48%)

Absolute Risk Reduction (ARR) = **Deterioration rate (TAU) _ Deterioration rate (CBT)**

= 52% – 13% = 39% or 0.39

Relative Risk Reduction (RRR) = $\frac{\text{Deterioration rate (TAU)} \_ \text{Deterioration rate (CBT)}}{\text{Deterioration rate (TAU)}}$

= (52– 13)/53 = 73% or 0.73

Note that this could also be expressed as a Benefit Increase rather than an Risk Reduction – the answer is the same

NUMBER NEEDED TO TREAT

	CBT	Usual Care (TAU)
Deterioration	3 (13%)	11 (52%)
No Deterioration	20 (83%)	10 (48%)

Absolute Risk Reduction (ARR) = 0.39

Number Needed to Treat (NNT) = 1/ARR = 1/0.39 = 2.56 (~ 3)

- **NNT is the number of patients that need to be treated with CBT, compared with treatment as usual, to prevent one patient deteriorating**
- **In this case, 3 patients have to be treated to prevent one patient deteriorating**
- **NNT is a very useful summary measure, but is commonly not given explicitly in published papers**

CONFIDENCE INTERVAL (CI)

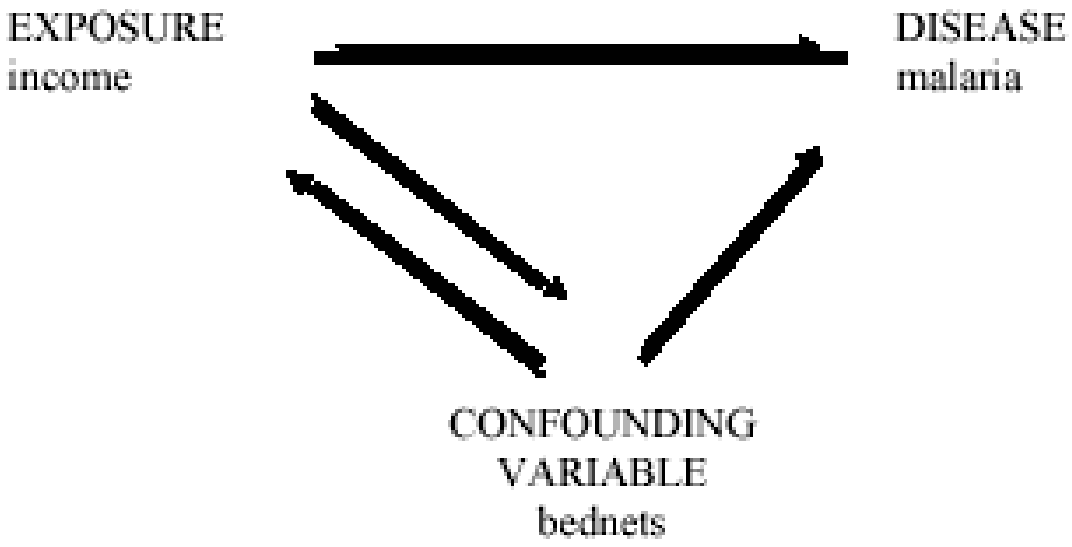
- Gives a measure of the precision (or uncertainty) of the results from a particular sample
- Key point – result is statistically ‘significant’ because the 95% CI does not include zero

CONFIDENCE INTERVAL OF ABSOLUTE RISK REDUCTION

- ARR = 0.39
- se = 0.13
- 95% CI of ARR = ARR ± 1.95 x se
- 95% CI = 0.39 ± 1.95 x 0.13
- 95% CI = 0.39 ± 0.25 = 0.14 to 0.64
- The calculated value of ARR is 39%, and the 95% CI indicates that the true ARR could be as low as 14% or as high as 64%

CONFOUNDING

There is a higher incidence of Lung cancer in people who carry matches or lighter with them



Criteria for confounding

- A confounder must be a cause of the disease (or a marker for a cause)
- A confounder must be associated with the exposure in the source population
- A confounder must not be affected by the exposure or the disease

- Association between cigar smoking and baldness
  - Age is confounder
- Second, third or fourth children are affected by downs syndrome
  - Maternal age
- Small hospitals have lower rates of nosocomial infections than the large hospitals
  - Number of well patients
- “I am probably allergic to leather because every time I go to bed with my shoes on, I wake up with a headache the next morning.”
  - Alcohol use

- Improved perinatal outcomes for birthing centers when compared to hospitals
  - highly motivated volunteers selecting the birthing center option
- Protective effect between animal companions and heart attack
  - pets require care and pet owners were more active or able to physically care for them
  - those who can tolerate pets are more easy-going (Type B personalities)

- Study design or Sample design
- Sample characteristics
  - Representativeness

    Pigeons I saw v/s Pigeons in the rest of the world
  - Randomness
- Source of information
  - Records
  - Observation
  - Interviews
  - Examination
  - Investigation(s)

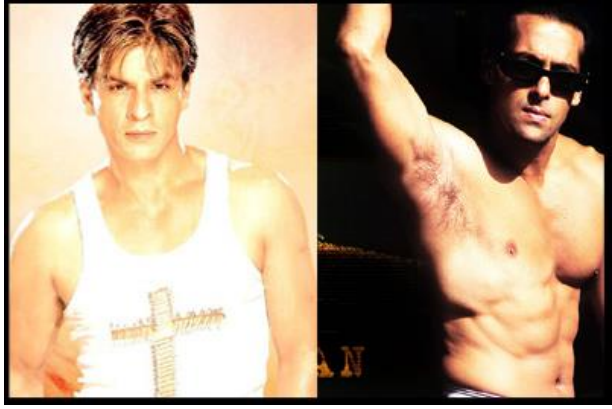
- Data analysis
- Data intepretation
- Writing the report
- Dissemination strategy

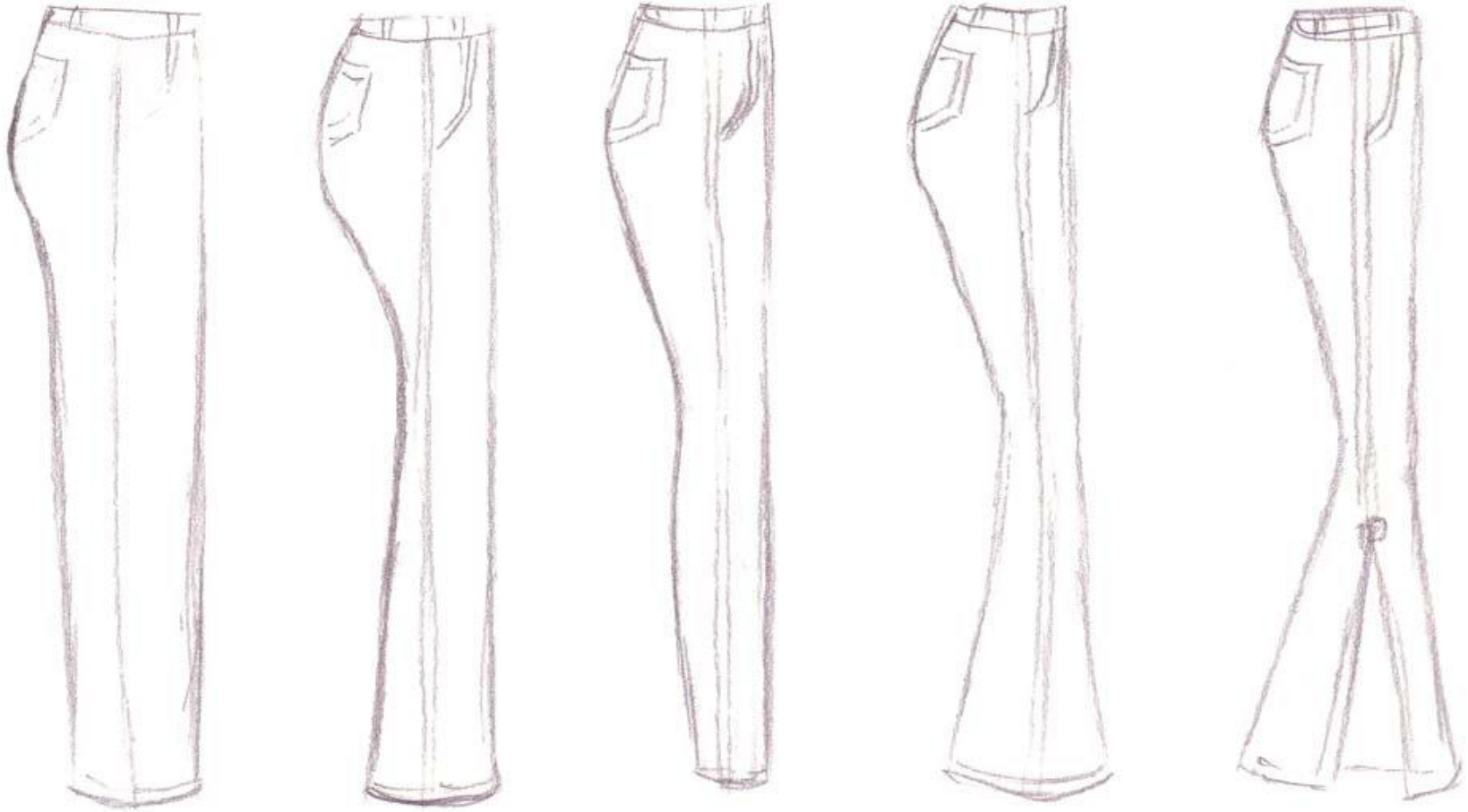
BMJ 1997;315:1636 (20 December) Editorial

Choosing the best research design for each question

It's time to stop squabbling over the "best" methods

Sackett D L and Wennberg J E





Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith and Jill P Pell

BMJ 2003;327;1459-1461

- **Objectives**
  - To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.
- **Design**
  - Systematic review of randomised controlled trials.
- **Data sources**
  - Medline,Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.
- **Study selection**
  - Studies showing the effects of using a parachute during free fall.
- **Main outcome measure**
  - Death or major trauma, defined as an injury severity score > 15.

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

- **Results**
  - We were unable to identify any randomised controlled trials of parachute intervention.
- **Conclusions**
  - As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data.We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.


Systematic Reviews
and Meta-analyses
Randomized
Controlled Double
Blind Studies
Cohort Studies
Case Control Studies
Case Series
Case Reports
Ideas, Editorials, Opinions
Animal research
In vitro ('test tube') research

- Doing research is imperative
- Doing good research is a choice
- Doing beneficial research with sound methods is a possibility
- Generating evidence for improving clinical and public health outcomes is to be the goal


"That's all Folks!"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